GOLD CATALYSIS: TOTAL SYNTHESIS OF THE ENGLERINS AND AN APPROACH TOWARDS SCHISANWILSONENE A

Nicolas Delpont

Dipòsit Legal: T.1321-2013

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Doctoral Thesis

Gold Catalysis: Total Synthesis of the Englerins and an Approach Towards Schisanwilsonene A

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Institut Català d'Investigació Química

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FAIG CONSTAR que aquest treball, titulat "Gold Catalysis: Total Synthesis of the Englerins and an Approach Towards Schisanwilsonene A", que presenta Nicolas Delpont per a l'obtenció del títol de Doctor, ha estat realitzat sota la meva direcció al Departament de Química Analítica i Química Orgánica d'aquesta Universitat i que acompleix els requeriments per poder optar a Menció Europea.

Tarragona, 5 de Abril de 2011

El Director de la Tesi Doctoral

Prof. Antonio M. Echavarren

This Doctoral Thesis has been carried out in l'Institut Català d'Investigació Química under the supervision of Professor Antonio M. Echavarren that I would like to thank for giving me the opportunity to spend nearly four wonderful years in his laboratory.

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At the printing of this manuscript, the results presented herein have been published in:

• Enantioselective Synthesis of (-)-Englerins A and B.

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

Patent Application EP10158271.6

Highlighted in *Nature Chemistry*, **2010**, *2*, 519-520 and *Synfacts*, **2010**, *9*, 9073.

Other publications not related to the topics covered in this manuscript are presented below:

• Metal–Arene Interactions in Dialkylbiarylphosphane Complexes of Copper, Silver, and Gold.

P. Pérez-Galán, N. Delpont, E. Herrero-Gómez, F. Maseras, A. M. Echavarren, *Chem. Eur. J.* **2010**, *16*, 5324-5332

• Gold-Catalyzed Olefin Cyclopropanation.

A. Prieto, M. R. Fructos, M. M. Díaz-Requejo, P. J. Pérez, P. Pérez-Galán, N. Delpont, A. M. Echavarren, *Tetrahedron* **2009**, *65,* 1790-1793.

Contents

Abbreviations and Acronyms

In this manuscript, abbreviations and acronyms have been used, according to the "guidelines for authors" of *The Journal of Organic Chemistry*.

A bookmark with the structures and the abbreviations of the most frequently used gold catalysts is also provided.

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

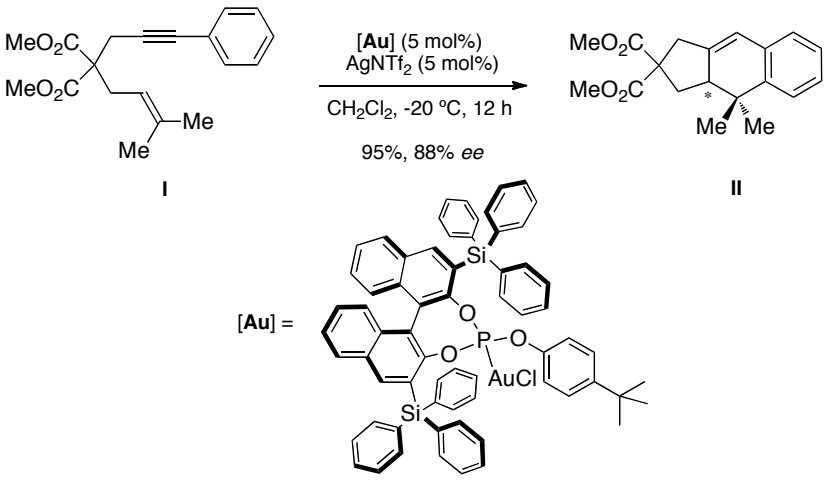
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-binaphthol
conv	conversion
decomp	decomposition
DIPEA	diisopropylethylamine
dppm	bis(diphenylphosphino)methane
e.r.	enantiomeric ratio
*m*CPBA	*meta*-chloroperoxybenzoic acid
MeOBIPHEP	bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
Oct	octanoate
PNBn	*para*-nitrobenzyl
PNP	*para*-nitrophenyl
quant	quantitative
r.r.	regioisomeric ratio
SEGPHOS	4,4'-bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphane)
TBAI	tetrabutyl ammonium iodide

TCCA	Trichloroacetic acid
TES	triethylsilyl
TDS	Thexyldimethylsilyl
tmbn	trimethoxybenzonitrile

Resumen de la Tesis

Durante los últimos años, en nuestro grupo de investigación se han desarrollado reacciones de activación de alquinos catalizadas por metales de transición.

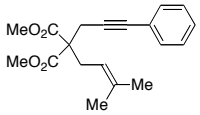
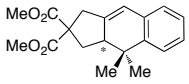
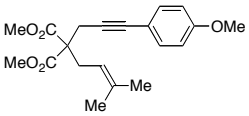
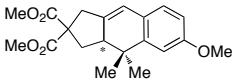
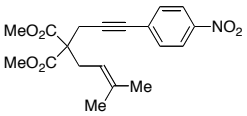
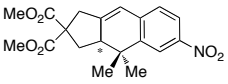
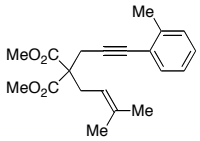
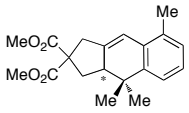
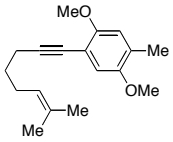
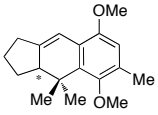
Un ejemplo, desarrollado en nuestro laboratorio es la reacción de ciclación [4+2] intramolecular de aril eninos. Sin embargo sólo existe un precedente en la literatura de la versión enantioselectiva de esta reacción. Por este motivo, uno de los objetivos de esta tesis ha sido el desarrollo de nuevos catalizadores quirales para realizar este tipo de ciclaciones, obteniéndose un sistema catalítico de Au(I) capaz de formar el producto ciclado **II** con un exceso enantiomérico del 88% (Esquema 1).



Esquema 1. Síntesis del cicloaducto **II** en 88% *ee*.

Este sistema catalítico ha sido aplicado en la ciclación de otros aril eninos y se han obtenido excesos enantioméricos desde un 17% hasta un 86 % (Tabla 1).

Tabla 1. Aplicación del sistema catalítico en la ciclación de otros aril eninos.

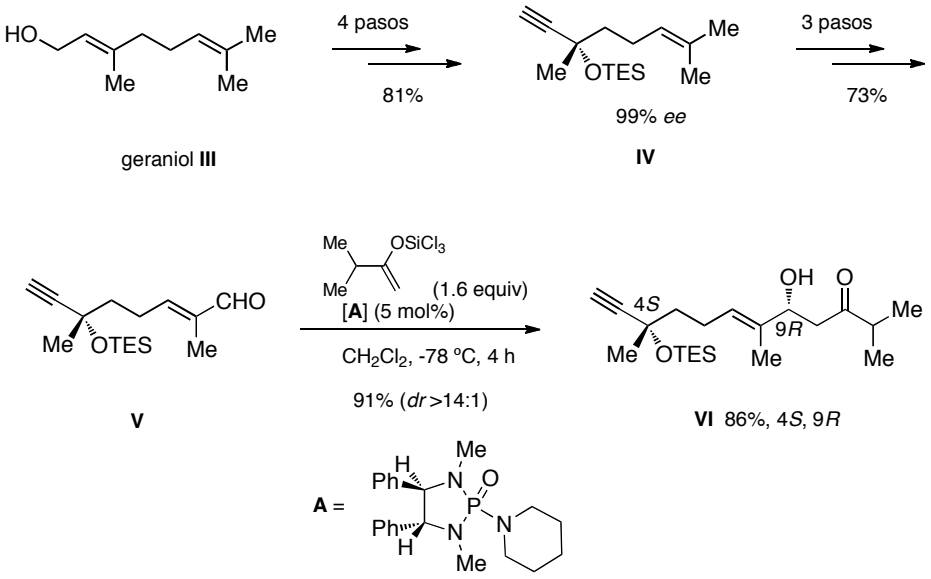
Entrada	*Sustrato*	*Producto*	*T(ºC)*	*t*	*Rendimiento %*	*ee (%)*
1			- 20	18 h	>95	88
2			- 20	30 h	85	86
3			0[a]	15 h	80	73
4			- 20	30 h	70	79
5			0[a]	48 h	62	17

Los otros capítulos de este manuscrito tratan de la aplicación de reacciones catalizadas por Au(I) en la síntesis de productos naturales.

De este modo, se ha completado la síntesis total de la (-)-englerina A, un compuesto natural que presenta una potente actividad biológica contra líneas tumorales de cáncer de riñón.

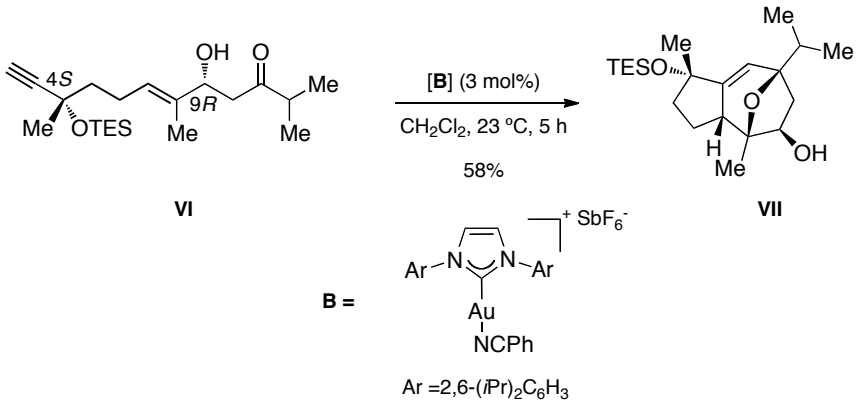
La síntesis enantioselectiva de la (-)-englerina A se comenzó a partir del geraniol comercial **III** (Esquema 2). Tras 4 pasos de reacción se obtuvo el intermedio **IV** con un rendimiento global del 81%. La ruptura oxidativa de **IV** proporcionó el aldehído que se empleó en la reacción de Wittig necesaria para la obtención de **V**, con un

rendimiento global del 73%. Este aldehído se usó en una reacción aldólica esteroselectiva empleando el catalizador de Denmark **A** para obtener **VI** con un 86% de rendimiento y un exceso diastereriisomérico del 86%.



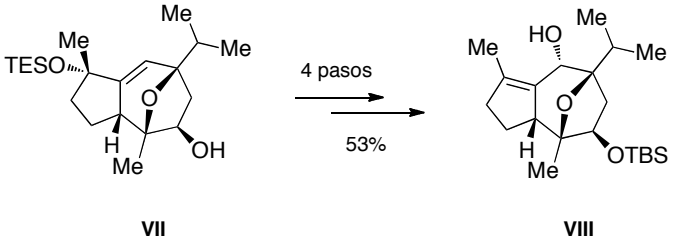
Esquema 2. Síntesis del intermedio **VI** desde el geraniol **III**.

La etapa clave de la síntesis fue la ciclación del alquino terminal **VI** empleando el catalizador de Au(I) **B,** obteniéndose el cicloaducto **VII** con un 58% de rendimiento (Esquema 3).



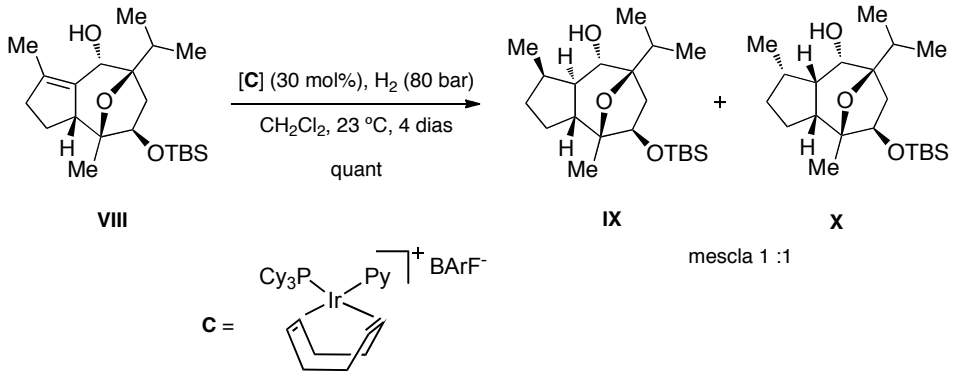
Esquema 3. Síntesis del intermedio **VII**.

La desprotección del alcohol sililado, protección del alcohol secundario, seguido de una migración 1,3 del alcohol alílico proporcionó el intermedio **VIII** con un 53% de rendimiento global (Esquema 4).



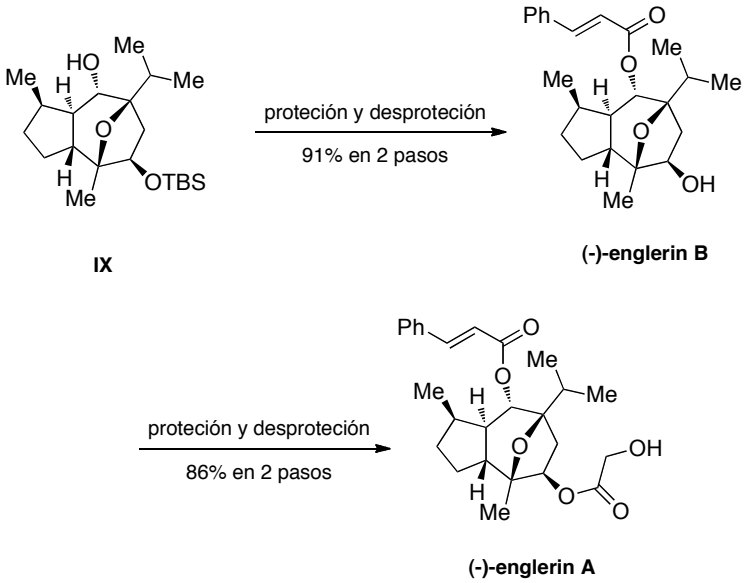
Esquema 4. Síntesis del intermedio **VIII**.

El producto **VIII** se sometió a una hidrogenación diastereoselectiva catalizada por el catalizador de Pfaltz de iridio **C** formándose una mezcla 1:1 de los compuestos **IX** y **X** (Esquema 5).



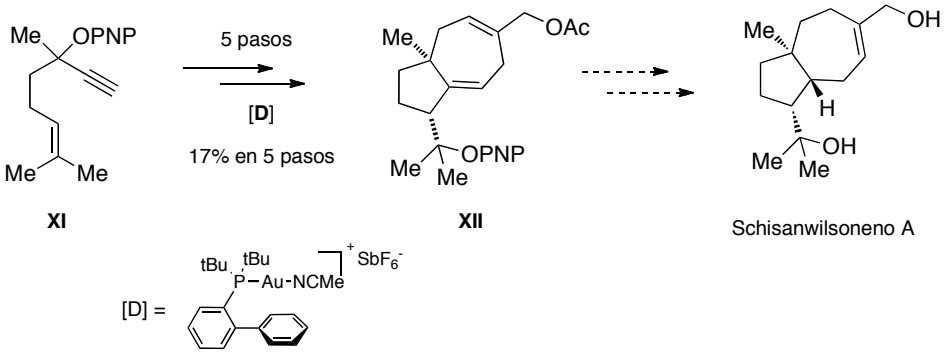
Esquema 5. Síntesis del intermedio **IX**.

La (-)-englerina B se formó tras la esterificación del alcohol libre y la desprotección del alcohol protegido desde **IX** con un rendimiento del 91%. La (-)-englerina A se obtuvo fácilmente a partir de la (-)-englerina B en dos pasos (Esquema 6).



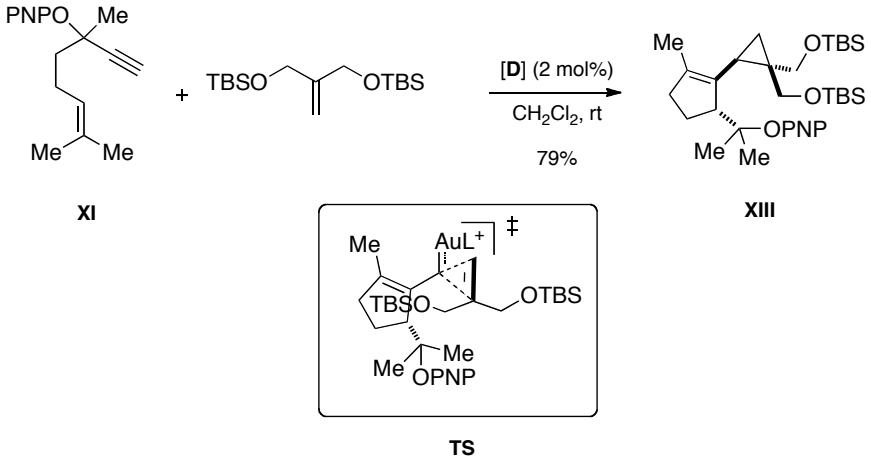
Esquema 6. Síntesis de las englerinas A y B desde el intermedio **IX**.

El tercer capítulo de este tesis es la aplicación de una ciclación catalizada por el catalizador de oro **D** en la síntesis desde el enino **XI** del intermedio **XII**, precursor del producto natural Schisanwilsoneno A, llevada a cabo en 5 pasos y con un rendimiento global de 17% (Esquema 7). El Schisanwilsoneno A es un terpeno dotado de una notable actividad antiviral contra la hepatitis B.



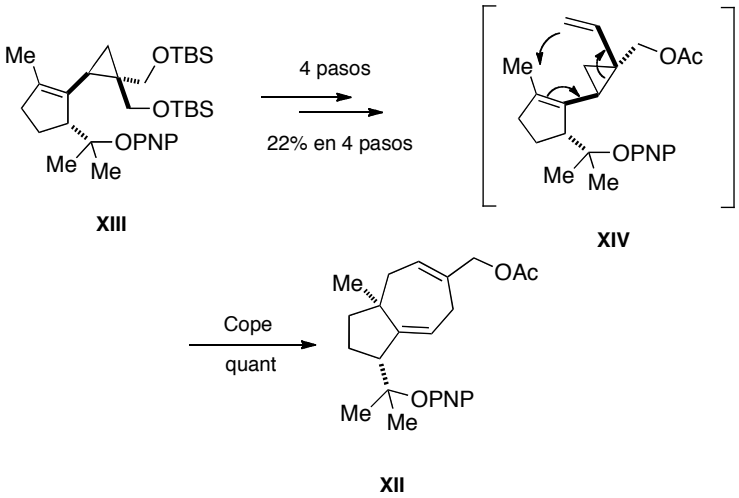
Esquema 7. Síntesis del intermedio **XII** en 5 pasos desde **XI**.

El intermedio **XIII** se obtuvo en el paso de ciclación con oro desde **XI** y un alqueno sustituido con 2 grupos OTBS (Esquema 8).



Esquema 8. Síntesis del intermedio **XIII** obtenido en el paso de ciclación con oro.

Tras 4 pasos de reacción se obtuvo el intermedio **XIV** con un rendimiento global del 22%. El intermedio **XIV** se convirtió directamente en el producto bicíclico **XII** con un reordenamiento de Cope (Esquema 9).



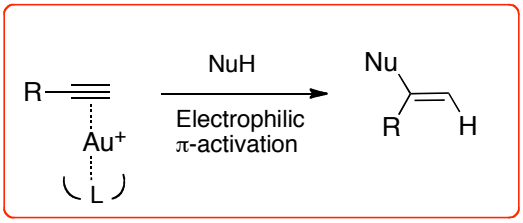
XIII **XIV** **XII**

Esquema 9. Obtención del intermedio **XII**.

General Introduction

Until recently, gold did not attract the interest of synthetic chemists, although it had fascinated alchemists before the advent of modern chemistry. The breakthrough came from the observations that gold, when sub-divided to the nano- or molecular scale, could be exceptionally active as catalyst. These observations spurred a great number of discoveries and the field has now evolved to be a true hot spot in catalysis.[1]

Under homogeneous conditions, gold complexes are remarkably reactive Lewis acids with a high-affinity for π-bonds as a result of the relativistic effect, which reaches a maximum in the periodic table with gold.[2] Therefore, gold complexes usually surpass the reactivity shown by other electrophilic metal salts and complexes for the activation of alkynes towards a variety of nucleophiles (Scheme A).[3]



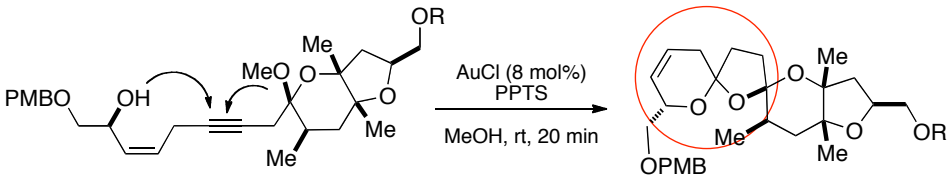
Scheme A. π-Activation by gold towards nucleophilic addition

After an initial focus on the development of new gold-catalyzed reactions, a growing number of applications in the total synthesis of natural products have been reported in recent years.

1. Hutchings, G. J.; Brust, M.; Schmidbaur, H. *Chem. Soc. Rev.* **2008**, *37*, 1759-1765.
2. Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395-403., and references therein.
3. For selected reviews on gold-catalyzed reactions, see: (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333-346. (b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239-3265. (c) Hashmi, A. S. K. *Nature* **2007**, *449*, 292-293. (d) For a recent report on ligand effects in homogeneous gold catalysis, see: Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351-3378.

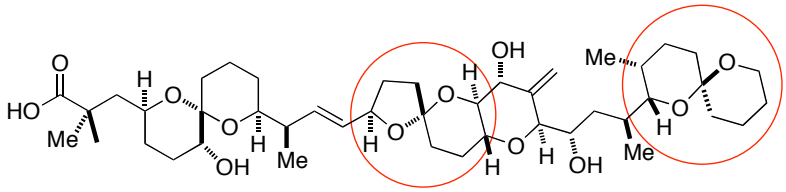
The addition of heteronucleophiles to alkynes and allenes is a classic application of gold catalysis in natural product synthesis that allows the delivery of heterocylic compounds with well-defined stereochemistry from chiral substrates.

This approach was used in the synthesis of the A-D rings of the toxin azaspiracid through the synthesis of the spiroketal framework from a two-fold intramolecular nucleophilic addition (Scheme B).[4]



Scheme B. Synthesis of a section of azaspiracid using a gold(I)-catalyzed spiroketalisation reaction.

A similar gold(I)-catalyzed transformation was reported as the key step in the formal total synthesis of okadaic acid (Figure A).[5]

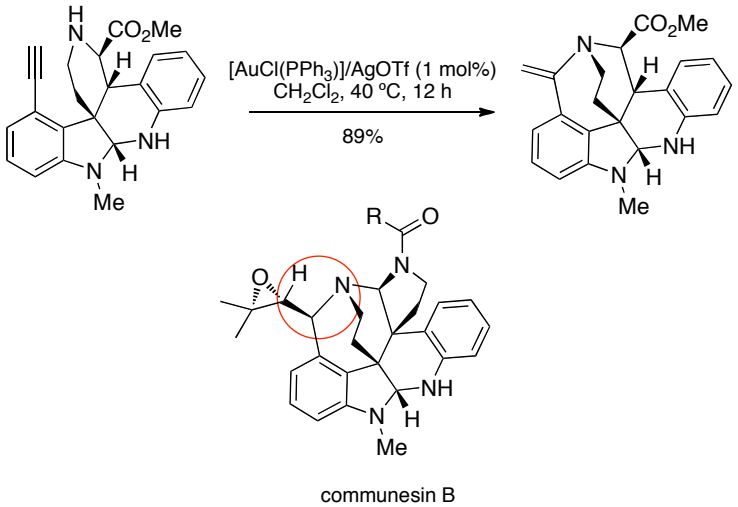


Okadaic acid

Figure A. Okadaic acid with two spiroketal frameworks obtained using a gold(I)-catalyzed reaction.

4. Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 279-282.
5. Fang, C.; Pang, Y.; Forsyth, C. J. *Org. Lett.* **2010**, *12*, 4528-4531.

The gold(I)-catalyzed addition of an amine to an alkyne was also employed at a late stage in the synthesis of communesin B (Scheme C).

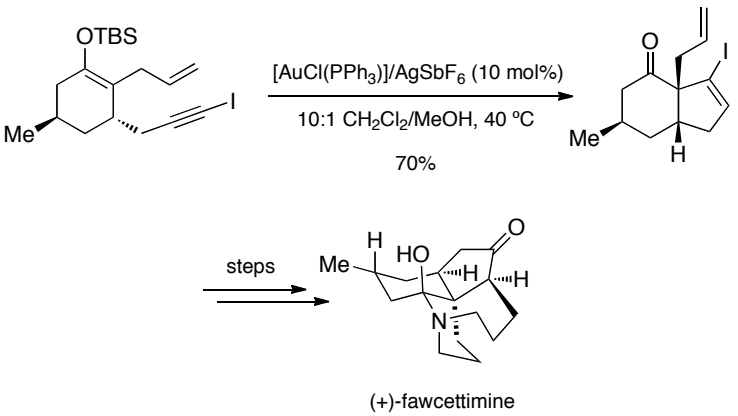


Scheme C. Gold(I)-catalyzed hydroamination in the synthesis of communesin B.

In the past few years, gold catalysis has contributed greatly to the broad field of enyne cycloisomerization chemistry.[6]

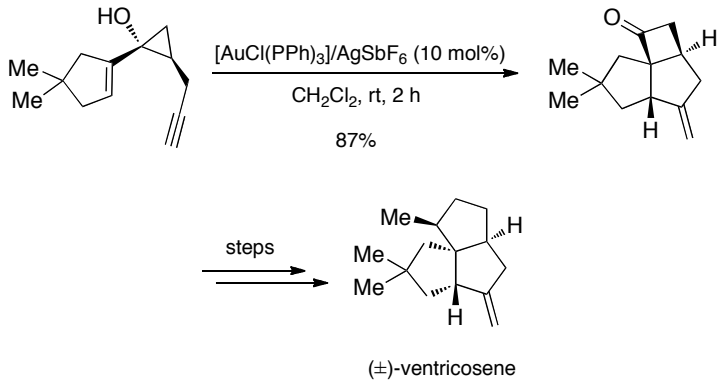
Amongst the numerous examples, an elegant application of the gold(I)-catalyzed Conia-type cyclization was demonstrated in the synthesis of alkaloid (+)-fawcettimine (Scheme D).[7]

6. For selected reviews on gold-catalyzed cycloisomerisations of enynes, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326-3350. (c) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268-4315.
7. Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671-7673.



Scheme D. Synthesis of (+)-fawcettimine.

The synthesis of the triquinane sesquiterpene (±)-ventricosene was carried out using the gold(I)-catalyzed cyclization of a 1,6-enyne, which proceeded with concomitant cyclopropanol expansion to form a four-membered ring (Scheme E).[8]



Scheme E. Synthesis of sesquiterpene (±)-ventricosene.

8. Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315-4318.

With the array of methodologies available for synthetic chemists, homogeneous gold chemistry is now a well-established tool for organic transformations and it should not be considered as an exotic Lewis acid anymore.

The increasing number of citations over the last five years confirms a real interest by the scientific community on the use of gold chemistry in total synthesis (Figure B).

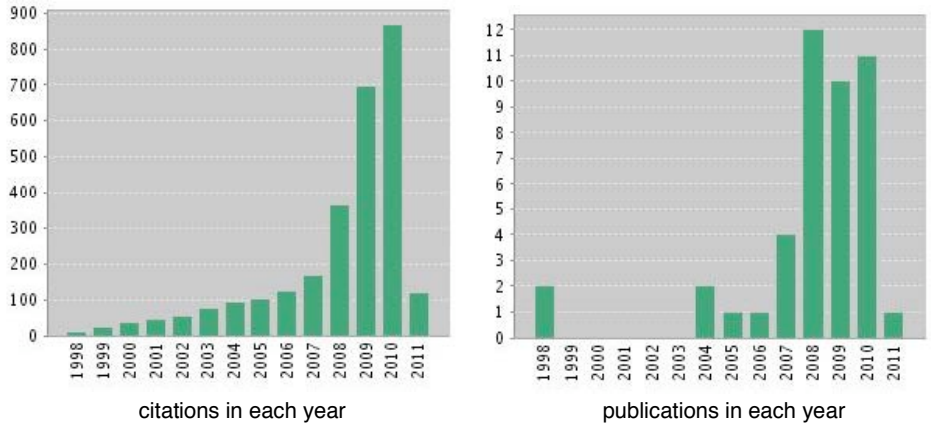


Figure B. Number of citations in scientific journals on gold catalysis in natural product synthesis and number of publications per year on the synthesis of natural product using gold catalysis.[9]

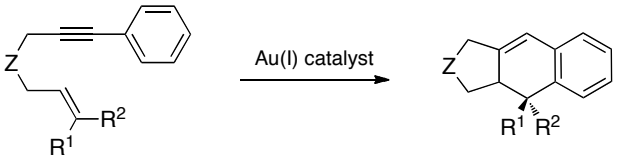
However, applications of gold chemistry towards the synthesis of natural products still have to face major drawbacks such as the need of careful optimizations to match substrate, catalyst and reaction conditions or the issue of functional group tolerance. Furthermore, enantioselective transformations are still scarce and mainly involve a chirality transfer from enantio-enriched substrates.

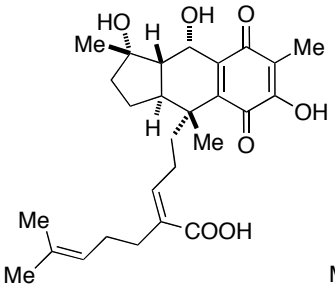
9. Graphics obtained using Web Of Knowledge (used request: “gold catalysis total synthesis”).

Objectives

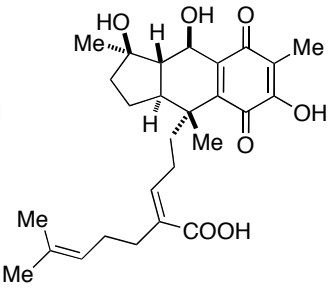
• The use of Au(I) complexes as catalysts for organic transformations has become increasingly common over the past decade. In contrast, enantioselective catalysis employing Au(I) complexes was until recently exceedingly rare. This is due in large part to the tendency of Au(I) to form linear two-coordinated complexes, in which the chiral ligand will be *trans* to the coordinated substrate in the enantiodetermining step.

Enynes substituted at the alkyne with an aryl group react with a variety of Au(I) catalysts to provide products resulting from a formal intramolecular [4+2] cycloaddition. The resulting tricyclic framework represents the core structure of the pycnanthuquinones that are highly functionalized terpenoids with an unusal quinone moiety.

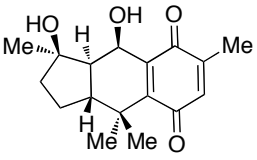




pycnanthuquinone A



pycnanthuquinone B

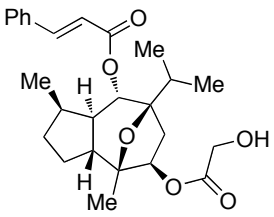


(-)-pycnanthuquinone C

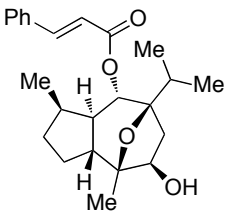
One of the objectives of this Thesis was the development of an enantioselective intramolecular [4+2] cycloaddition with new chiral Au(I) phosphites in order to apply this reaction to the enantioselective synthesis of natural products such as the pycnanthuquinones.

- A second objective of this Thesis was the application of two methodologies that were developed in our laboratory for the synthesis of natural compounds.

(-)-Englerins A and B are guaiane sesquiterpenes isolated in 2009. They show a high activity against renal cancer cell growth. We synthesized these two natural products by using a gold(I)-catalyzed cascade reaction from geraniol, a commercially available compound.

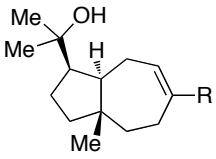


(-)-Englerin A



(-)-Englerin B

Schisanwilonenes A-C are carotane sesquiterpenes isolated in 2009 with anti-hepatitis B virus activity. We decided to synthesize these natural compounds using a gold(I)-catalyzed intramolecular 1,5-migration reaction followed by a Cope rearrangement to acces to the bicyclo[5.3.0]decane skeleton.



Schinsanwilsonenes A-C
A: R = CH_2OH
B: R = CH_2OAc
C: R = CHO

I. Towards an Enantioselective Au(I)-Catalyzed Intramolecular [4+2] Cycloaddition of Arylenynes

A. Introduction

The development in gold catalysis did not immediately extend to chiral catalysts although one of the pioneering examples in gold chemistry referred to the use of a chiral ferrocenylphosphine-Au(I) complex in the reaction between aldehydes and α-isocyanoacetate esters.[10] This relatively slow development of efficient chiral systems is rationalized by the structural features of Au(I) complexes. Indeed, Au(I) forms linear two-coordinated complexes, which alleviates the chiral induction and makes asymmetric catalysis extremely difficult.[11,12] The problem due to the distance between the ligand and the substrate is further exacerbated by the outer-sphere attack of the nucleophile to the gold/alkyne intermediate (Figure 1).[13]

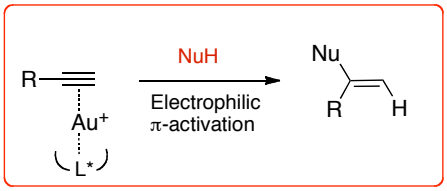
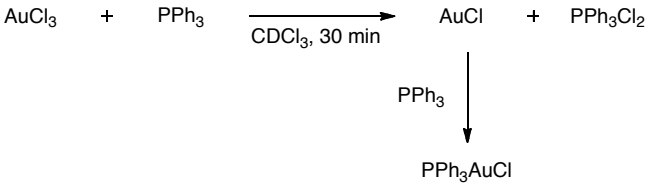


Figure 1. Electrophilic activation of alkynes by Au(I).

10. Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405-6406.
11. For a review on coordination numbers in d^{10} complexes of group 11 metals, see: Carvajal, M. A.; Novoa, J. J.; Alvarez, S. *J. Am. Chem. Soc.* **2004**, *126*, 1465-1477.
12. For a recent study on Au(I)-ligand interactions in gold dialkylbiarylphosphane, see: Pérez-Galán, P.; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. *Chem. Eur. J.* **2010**, *16*, 5324-5332.
13. For a mechanistic study of the gold(I)-catalyzed Conia-ene reaction, see: Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526-4527.

Naturally, the use of Au(III) would be the intuitive choice for asymmetric gold catalysis regarding the four possible coordination sites around the metal, with a typical square-planar geometry that is generally found in d^8 electron complexes of the second and third row. However only few examples of successful asymmetric synthesis have been reported,[14] mainly due to the paucity of transformations catalyzed by Au(III) complexes that contain donor ligand. Moreover, it has been demonstrated that Au(III) could be reduced to Au(I) during the catalytic process when phosphine ligands were used (Scheme 1).[15] Indeed, mixing $AuCl_3$ and triphenylphosphine quickly leads to the formation of PPh_3AuCl and PPh_3Cl_2 in a 1:1 ratio.



Scheme 1. Reduction of Au(III) to Au(I) by triphenylphosphine.

Much of the progress concerning enantioselective C-C multiple bond activation catalyzed by gold has been achieved over the last few years and has mainly involved intramolecular reactions using Au(I).[16] The electrophilic π-activation of allenes by chiral Au(I) catalysts has concentrated the bulk of the effort in this area and the inherent axial

14. (a) Debono, N.; Iglesias, M.; Sánchez, F. *Adv. Synth. Catal.* **2007**, *349*, 2470-2476. (b) Corma, A.; Domínguez, I.; Doménech, A.; Fornés, V.; Gómez-García, C. J.; Ródenas, T.; Sabater, M. J. *J. Catal.* **2009**, *265*, 238-244.
15. Chao, C.-M.; Genin, E.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *J. Organomet. Chem.* **2009**, *694*, 538-545.
16. For recent reviews on asymmetric gold catalysis, see: (a) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382-5391. (b) Bongers, N.; Krause, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 2178-2181. (c) Lee, A.-L. *Annu. Rep. Prog. Chem., Sect. B* **2010**, *106*, 428-446. (d) Sengupta, S.; Shi, X. *ChemCatChem* **2010**, *2*, 609-619.

chirality of allenes combined to its high reactivity make them excellent substrates for stereoselective gold catalysis. Electrophilic activation of alkynes by Au(I) towards a tethered alkene in enyne is also a well developed topic in research,[6] but asymmetric versions are still scarce and no general chiral catalysts have been discovered so far. All of the reported procedures are also limited in scope, particularly with respect to substitutions along the alkyl chain.

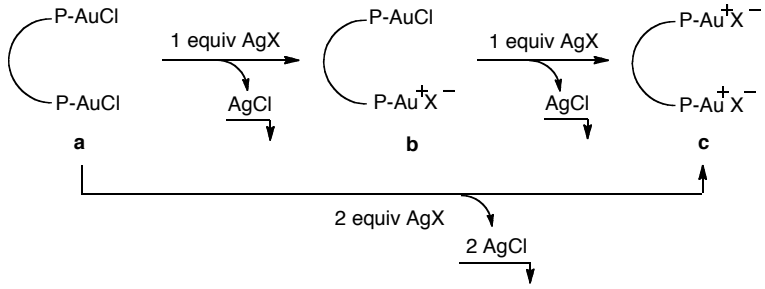
In the next chapters, we will briefly review the different type of chiral ligands in the gold(I)-catalyzed formation of C-C bonds with an emphasis on phosphorous based ligands. Then, we will focus on the gold(I)-catalyzed intramolecular [4+2] cycloaddition.

1. Asymmetric Gold Catalysis – State of the Art

a) Diphosphine-gold Complexes in Chiral Gold Catalysis

With few exceptions, efficient enantioselective gold(I)-catalyzed reactions have so far employed diphosphine-gold complexes $[(P\text{-}P)(AuCl)_2]$ as precatalysts where (P-P) is a chiral diphosphine ligand. The active species is generated in situ by treatment of the precatalyst with an appropiate silver salt (AgX). A 1:1 Au(I) complex to silver salt ratio (i.e. 1:1 Au/Ag ratio) affords the monocationic complex (**b**) while a 1:2 Au/Ag ratio leads to the dicationic complex (**c**) (Scheme 2).

6. For selected reviews on gold-catalyzed cycloisomerisations of enynes, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326-3350. (c) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268-4315.



Scheme 2. Formation of monocationic Au(I) complex **b** and dicationic Au(I) complex **c**.

The most common diphosphine ligands are either BINAP or MeOBIPHEP derivatives that contain sterically hindered P-bound aryl groups (Figure 2).

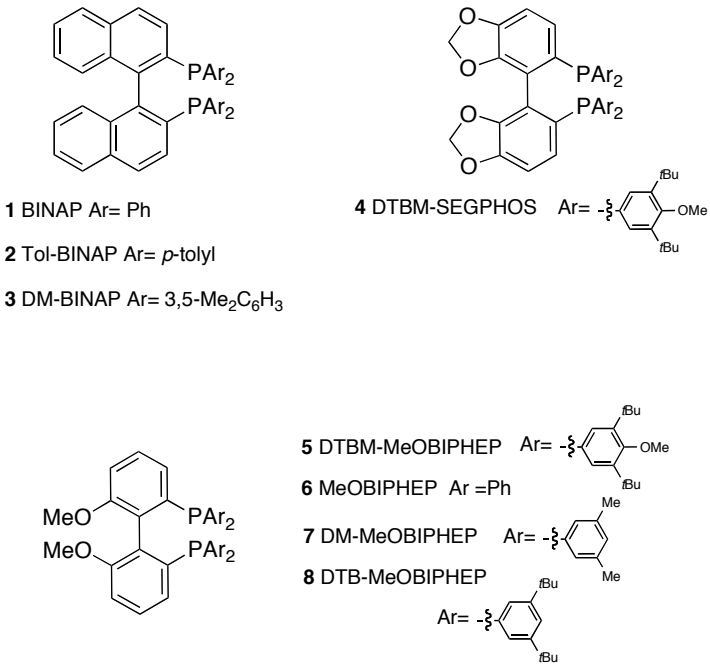


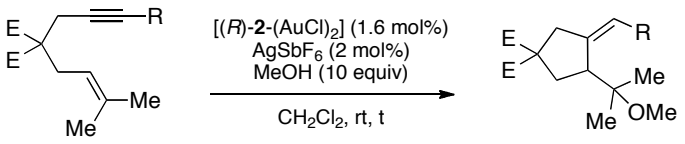
Figure 2. Most commonly used diphosphine ligands in asymmetric Au(I) catalysis.

(1) BINAP as Ligands in Chiral Gold Catalysis

In 2005, our group reported the first gold(I)-catalyzed enantioselective alkoxycyclization of 1,6-enynes.[17] In a study of the ligand effect in gold and platinum-catalyzed cyclization of enynes, it has been discovered that Au(I) was an efficient catalyst to promote alkoxycyclization reactions, excluding an Alder-ene-type cycloisomerization pathway.[18,19,20] The reaction proceeded at room temperature, in contrast to that found in the asymmetric version catalyzed by Pt(II).

Amongst the catalysts tried, a 1:1.25 mixture of [(*R*)-Tol-BINAP($AuCl)_2$] (Figure 2, ligand **2**) and $AgSbF_6$ gave the best results, although with moderate enantioselectivity. With these conditions, the monocationic species was formed (Scheme 2). Product of methoxycyclization **I-2a** was obtained in 89% yield from enyne **I-1a** with 53% *ee* (Table 1, entry 1). Variation of the Au/Ag ratio from 1:1.25 to 1:1 had a surprising effect by lowering the asymmetric induction and affording the opposite enantiomer as the major product (Table 1, entry 2). Phenyl-substituted alkyne **I-1b** gave the corresponding product **I-2b** in moderate yield and longer reaction time, but with very high enantioselectivity (Table 1, entry 3)

17. Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293-1300.
18. For a report on the *exo*- and *endo*- cyclization of enynes catalyzed by cationic Au(I) complexes, see: Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406.
19. For a review on asymmetric cycloisomerization of 1,6- and 1,7- enynes by transition-metal catalysts, see: Fairlamb, I. J. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1048-1052.
20. For recent reports on the enantioselective platinum-catalyzed cyclizations of 1,6-enynes, see: (a) Toullec, P. Y.; Chao, C.-M.; Chen, Q.; Gladiali, S.; Genêt, J.-P.; Michelet, V. *Adv. Synth. Catal.* **2008**, *350*, 2401-2408. (b) Brissy, D.; Skander, M.; Jullien, H.; Retailleau, P.; Marinetti, A. *Org. Lett.* **2009**, *11*, 2137-2139.



I-1 **I-2**

Table 1. Methoxycyclization reaction of enynes **I-1** using [(*R*)-**2**-$(AuCl)_2$].

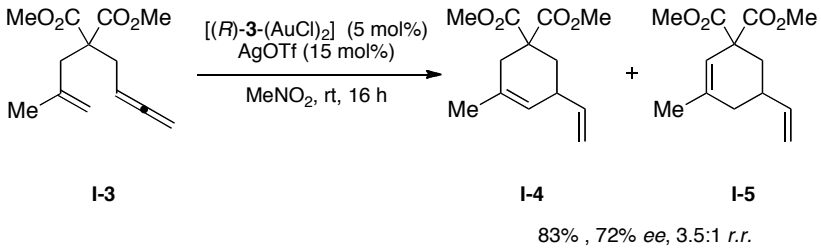
Entry	*Substrate*	*R*	*E*	*t*	*Yield (%)*	*ee (%)*
1	**I-1a**	H	$(SO_2Ph)_2$	4 h	89	53
2[a]	**I-1a**	H	$(SO_2Ph)_2$	30 h	98	14
3	**I-1b**	Ph	$(SO_2Ph)_2$	7 days	52	94
4	**I-1c**	H	$(CO_2Me)_2$	7 h	91	2

[a] Reaction carried out with a 1:1 Au/Ag ratio. The opposite enantiomer was isolated.

Surprisingly, the nature of the tether was also crucial with a racemic mixture obtained when a malonate was used instead of a sulfone (Table 1, entry 4).

In 2007, an asymmetric gold(I)-catalyzed cycloisomerization of eneallenes to vinylcyclohexene derivatives using BINAP ligand was reported.[21] Cyclohexene **I-4** was obtained from **I-3** in 83% yield and 72% *ee* along with **I-5** (3.5:1 *r.r.*). A 1:3 mixture of [(*R*)-DM-BINAP$(AuCl)_2$] (Figure 2, ligand **3**) and AgOTf was used as catalytic system (Scheme 3).

21. Tarselli, M. A.; Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 6670-6673.



Scheme 3. Asymmetric gold(I)-catalyzed cycloisomerization of eneallenes **I-3**.

Both the regioselectivity and the enantioselectivity of the products were dependent on the choice of solvent and counterion. Employing OTs^- as a counterion instead of OTf^- produced lower enantioselectivity but higher regioselectivity (50% *ee* with 10:1 *r.r.*). The counterion was assumed to act as a weak base in the β-elimination step affording vinylcyclohexene **I-4** or **I-5**.[22] Interestingly, X-ray crystallographic data of [(*R*)-**3**-$(AuCl)_2$] shows a π-π stacking interaction between two P-bound aryl groups that lends the structure a degree of rigidity and establishes a well-defined chiral environment in the solid state (Figure 3). The same conformational preference was observed with [(*R*)-**2**-$(AuCl)_2$].

22. For similar observations on the counterion effects, see: Davies, P. W.; Martin, N. *Org. Lett.* **2009**, *11*, 2293-2296.

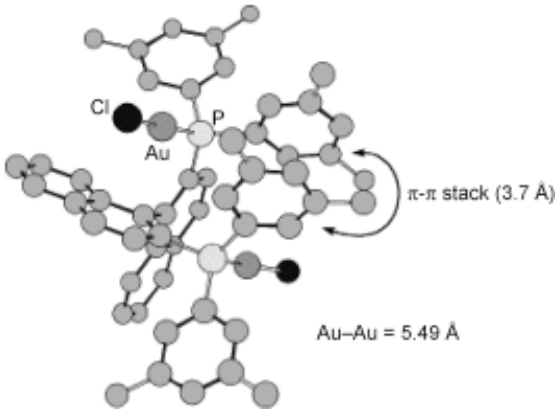


Figure 3. X-Ray structure of [(*R*)-**3**-$(AuCl)_2$] showing a well-defined chiral environment.

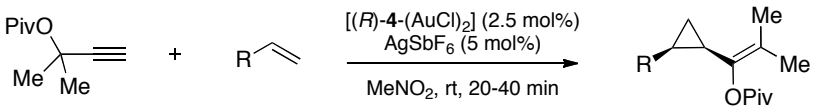
When [(*R*)-**3**-$(AuOBz)_2$][23] or [(*R*)-**3**-$(AuOTf)_2$] were used as catalysts, low enantioselectivities and low reaction rates were observed. In the former case, addition of 3 equiv of AgOTf or AgCl could restore the activity of the catalyst although with moderate enantioselectivity (less than 34% *ee*). These results highlight a possible effect (or cooperative effect) of silver in the catalytic process. A study of the silver to gold ratio would have been noteworthy in regards to the observations made by our group on the different reactivity of mono- and dicationic gold complexes with (*R*)-Tol-BINAP as a ligand (Figure 2, ligand **2**).[17]

23. For two seminal papers on di(gold)-(*para*-nitrobenzoate)complex and its applications in catalysis, see: (a) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452-2453. (b) LaLonde, R. L.; Wang, Z. J.; Mba, M.; Lackner, A. D.; Toste, F. D. *Angew. Chem. Int. Ed.* **2010**, *49*, 598-601.

17. Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293-1300.

(2) SEGPHOS as Ligands in Chiral Gold Catalysis

In 2005, the use of DTBM-SEGPHOS (Figure 2, ligand **4**) as a chiral phosphine ligand was reported for the enantioselective intermolecular cyclopropanation reaction between sterically hindered pivalate propargylic ester **I-6** and styrenes **I-7** (Table 2, entries 1-3).[24]



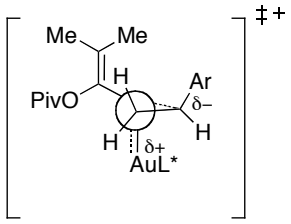
I-6 **I-7** **I-8**

Table 2. Enantioselective intermolecular cyclopropanation of olefin **I-7**.

Entry	*Substrate*	*R*	*Yield (%)*	*ee (%)*
1	**I-7a**	phenyl	70	81
2	**I-7b**	2-Me-Ph	83	87
3	**I-7c**	2,6-Me-4-*t*Bu-Ph	71	94

Cyclopropane **I-8c** could be isolated from **I-7c** in 94% *ee* and 71% yield from 2,6-Me-4-*t*Bu-styrene (Table 2, entry 3). A proposed transition state **I-TS1** showed an outer-sphere attack of the vinyl group by a 90º angle to the gold carbene leading to a favorable approach for a chiral induction by the ligand (Figure 4).

24. Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003.



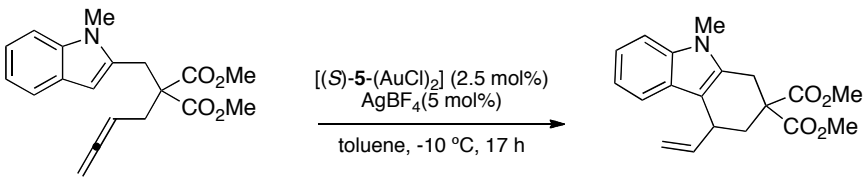
I-TS1

Figure 4. Transition state **I-TS1** of the gold(I)-catalyzed enantioselective cyclopropanation.

BINAP derivatives (Figure 2, ligands **1** and **2**) were inefficient in this reaction leading to less than 30% *ee* in different solvents.

(3) BIPHEP as Ligands in Chiral Gold Catalysis.

In 2007, the synthesis of tricyclic derivative **I-10** from **I-9** was reported in 88% yield and 92% *ee* with a 1:2 mixture of [(*S*)-**5**-$(AuCl)_2$] (Figure 2, ligand **5**) and $AgBF_4$ (Scheme 4).[25]



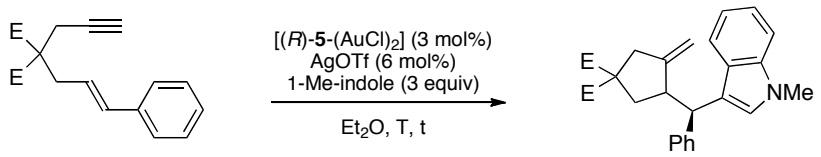
I-9 **I-10** 88%, 92% *ee*

Scheme 4. Asymmetric gold(I)-catalyzed intramolecular hydroarylation of indole **I-9**.

25. Liu, C.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 1935-1938.

A study on the asymmetric gold(I)-catalyzed cyclization of 1,6-enynes affording functionalized cyclic alkenes was reported in 2009.[15,26]

Similarly, hindered and electron rich bis-phosphine DTBM-MeOBIPHEP (Figure 2, ligand **5**) gave the best results for this reaction compared to less selective BINAP or MeOBIPHEP (Figure 2, ligand **1** and **6**). Product **I-12** from enyne **I-11** and 1-methylindole was obtained in 83% *ee* and 99% yield using a 1:2 mixture of [(*R*)-**5**-$(AuCl)_2$] and AgOTf (Table 3, entry 1).



I-11 **I-12**

Table 3. Asymmetric gold(I)-catalyzed hydroarylation/cyclization.

Entry	*E*	*T (ºC)*	*t*	*Yield (%)*	*ee (%)*
1	CO_2Me	rt	48 h	99	83
2[a]	CO_2Me	0	2 h	95	74
3[b]	CO_2Me	rt	-	n.r.	n.r.
4	CO_2iPr	rt	15-20 h	94	95
5	CO_2Bn	rt	15-20 h	99	81
6	SO_2Ph	rt	15-20 h	37	88

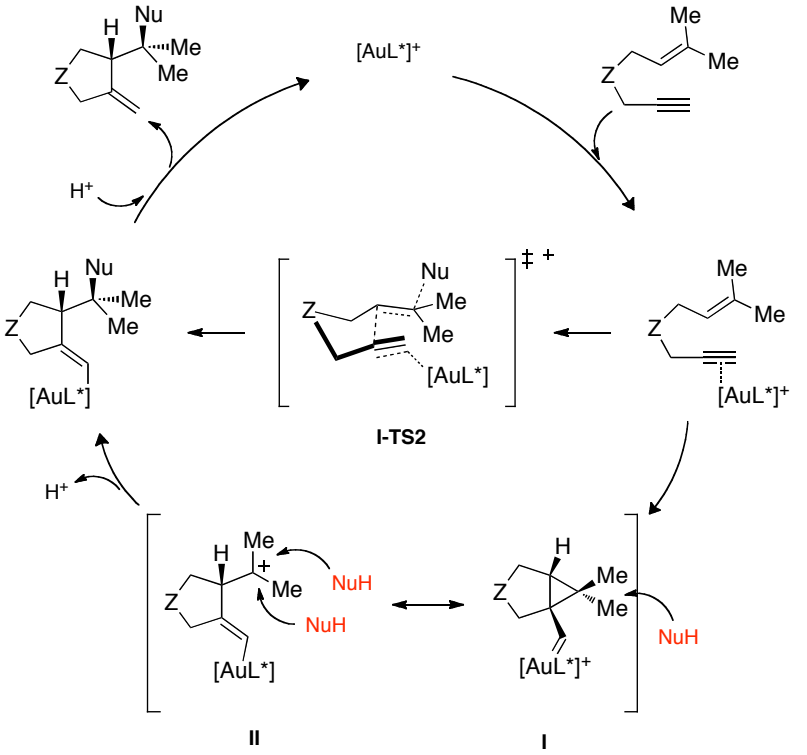
[a] A 1:1 Au/Ag ratio was used. [b] Reaction run with 10 mol% triflic acid and no catalyst.

15. Chao, C.-M.; Genin, E.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *J. Organomet. Chem.* **2009**, *694*, 538-545.

26. (a) Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Chem. Eur. J.* **2009**, *15*, 1319-1323. (b) Chao, C.-M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, 6988-6990.

Lowering the Au/Ag ratio to 1:1 led to lower enantioselectivity (74% *ee*) and no conversion was observed with 10 mol% triflic acid, ruling out a Brønsted acid catalysis (Table 3, entry 2 and 3). Steric crowding of the tethering ring moiety was also studied and higher enantioselectivity was observed with *i*PrO group (Table 3, entry 4) compared to MeO or BnO (Table 3, entries 1 and 5). Up to 88% *ee* was obtained by replacing a malonate by a sulfone, but in moderate yield (Table 3, entry 6).

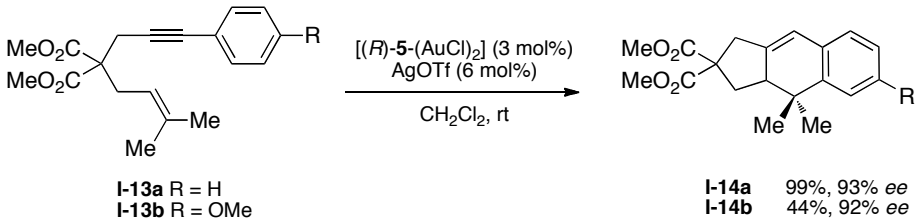
In order to rationalize these observations, a model was proposed to explain the influence of both nucleophiles and substrates on the enantioselectivity *via* a "chair-like" η^2-complex **I-TS2** (Scheme 5).



Scheme 5. Mechanistic proposal for the asymmetric gold(I)-catalyzed hydroarylation/cyclization.

Previous models had proposed a transient cyclopropylcarbene **I** in resonance with a carbocation intermediate **II**.[27]

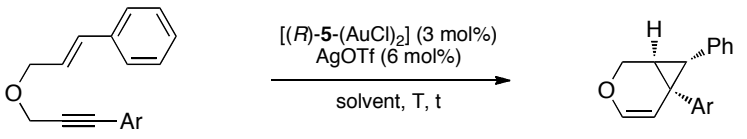
Closely related to our topic, an example of the synthesis of tricylic compound **I-14a** was also reported from aryl enyne **I-13a** in 99% yield and 93% *ee* ($[\alpha]_D^{20}$ = +14.8 ($CHCl_3$, c = 0.93)). In addition, compound **I-14b** could be obtained in 92 % *ee* but in a moderate yield of 44% (Scheme 6).



Scheme 6. Asymmetric gold(I)-catalyzed cyclization of arylenynes **I-11**.

In the asymmetric gold(I)-catalyzed synthesis of bicyclo[4.1.0]heptene derivatives from 1,6-enynes, [(*R*)-**5**-$(AuCl)_2$] was found to be the best chiral catalyst and compound **I-16** was obtained from enyne **I-15** in moderate yield and high enantioselectivity in toluene at 0 ºC (56% yield, 96% *ee*) (Table 4, entry 2). The reaction was found to be highly solvent–dependent as enantioselectivity vary from 70% to 92% *ee* (Table 4, entries 1, 3-6). The use of nitromethane led to sluggish reaction (Table 4, entry 3).

27. For recent discussions on the nature of gold intermediates in cyclization reactions, see: (a) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2008**, *47*, 6754-6756. (b) Fürstner, A.; Morency, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 5030-5033. (c) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nat Chem* **2009**, *1*, 482-486. (d) Pérez-Galán, P.; Martin, N. J. A.; Campaña, A. G.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Asian J.* **2010**, *6*, 482-486.



I-15 **I-16**

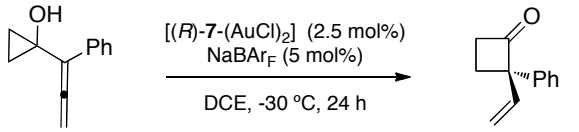
Table 4. Asymmetric gold(I)-catalyzed synthesis of bicyclo[4.1.0]heptene **I-16**-influence of the solvents.

Entry	*Solvent*	*T (ºC)*	*t*	*Yield /%)*	*ee (%)*
1	toluene	rt	30 min	57	92
2	toluene	0	2 h	56	96
3	$MeNO_2$	rt	-	n.r.	-
4	CH_2Cl_2	rt	25 min	26	70
5	THF	rt	25 min	43	85
6	Et_2O	rt	25 min	35	91

Chiral diphosphine-gold complexes with BIPHEP derivatives as ligands have been widely used and successfully applied to other types of gold(I)-catalyzed reactions.

In 2009, the synthesis of cyclobutanone **I-18** from allenylcyclopropanol **I-17** was achieved by employing a 1:2 mixture of [(*R*)-DM-MeOBIPHEP(AuCl)$_2$] (Figure 2, ligand **7**) and $NaBAr_F$ in 76% yield an 91% *ee* (Scheme 7).[28] Noteworthy, a slight improvement was obtained when $NaBAr_F$ was used instead of $AgNTf_2$, presumably due to a background reaction by traces of $HNTf_2$.

28. Kleinbeck, F.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 9178-9179.

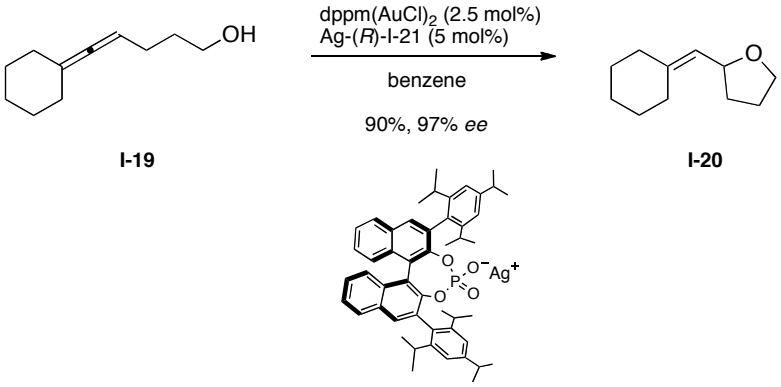


I-17 **I-18**

76%, 91% ee

Scheme 7. Asymmetric gold(I)-catalyzed ring expansion of allenylcyclopropanol **I-17**.

The pronounced effect of the counterion in gold(I)-catalyzed transformations was exploited with a novel chiral counterion approach towards the hydrofunctionalization of allenes.[29] **I-20** was obtained in 90% yield and 97% *ee* from **I-19** using chiral silver phosphate complex Ag-(*R*)-**I-21** (Scheme 8).



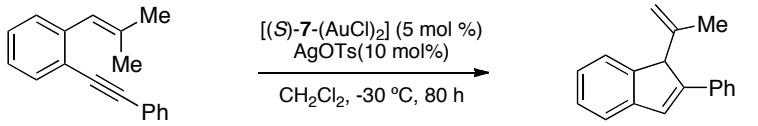
I-19 **I-20**

Ag-(*R*)-I-21

Scheme 8. Chiral counterion strategy towards the hydrofuncionalization of allenol **I-19**.

29. Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007,** *317*, 496-499.

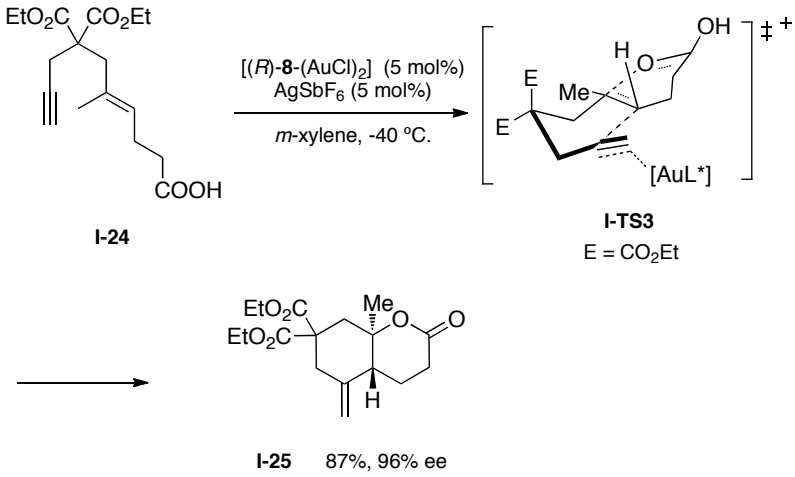
In 2010, the synthesis of indene **I-23** from enyne **I-22** was reported in 81% yield and 82% *ee* using a 1:2 mixture of [(*S*)-**7**-$(AuCl)_2$] and AgOTs (Scheme 9).[30]



I-22 **I-23** 81%, 82% *ee*

Scheme 9. Gold(I)-catalyzed enantioselective synthesis of indene **I-20**.

Recently, gold(I)-catalyzed enantioselective polycyclization reactions were achieved by using monocationic diphosphine-gold complex (Scheme 10).[31]



I-24 **I-TS3**
E = CO_2Et

I-25 87%, 96% ee

Scheme 10. Gold(I)-catalyzed enantioselective polycyclization of enyne **I-24**.

30. Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem. Int. Ed.* **2010**, *49*, 4633-4637.
31. Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276-8277.

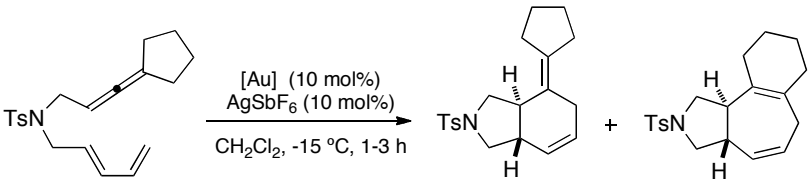
Enyne **I-24** could be converted to the corresponding bicyclic compound **I-25** in 87% yield and 96% *ee* with a 1:1 mixture of [(*R*)-DTB-MeOBIPHEP(AuCl)$_2$] (Figure 2, ligand **8**) and $AgSbF_6$. A concerted mechanism based on the Stork-Eschenmoser postulate was proposed to explain the observed stereochemistry (Scheme 10, **I-TS3**).

b) Monophosphine-gold Complexes

As an alternative to diphosphine-gold complexes and providing simpler model for optimization, new catalysts with a single gold atom have been recently developed.

(1) Phosphoramidites as Ligands in Chiral Gold Catalysis

The first chiral gold phosphoramidite-based catalysts have been reported in 2009 in the enantioselective gold(I)-catalyzed intramolecular [4+2] cycloaddition of allenedienes.[32] Cycloadduct **I-27** was obtained along with **I-28** in excellent yield and high enantioselectivity from allenediene **I-26** using bulky phosphoramidite. A positive influence on the enantioselectivity of bulky substituents at the 3 and 3' position of the binaphtol units was observed (Table 5, entries 1-4)



I-26 **I-27** **I-28**

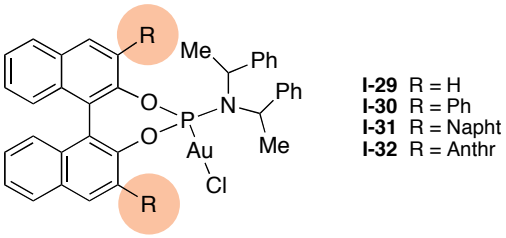
Table 5. Enantioselective gold(I)-catalyzed intramolecular [4+2] cycloaddition of allenediene **I-26**.

Entry	*[Au]*	***I-27*:*I-28*** *(ratio)*	*ee (%)* ***I-27***
1[a]	(*S*,*S*,*S*)-**I-29**	4.5:1	20
2	(*S*,*S*,*S*)-**I-30**	8:1	74

32. Alonso, I.; Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020-13030.

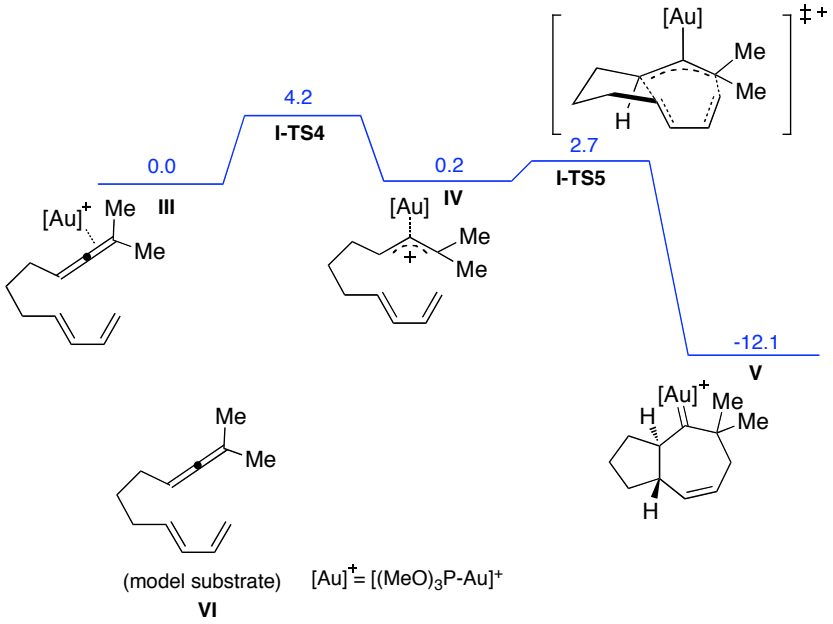
Entry	*[Au]*	***I-27*:*I-28* (ratio)**	*ee (%)* ***I-27***
3	(*R*,*R*,*R*)-**I-31**	8:1	80
4	(*R*,*R*,*R*)-**I-32**	16:1	91

[a] Reaction carried out at room temperature.



The chirality of the bis(phenylethyl)amine moiety on the chiral phosphoramidite was also found to define the absolute stereochemical outcome of the cycloadduct **I-27**. Interestingly, a 1:1 mixture of diphosphine-gold complexes [(*S*)-**1**-$(AuCl)_2$] or [(*R*)-**4**-$(AuCl)_2$] (Figure 2, ligand **1** and **4**) and $AgSbF_6$ gave lower enantioselectivity.

DFT calculations were run using substrate model **VI** and $[(MeO)_3PAu]^+$ as catalyst. As depict below (Scheme 11), the mechanism starts with initial coordination of the Au(I) catalyst to the allene **VI** to give **III**, selected as the energy reference, that evolves to the Au(I)-allyl cation **IV** through transition state **I-TS4**. The next transformation is the enantio-determining step and proceeds through a concerted *exo*-like cycloaddition between the diene and the allyl-Au cation **I-TS5** to give **V**, a common intermediate to compounds like **I-27** or **I-28.**



Scheme 11. DFT calculations of the enantioselective gold(I)-catalyzed intramolecular [4+2] cycloaddition of model substrate **VI** (relative energies are given in kcal/mol).

A DFT calculated stucture of **I-TS5** shows an orthogonal attack of the diene to the allyl Au(I) cation leading to a favorable environment for chiral induction (Figure 5).

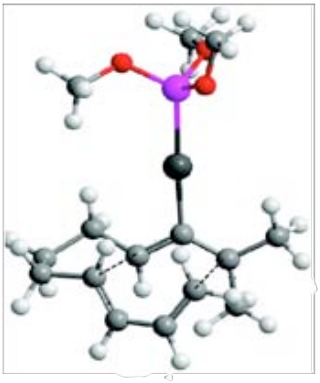
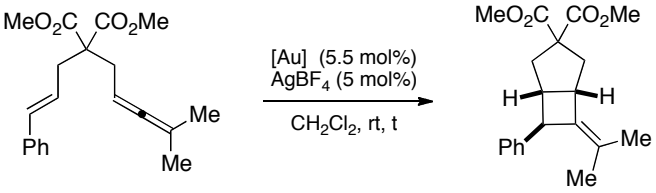


Figure 5. DFT calculated structure of **I-TS5**.

In 2010, a new phosphoramidite ligand for the gold(I)-catalyzed [2+2] cycloaddition of allenenes was reported.[33] Using TADDOL-derived phosphoramidite as a chiral ligand, cycloadduct **I-34** was obtained in 93% yield and 84% *ee* from **I-33** (Table 6, entry 1). A striking influence of the arene moiety of the TADDOL ligand was observed. Whereas phenyl and *para*-methoxyphenyl gave good enantioselectivity (Table 6, entries 1 and 2), phenyl groups containing electron-withdrawing substituents led to lower enantioselectivity (Table 6, entries 3 and 4).



I-33 **I-34**

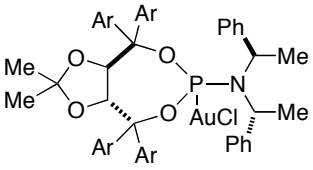
Table 6. Enantioselective gold(I)-catalyzed [2+2] cycloaddition of **I-33**.

Entry	*[Au]*	*t*	*Yield (%)*	*ee (%)*
1	**I-35**	2 h	93	84
2	**I-36**	16 h	90	86
3	**I-37**	1 h	95	75
4	**I-38**	1 h	84	39

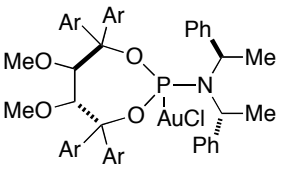
33. (a) Teller, H.; Flügge, S.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1949-1953. (b) During the preparation of this manuscript, an additional paper on the use of chiral phosphoramidites towards the gold(I)-catalyzed [2+2] cycloaddition of allenenes was published: González, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, DOI: 10.1021/ja200084a.

5[a]	**I-39**	-	> 90	94
6[a]	**I-40**	-	91	≥ 99

[a] Reaction carried out at 0ºC.



I-35 Ar = Phenyl
I-36 Ar = *p*-methoxyphenyl
I-37 Ar = *p*-chlorophenyl
I-38 Ar = *p*-fluorophenyl



I-39 Ar = phenyl
I-40 Ar = *p*-*tert*butylphenyl

To rationalize these observations, a through-space interaction between the arenes and the electron deficient Au(I) center of the catalyst was proposed on the basis of DRX analysis (Figure 6). Electron rich aromatic rings would tighten the chiral pocket with a stronger arene-Au(I) cationic interaction and thereby would afford higher enantiomeric excess.

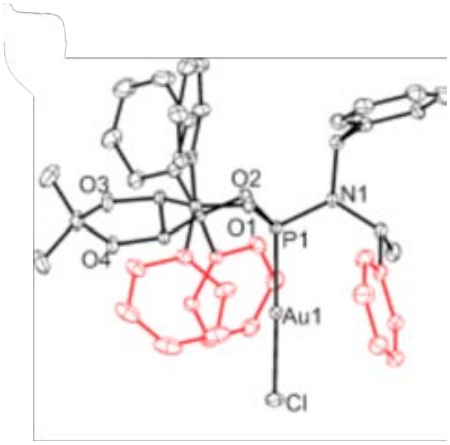
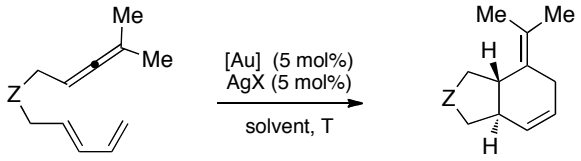


Figure 6. X-Ray structure **I-35**.

In order to promote these interactions, a phosphoramidite ligand with an acyclic TADDOL backbone was synthesized (Table 6, catalyst **I-39**). Gratifyingly, cycloadduct **I-34** was obtained in 94% *ee* with catalyst **I-39** and more than 99% *ee* with catalyst **I-40** (Table 6, entries 5 and 6).

(2) Phosphites and Diphosphonites as Ligand in Chiral Gold Catalysis

In a related work on the enantioselective gold(I)-catalyzed intramolecular [4+2] cycloaddition of allenedienes,[34] cycloadduct **I-42** was obtained from **I-41** by employing C_3-symmetric monodentate phosphite gold(I) complexes (Table 7, entries 1-3).[35] In addition to these catalysts, a chiral phosphoramidite with bulky pyrenyl groups at the 3 and 3' position of binaphol unit was also synthesized and afforded cycloadduct **I-42b** with high enantioselectivity (Table 7, entry 4).



I-41a Z = $C(CO_2Me)_2$
I-41b Z = NTs

I-42a Z = $C(CO_2Me)_2$
I-42b Z = NTs

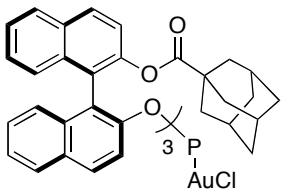
Table 7. Enantioselective gold(I)-catalyzed intramolecular [4+2]-cycloaddition of allenedienes **I-27**.

Entry	*Substrate*	*AgX*	*[Au]*	*t*	*Yield (%)*	*ee (%)*
1[a, c]	**I-41a**	$AgSbF_6$	(*S*)-**I-43**	3 h	90	66

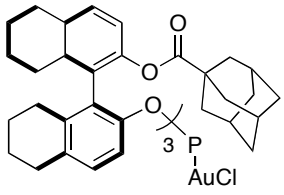
34. González, A. Z.; Toste, F. D. *Org. Lett.* **2009**, *12*, 200-203.
35. For a review on helical triskelion monophosphites as ligands in asymmetric Rh(I) catalysis, see: Reetz, M. T.; Guo, H.; Ma, J.-A.; Goddard, R.; Mynott, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 4136-4142.

Entry	*Substrate*	*AgX*	*[Au]*	*t*	*Yield (%)*	*ee (%)*
2[b,c]	**I-41a**	$AgBF_4$	(*S*)-**I-44**	12 h	87	92
3[b, c]	**I-41b**	$AgSbF_6$	(*S*)-**I-44**	24 h	86	34
4[a, d]	**I-41b**	$AgSbF_6$	(*S*,*S*,*S*)-**I-45**	12 h	83	≥99

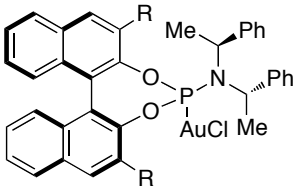
[a] Reaction carried out in CH_2Cl_2 [b] Reaction carried out in C_6H_6. [c] Reaction carried out at rt. [d] Reaction carried out at -15 ºC.



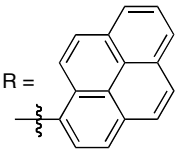
(*S*)-**I-43**



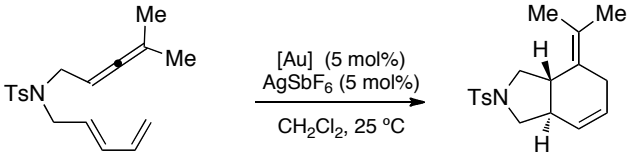
(*S*)-**I-44**



(*S*,*S*,*S*)-**I-45** R =



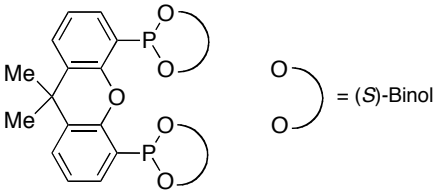
This work was extended to the use of chiral diphosphonites as ligands.[34] However, catalyst **I-46** and **I-47** failed to produce the desired cycloadduct **I-42b** (Table 8, entries 1-2) and a racemic mixture was obtained when catalyst **I-48** was employed, although in good conversion (Table 8, entry 3).



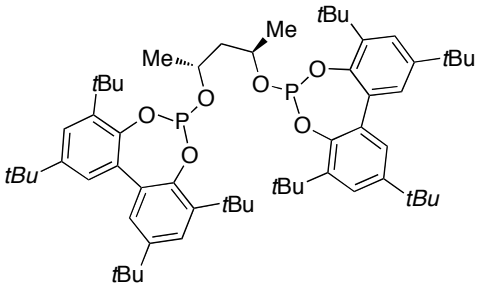
I-41b **I-42b**

Table 8. Enantioselective gold(I)-catalyzed intramolecular [4+2]-cycloaddition of allenes **I-41b** using chiral diphosphonites as ligands.

Entry	*[Au]*	*t*	*Yield (%)*	*ee (%)*
1	**I-46**	-	n.r.	-
2	**I-47**	-	n.r.	-
3	**I-48**	12 h	91	0



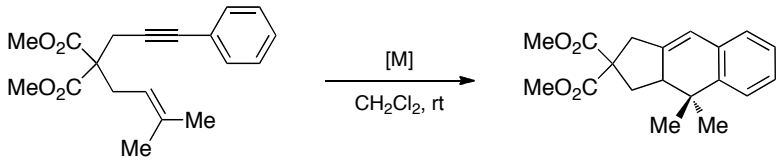
I-46 **I-47**



I-48

2. Gold(I)-Catalyzed Intramolecular [4+2] Cycloaddition of Arylenynes

Enynes substituted at the alkyne with an aryl group react with a variety of Au(I) catalysts to provide products resulting from a formal intramolecular [4+2] cycloaddition.[36,37] Tricyclic adduct **I-14a** is quantitatively obtained with a bulky biphenyl phosphine Au(I) catalyst **BiP1** (Table 9, entry 1) and phosphite Au(I) catalyst **TriP** (Table 9, entry 2). However, $PtCl_2$ was inefficient under these conditions (Table 9, entry 3). The reaction was clearly accelerated when it was carried out under microwave heating (Table 9, entry 4).



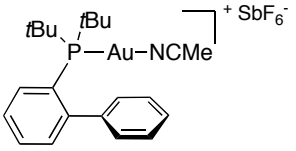
I-13a **I-14a**

Table 9. Cyclization of arylenyne **I-11a** with different catalysts.

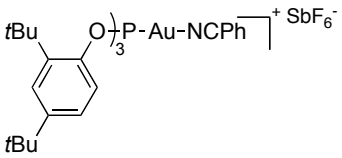
Entry	*[M]*	*t*	*Yield (%)*
1	**BiP1**	2 h	83
2	**TriP**	2 h	99
3	$PtCl_2$	24 h	< 2
4[a]	**TriP**	< 10 min	95

[a] Reaction run under microwave heating, 50 ºC, 10 min.

36. Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179.
37. Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *130*, 269-279.

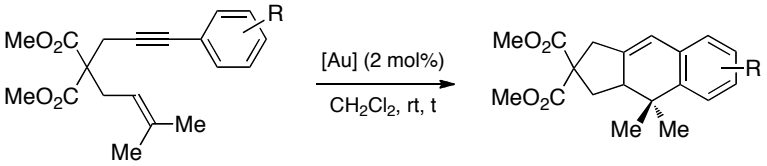


BiP1



TriP

Electron-releasing groups (Table 10, entries 1 and 2) and electron withdrawing substituents (Table 10, entries 3 and 4) were well tolerated on the arene moiety and faster reactions were observed when **TriP** was used as a catalyst.



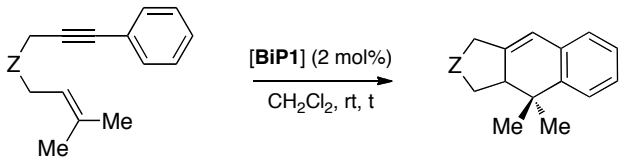
I-13 **I-14**

Table 10. Substrates scope in the gold(I)-catalyzed cyclization of arylenynes: influence of the substitution pattern.

Entry	*Substrate*	*[Au]*	*t*	*Yield (%)*
1	R = *p*-OMe **I-13b**	**BiP1**	2 h	50
2	R = *o*-OMe	**BiP1**	3 h	70
	I-13c	**TriP**	1 h	82
3	R = *p*-NO_2	**BiP1**	3 h	74
	I-13d	**TriP**	20 min	65
4	R = *p*-CN	**BiP1**	96 h	68
	I-13e	**TriP**	3 h	80

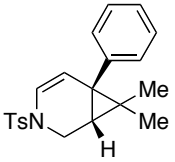
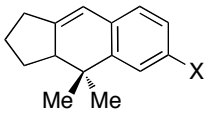
E = CO_2Me. Reaction run with 2 mol% catalyst in CH_2Cl_2 at room temperature.

Interestingly, a dramatic effect of the tether group was observed with no reaction when the malonate moiety was replaced by a sulfone (**I-1b**) or an ether (**I-13g**) (Table 11, entries 1 and 3). A through-bond effect from these electron-withdrawing groups was assumed to disfavor the formation of the initial Au(I)-alkyne complex. Product **I-14f** was obtained instead of the normal tricyclic product when a tosylamide was used as a tethered group (Table 11, entry 2). On the opposite, enynes **I-13h** and **I-13i** gave tricyclic adducts **I-14h** and **I-14i** in good yield (Table 11, entry 4).



I-13 **I-14**

Table 11. Substrates scope in the gold(I)-catalyzed cyclization of arylenynes: influence of the substituents at the tether.

Entry	*Substrate*	*Product*	*t*	*Yield (%)*
1	Z = $(SO_2Ph)_2$ **I-1b**	-	40 h	n.r.
2	Z = NTs **I-13f**	 **I-14f**	12 h	70 (**I-14f**)
3	Z = O **I-13g**	-	40 h	n.r.
4	Z = CH_2 **I-13h X = H** **I-13i X = Me**	 **I-14h** X = H **I-14i** X = Me	3 h	92 (**I-14h**) 85 (**I-14i**)

Products somewhat related to tricylic compound **I-14** have been obtained *via* Pd-catalyzed intermolecular [2+2+2] cycloaddition reaction of enynes with aryl or vinyl halides,[38] or by intramolecular Pd-catalyzed tandem cyclization of bromoenynes.[39] However, these reactions take place by a different mechanism and at higher temperature compared to the ones catalyzed by gold.

According to the experimental results and DFT calculations, the mechanism of the [4+2] cycloaddition of arylenynes proceeds by a stepwise process (Figure 7).[37] Au(I) complex of hept-6-en-1-ynylbenzene **VII** react through a *5-exo-dig* pathway to give *anti*-cyclopropylgold(I) carbene **I-TS6** that opens to form the aryl stabilized π-cation complex **VIII** (substituents stabilizing the cationic charge of the tertiary carbocation are also essentials). This step is considered to be enantiodetermining and the chirality of the sp^3 carbone is defined during this transformation. As depicted below, the gold metal is pointing in the opposite direction to the nucleophile rending a chiral induction from the ligand harder (outer-sphere coordination attack). Intermediate **VIII** reacts by a Friedel-Crafts-type reaction **I-TS7** to give final product **IX** after re-aromatization and proto-demetalation.

38. Brown, S.; Clarkson, S.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 157-160.
39. (a) Ohno, H.; Miyamura, K.; Takeoka, Y.; Tanaka, T. *Angew. Chem. Int. Ed.* **2003**, *42*, 2647-2650. (b) Ohno, H.; Yamamoto, M.; Iuchi, M.; Tanaka, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 5103-5106.
37. Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *130*, 269-279.

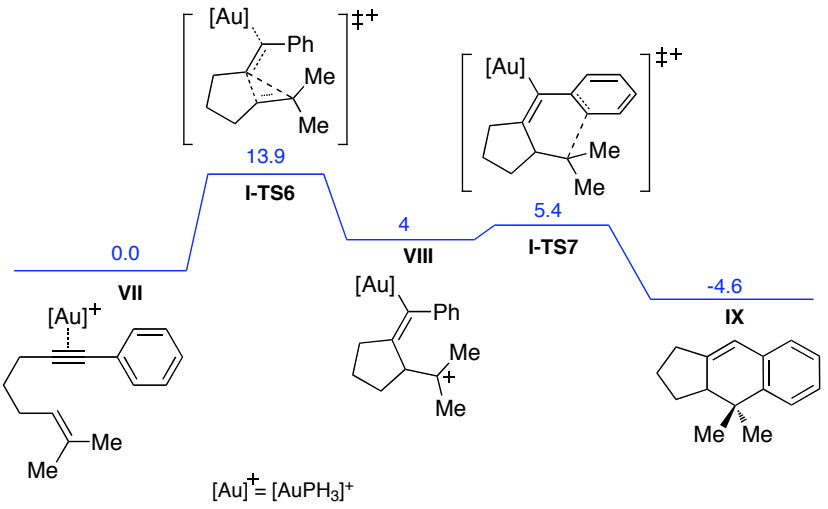


Figure 7. DFT calculations of the gold(I)-catalyzed [4+2] cycloaddition of arylenyne **I-13h**.

Beyond the great challenge of developing a chiral version of the intramolecular [4+2] cycloaddition of arylenynes, several natural products containing this tricylic framework could be readily obtained in an enatiomerically pure form. Pycnanthuquinones are terpenoid-type quinone structures containing a fused 6,6,5-ring skeleton (Figure 8).

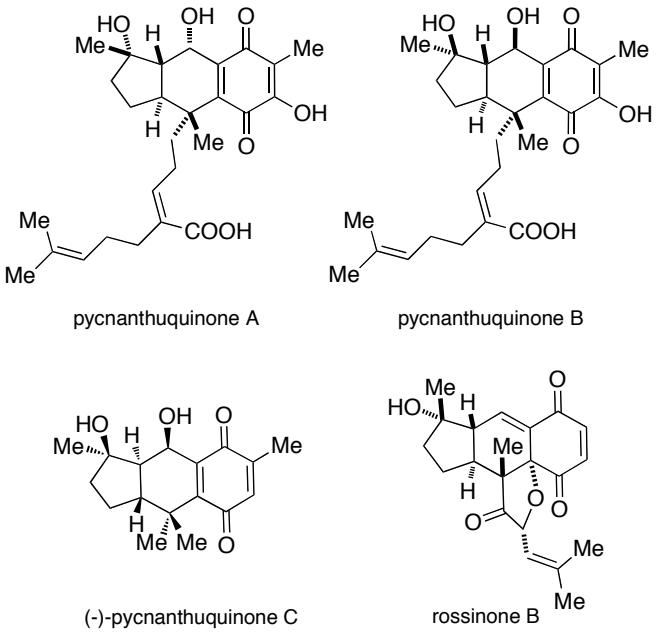
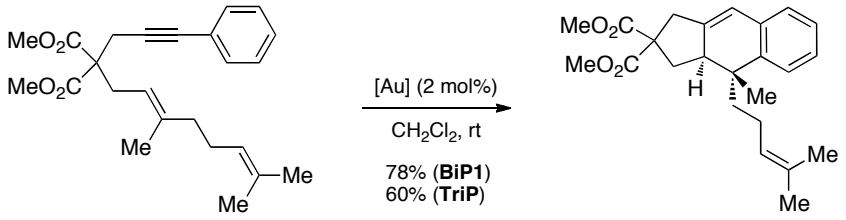


Figure 8. Pycnanthuquinones.

These compounds have been isolated from an African tree and display antihyperglycemic activity.[40,41,42] Recently, pycnanthuquinone C and rossinone B have been synthesized by a Diels-Alder strategy.[43,44]

Structurally related to pycnanthuquinone A and B, racemic key intermediate **I-50** was obtained from **I-49** in 60% yield using catalyst **TriP** and in 78% yield with catalyst **BiP1** (Scheme 12).



I-49 **I-50**

Scheme 12. Synthesis of intermediate **I-50** from **I-49** using catalyst **BiP1** and **TriP**.

40. Isolation of pycnanthuquinone A and B, see: Fort, D. M.; Ubillas, R. P.; Mendez, C. D.; Jolad, S. D.; Inman, W. D.; Carney, J. R.; Chen, J. L.; Ianiro, T. T.; Hasbun, C.; Bruening, R. C.; Luo, J.; Reed, M. J.; Iwu, M.; Carlson, T. J.; King, S. R.; Bierer, D. E.; Cooper, R. *J. Org. Chem.* **2000**, *65*, 6534-6539.
41. Isolation of pycnanthuquinone C, see: Laird, D. W.; Poole, R.; Wikström, M.; van Altena, I. A. *J. Nat. Prod.* **2007**, *70*, 671-674.
42. Isolation of rossinone B, see: Appleton, D. R.; Chuen, C. S.; Berridge, M. V.; Webb, V. L.; Copp, B. R. *J. Org. Chem.* **2009**, *74*, 9195-9198.
43. Total synthesis of (-)-pycnanthuquinone C, see: Löbermann, F.; Mayer, P.; Trauner, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 6199-6202.
44. Total synthesis of (±)–rossinone B, see: Zhang, Z.; Chen, J.; Yang, Z.; Tang, Y. *Org. Lett.* **2010**, *12*, 5554-5557.

B. Results

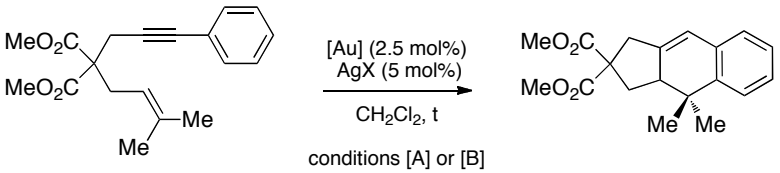
As mentioned above, most of the efficient enantioselective gold(I)-catalyzed reactions have so far employed diphosphine-gold complexes [(P-P)$(AuX)_2$] as catalyst, generated in situ by treatment of gold chloride precatalysts with an appropiate silver salt (Scheme 2). However, diphosphine-gold complexes are difficult to modify and need careful optimization to match substrate, catalyst and reaction conditions. In addition, several reports pointed out inconsistent results either with the monocationic or the dicationic gold(I) complexes and there is still a lack of mechanistic data to support the participation of both gold centers in the bond-forming/bond-breaking processes.[45] Therefore, alternative approaches with more simple catalysts are highly desirable and recent publications have proved that phosphoramidite-derivative Au(I) complexes can be used to achieved cyclization in good to excellent yield (e.g, catalysts **I-32**, **I-40**, **I-45**).

When this work was in progress, only one example of an enantioselective intramolecular [4+2] cycloaddition of arylenyne has been reported with [(*R*)-**5**-$(AuCl)_2$] as catalyst, offering the tricyclic product **I-14a** in 99% yield and 93% *ee* (Scheme 6).[26]

Early work made in our group on the enantioselective gold(I)-catalyzed intramolecular [4+2] cycloaddition of arylenyne were a starting point in the development of new chiral phosphites.[46] A series of chiral Au(I) complexes reported in the literature was prepared,[17] and arylenyne **I-13a** was chosen as model substrate for preliminary studies. Reaction

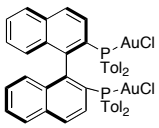
45. For a review on Au-Au interactions, see: Schmidbaur, H.; Schier, A. *Chem. Soc. Rev.* **2008**, *37*, 1931-1951.
26. (a) Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Chem. Eur. J.* **2009**, *15*, 1319-1323. (b) Chao, C.-M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, 6988-6990.
46. This part of the work was carried out by Dr. Christophe Bour and Patricia Pérez Galán.
17. Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293-1300.

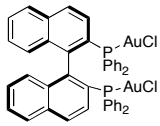
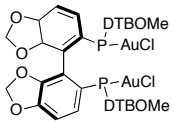
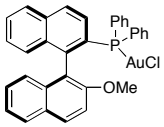
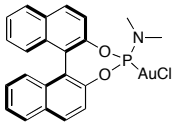
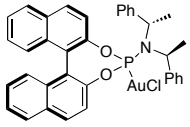
were carried out in CH_2Cl_2 either at room temperature (condition A) or under microwave heating (condition B), as it was demonstrated to clearly accelerate the reaction (Table 9, entry 4). Diphosphine-gold complexes, [(*R*)-**2**-$(AuCl)_2$], [(*R*)-**1**-$(AuCl)_2$] and [(*R*)-**4**-$(AuCl)_2$] (Figure 2, ligands **1**, **2** and **4**) were investigated first. Cycloadduct **I-14a** was obtained in good to excellent yield but only moderate enantioselectivities were obtained (Table 12, entries 1-3). Up to 56% *ee* could be reached when the reaction was carried out with [(*R*)-**2**-$(AuCl)_2$] in $CHCl_3$ using $AgPF_6$ under both conditions A and B (Table 12, entry 1). In addition, other types of silver salts were screened with no improvements (e.g., $AgBF_4$, AgOTf, $AgAsF_6$) and no reaction occurred when toluene was used as the solvent. Noteworthy, all reactions were carried out using a 1:2 ratio of Au/Ag. Indeed, monocationic species generated with a 1:1 mixture only gave low enantioselectivites. The use of biaryl gold-phosphine (*R*)-MOP **I-51** gave only moderate yield and enantiomeric excess (Table 12, entry 4). Binol derived phosphoramidites with methyl groups **I-52** or phenylethyl substituents on the amine moiety **I-29** afforded cycloadduct **I-14a** in good yield but with poor enantioselectivity (Table 12, entries 5 and 6).



I-13a **I-14a**

Table 12. Gold(I)-catalyzed intramolecular [4+2] cyclization of arylenyne **I-13a**.

Entry	*Catalyst*	*AgX*	*t*		*Yield (%)*		*ee (%)*	
			[A]	*[B]*	*[A]*	*[B]*	*[A]*	*[B]*
1	 [(*R*)-**2**-$(AuCl)_2$],	$AgSbF_6$[a]	30 h		91		38	
		$AgSbF_6$	30 h	18 min	90	80	25	38
		$AgPF_6$[a]	24 h	15 min	89	89	56	56

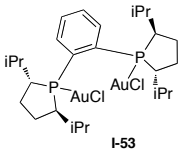
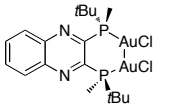
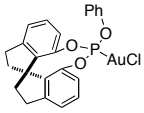
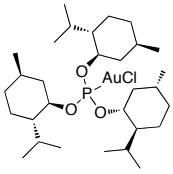
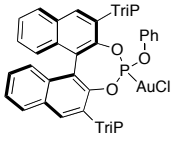
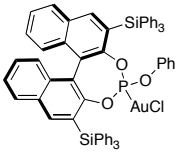
Entry	*Catalyst*	*AgX*	*t*		*Yield (%)*		*ee (%)*	
			[A]	*[B]*	*[A]*	*[B]*	*[A]*	*[B]*
2	 [(*R*)-**1**-(AuCl)$_2$]	$AgSbF_6$	24 h	18 min	71	92	24	6.5
		$AgPF_6$	24 h	18 min	81	90	31	39
3	 [(*R*)-**4**-(AuCl)$_2$]	$AgBF_4$	16 h		91		25	
4	 **I-51**	$AgSbF_6$	78 h	18 min	56	78	18	20
		$AgPF_6$	78 h	18 min	67	84	23	25
5	 **I-52**	$AgSbF_6$	24 h	18 min	91	95	8	12
		$AgPF_6$	24 h	18 min	88	94	9	14
6	 **I-29**	$AgSbF_6$		18 min		95		5
		$AgPF_6$		18 min		94		4

Conditions [A]: reaction carried out at room temperature. Conditions [B]: reaction carried out under microwave heating at 80 ºC. [a] Reaction carried out in $CHCl_3$.

In a second series of experiments, new Au(I) catalysts were synthesized with an emphasis on bulky ligand. Diphosphine-gold complexes **I-53** and **I-54** complexes prepared from (*R*,*R*)-*i*Pr-DuPhos and (*S*)-QuinoxP gave only moderate enantiomeric excess (Table 13, entries 1 and 2). Au(I) complex of spiro monophosphite (*S*)-ShiP **I-55** afforded cycloadduct **I-14a** in a similar 26% *ee* (Table 13, entry 3). (-)-Menthol

derivative C_3-symmetric phosphite **I-56** gave a racemic mixture, although in good yield and short reaction time (2 h) (Table 13, entry 4).

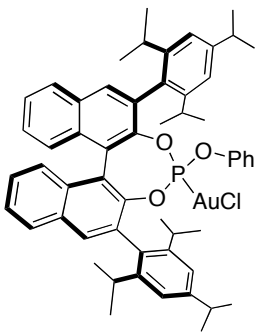
Table 13. Gold(I)-catalyzed intramolecular [4+2] cyclization of arylenyne **I-13a**.

Entry	*Catalyst*	*AgX*	*Conditions*	*t*	*Yield (%)*	*ee (%)*
1	 **I-53**	$AgSbF_6$	B	18 min	92	20
		$AgPF_6$		18 min	91	20
2	 **I-54**	$AgSbF_6$	B	18 min	92	20
		$AgPF_6$		18 min	91	20
3	 **I-55**	$AgSbF_6$	A	12 h	92	26
4	 **I-56**	$AgSbF_6$	A	2 h	98	<1
5	 **I-57**	$AgSbF_6$	A	12 h	92	26
6	 **I-58a**	$AgSbF_6$	A	12 h	99	57
		$AgBF_4$		16 h	90	57

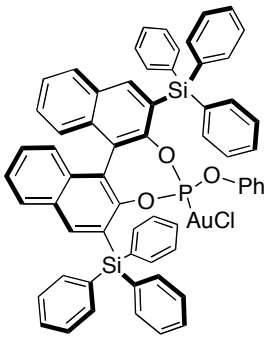
Conditions [A]: reaction carried out at room temperature. Conditions [B]: reaction carried out under microwave heating at 80 ºC.

The breakthrough came by employing BINOL derivative phosphite ligands with bulky groups at the 3 and 3' position of the binaphol unit (Table 13, entries 5 and 6). Triisopropylphenyl substituents on the BINOL ligand (Figure 9, **I-57**) afforded cycloadduct **I-14a** in moderate enantiomeric excess (26% *ee*) (Table 13, entry 5). Gratifingly, a promising result was obtained with catalyst bearing triphenylsilyl substituents on the BINOL framework (Figure 9, **I-58a**) at room temperature (57% *ee*) (Table 13, entry 6). Changing the silver salt $AgSbF_6$ for $AgBF_4$ did not improve the selectivity.

Au(I) Catalysts **I-57** and **I-58a** (Figure 9) were crystallized to give X-ray structures in order to understand the three dimensional environment around the Au(I) center of these catalysts.



I-57



I-58a

Figure 9 . Structure of chiral Au(I) phosphite **I-57** and **I-58a**.

Structure of Au(I) complex **I-58a** in the solid state shows a cone-shaped binding pocket surrounding the gold center (Figure 10, aryl rings in black colour around the metal).

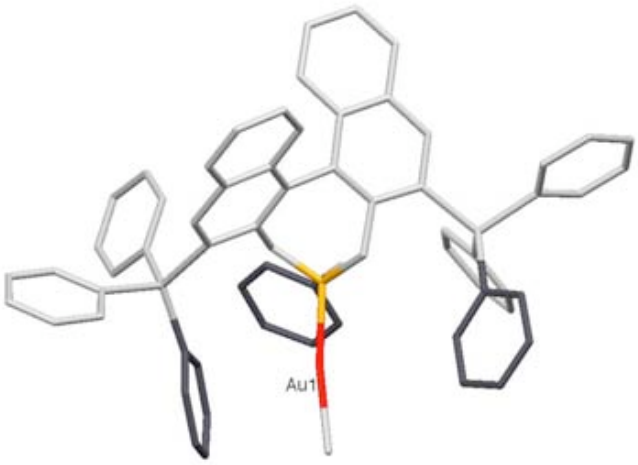


Figure 10. X-Ray structure of Au(I) complex **I-58a** with the chiral pocket around the gold center.

A metal arene interaction between the metal center and an aryl ring can be observed (3.304 Å) (Figure 11). Au-arene interactions were studied in the case of bulky and electron rich phosphine developed by Buchwald and distances from 3.0 to 3.2 Å were generally observed.[12] Although gold–arene bonds are considered to be weaker than gold–alkyne or gold–alkene bonds,[47] this interaction could play a role in the catalytic process by establishing a well-defined chiral environment. Contact distances between the AuCl unit and the C_{ipso} of the phenyl rings of the triphenylsilyl units are 3.705 Å and 4.481 Å.

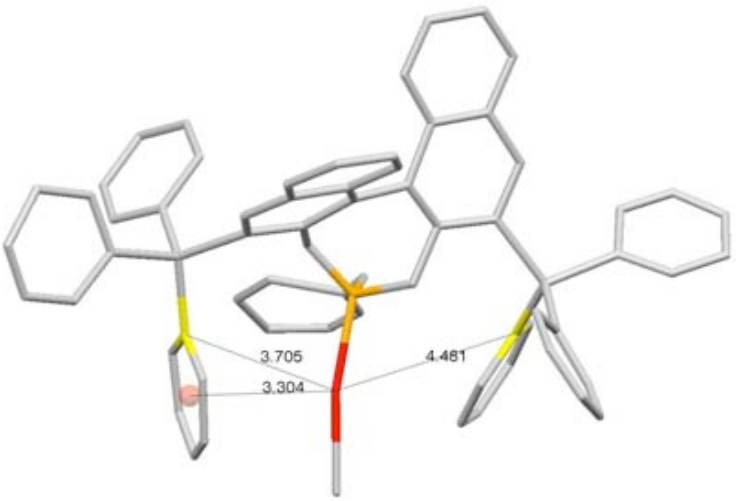


Figure 11. X-Ray structure of Au(I) complex **I-58a**. Au-C_{ipso} distances of two phenyl rings (3.705 Å and 4.481 Å) and closest Au-phenyl ring interaction distance (3.304 Å) are calculated.

12. For a recent study on Au(I)-ligand interactions in gold dialkylbiarylphosphane, see: Pérez-Galán, P.; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. *Chem. Eur. J.* **2010**, *16*, 5324-5332.
47. For a review on η^2 coordination of alkenes, alkynes, and aromatic compounds to Au(I), see: Schmidbaur, H.; Schier, A. *Organometallics* **2009**, *29*, 2-23.

In addition to the known effect of the binol framework in the chirality transfert, the phenol moiety may also have a role to play. Indeed, steric hindrance from the triphenylsilyl units cannot be ruled out, forcing the phenol ring to point towards the gold center and to induce chirality. The Au-arene length between the metal and the phenol ring is 4.085 Å with a Au-P-O angle of 102.9º (Figure 12).

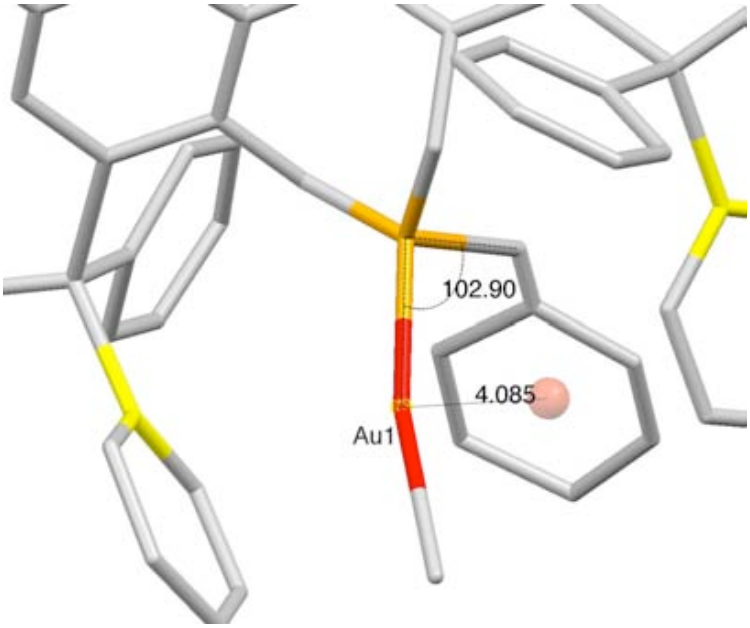


Figure 12. Magnification of the X-ray structure of Au(I) complex **I-58a**. The Au-phenol interaction distance (4.085 Å) and the Au-P-O angle (102.90º) are calculated.

Analysis of the X-ray structure of Au(I) complex **I-57 (**Figure 9**)** supports also this hypothesis. The triisopropylphenyl rings from the BINOL framework are pointing up, pushing the phenol ring in the opposite direction, towards the metal. The Au-arene length between the metal and the phenol ring is similar (i.e. 4.068 Å) but with a higher Au-P-O angle of 114.98 º (Figure 13).

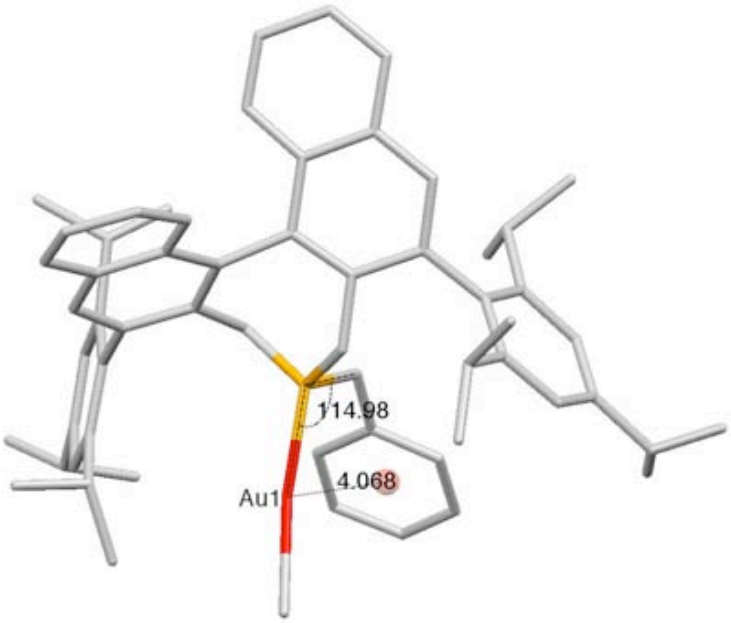
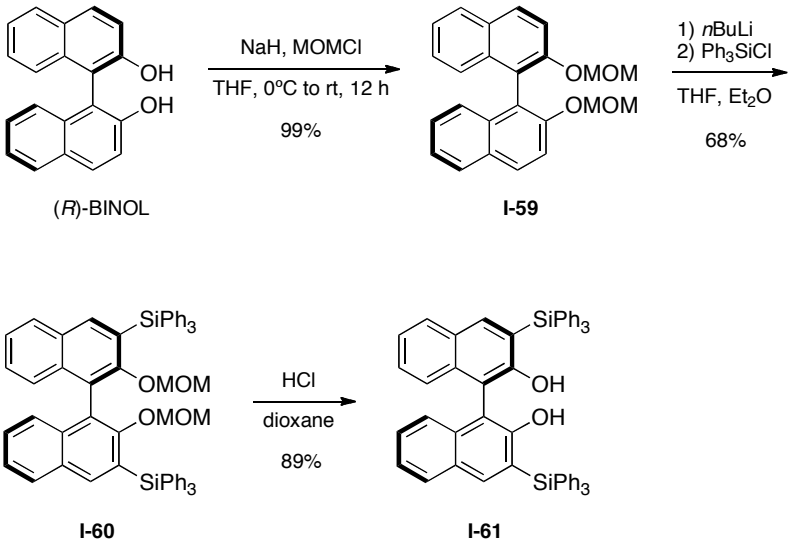


Figure 13. X-Ray structure of Au(I) complex **I-57**. The Au-phenol ring distance (4.068 Å) and the Au-P-O angle (114.98º) are calculated.

The isopropyl groups of the TriP rings are also close to the metal (range distance 2.8-3.1 Å) but the difference of enantioselectivity between catalysts **I-57** and **I-58a** may be rationalized by the presence of the metal-arene interaction in Au(I) phosphite **I-58a** (*vide supra*).

With these preliminary results, we decided to continue our investigations with Au(I) phosphite **I-58a** as a starting point for our studies towards the development of a chiral version of the intramolecular [4+2] cycloaddition of arylenyne. Indeed, the preparation of a series of phosphite ligands from commercially available (*R*)-BINOL intermediate is

easy and phosphite ligands have the advantage to be less sensitive to air and other oxidizing agents than phosphines.[48] The triphenylsilyl units attached to the 3 and 3' positions of the BINOL scaffold were unchanged and only the phenol moiety was modified. BINOL derivative **I-61** was synthesized in 3 steps and 60% overall yield following a reported procedure (Scheme 13).[49]

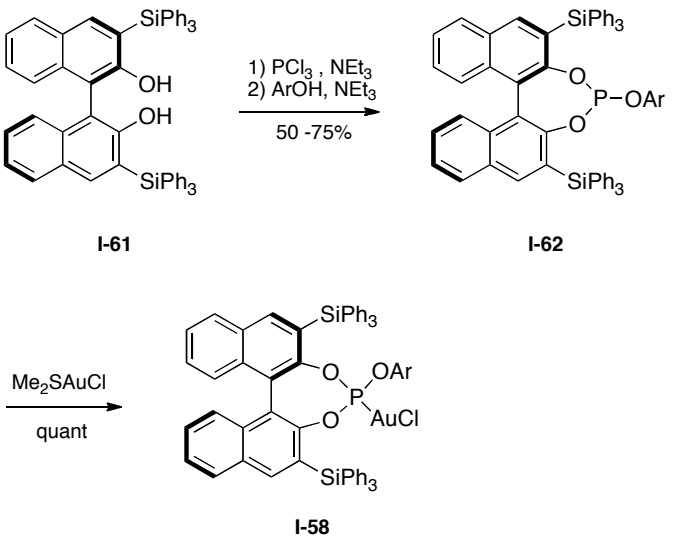


Scheme 13. Synthesis of BINOL derivative **I-61** from (*R*)-BINOL.

Synthesis of Au(I) phosphite **I-58** was achieved in two steps from a reported procedure.[50] **I-61** was mixed with PCl_3 to afford the BINOL-derived chlorophosphite *in*

48. For a review on phosphite-containing ligands for asymmetric catalysis, see: Leeuwen, P. W. N. M. v.; Kamer, P. C. J.; Claver, C.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077-2118.
49. For the synthesis of BINOL derivative **I-61**, see: Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *128*, 84-86. and references quoted herein.
50. Albrow, V. E.; Blake, A. J.; Fryatt, R.; Wilson, C.; Woodward, S. *Eur. J. Org. Chem.* **2006**, 2549-2557.

situ that was trapped with the desired phenol ArOH to give **I-62** in good yield (i.e. 50% to 75% yield) (Scheme 14). Then, the phosphite **I-62** reacted with $(Me)_2SAuCl$ to give **I-58** in quantitative yields.



Scheme 14. Synthesis of Au(I) phosphite **I-58** from BINOL derivative **I-61**.

Phosphite ligands **I-62** possess moderate oxidative and hydrolytic stability that allow a purification using normal silica gel under inert atmosphere.

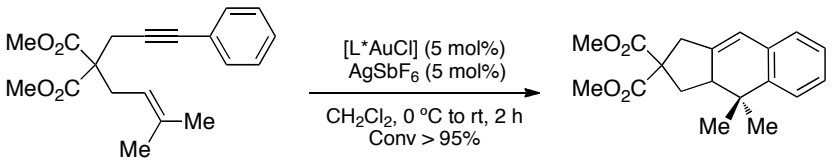
A series of phosphites **I-62** were synthesized[51] and the corresponding Au(I) Chloride complexes **I-58** were prepared. The catalytic activities of these catalysts were studied towards the enantioselective intramolecular [4+2] cycloaddition of arylenyne with model

51. For the synthesis and characterization of the phosphite ligands and the corresponding Au(I) chloride phosphite complexes used in Table 14 and Table 15, see the experimental part at the end of this chapter.

substrate **I-13a**. Based on the first set of experiments, CH_2Cl_2 and $AgSbF_6$ were used for this reaction. (Table 13, entry 7).[52]

All reactions were run at 0 ºC and slowly warmed to room temperature over 2 h with quantitative conversions observed in all cases. Active catalysts were formed at 0 ºC over 30 min by mixing the desired Au(I) chloride phosphite and $AgSbF_6$ followed by the addition of arylenyne **I-13a**.

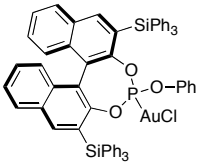
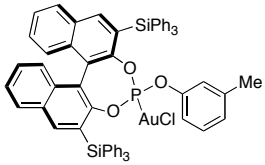
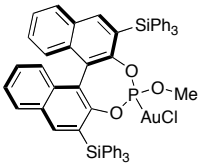
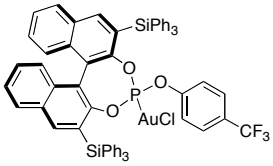
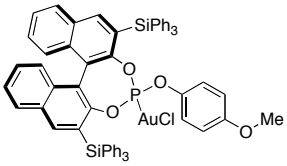
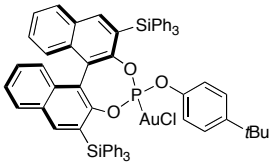
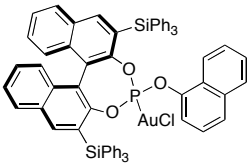
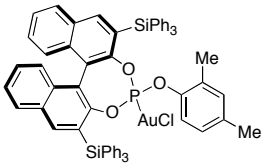
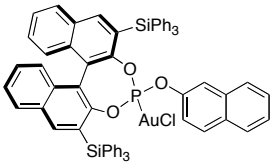
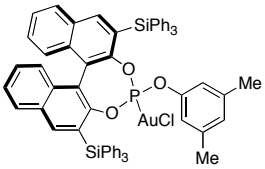
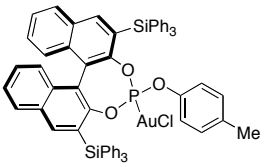
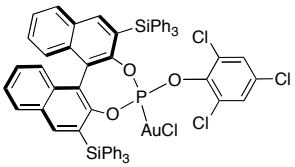
The positive role played by an aryl group was confirmed when the phenol substituent **I-58a** was replaced by a methoxy group **I-58b** affording cycloadduct **I-14a** in quantitative yield but with 5% *ee* (Table 14, entries 2). Substitutions by electron rich or electron poor phenols gave similar results without improving the enantioselectivity (Table 14, entries 3, 8), except with trichlorophenol that gave cycloadduct **I-14a** in a moderate 46% *ee* (Table 14, entry 13). Changing a methyl group from the *meta*- to the *para*-position had a positive influence by increasing the enantioselectivity from 72% *ee* to 80% *ee* (Table 14, entries 6 and 7) and a similar improvement was made when 1-naphtol was replaced by 2-naphtol (Table 14, entries 4 and 5). Changing the methyl group at the *para*-position by a more hindered *tert*-butyl group led to a slight improvement, 82% *ee* instead of 80% *ee* (Table 14, entry 9). Noteworthy, substitution by two methyl groups on both *meta*-positions gave a better result than substitution on both *ortho*- and *meta*-positions (Table 14, entries 10 and 11). In addition, lowering the temperature to -20 ºC had a positive effect on the enantioselectivity and cycloadduct **I-14a** was obtained in 83% *ee* by using Au(I) phosphite with a *para*-methyl phenol (Table 14, entry 6).



I-13a **I-14a**

52. This part of the work and the following optimization studies were carried out in collaboration with Dr. Dirk Spiegl.

Table 14. Catalysts screen using BINOL derivative phosphite Au(I) complexes **I-58**. Part 1.

Entry	*[L*AuCl]*	*ee (%)*	*Entry*	*[L*AuCl]*	*ee (%)*
1 **I-58a**		70	7 **I-58g**		72
2 **I-58b**		5	8 **I-58h**		60
3 **I-58c**		60	9 **I-58i**		82
4 **I-58d**		60	10 **I-58j**		74
5 **I-58e**		70	11 **I-58k**		81
6 **I-58f**		80 83[a]	12 **I-58l**		46

Reactions were carried out at 0 ºC and slowly warmed to room temperature over 2 h. Enantiomeric excess was measured by chiral HPLC. [a] Reaction carried out at -20 ºC over 4 h.

These results highlight the need of aryl groups rather than alkyl chains and substitution patterns ideally located on the *para*- position of the aryl ring to achieve good enantioselectivity. Au(I) phosphite **I-58i** with a *para*-*tert*-butyl phenol (Table 14, entry 9) gave a promising hit by performing the best result amongst the catalysts investigated.

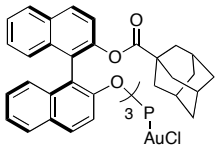
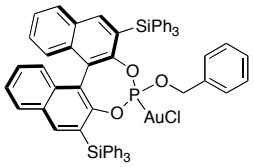
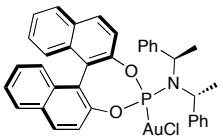
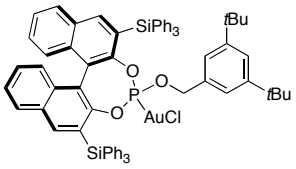
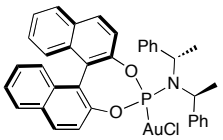
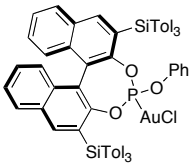
Reetz's helical C_3-symmetric monophosphite ligand,[35] also used in gold(I)-catalyzed [4+2] cycloaddition of allenedienes,[34] was investigated (**I-63**). However, only a moderate enantioselectivity was obtained with 36% *ee* (Table 15, entry 1). Phosphoramidite ligands developed by Feringa *et al.*[53] were tried again but afforded low enantioselectivity as expected (see Table 12, entry 6 and Table 15 entry 2 for the match case (*R*,*R*,*R*)-**I-29**, and Table 15 entry 3 for the mismatch case (*R*,*R*,*S*)-**I-29**. These results are in agreement with the low enantioselectivities observed in recently reported asymmetric gold(I)-catalyzed cyclizations of allenes with these two ligands.[32,34]

Based on the analysis of the X-ray structure of **I-58a** (Figure 12), we assumed that changing the phenol group by a benzyl alcohol could induce a higher enantioselectivity by increasing the interaction between the aryl ring and the metal. The enantioselectivity obtained with such a complex bearing a simple benzyloxy substituent (**I-58m**) gratifyingly afforded product **I-14a** good with 81% *ee* (Table 15, entry 4). However, longer reaction time was required (36 h). Adding two *tert*-butyl groups to the meta-position of the benzyl moiety (**I-58n**) gave the product in 74% *ee* after 3 days at room temperature, and no reaction occurred when the cyclization was run at 0 ºC. This low

35. For a review on helical triskelion monophosphites as ligands in asymmetric Rh(I) catalysis, see: Reetz, M. T.; Guo, H.; Ma, J.-A.; Goddard, R.; Mynott, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 4136-4142.
34. González, A. Z.; Toste, F. D. *Org. Lett.* **2009**, *12*, 200-203.
53. For a review on phosphoramidite in asymmetric catalysis, see: Teichert, J. F.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 2486-2528.
32. Alonso, I.; Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020-13030.

reactivity is remarkable and could be due to the greater steric hindrance that a benzyl group provides compared to a phenyl ring.

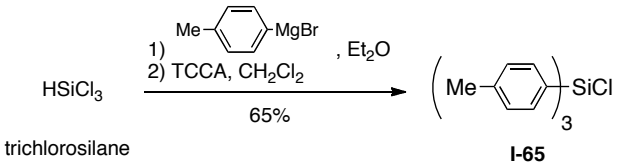
Table 15. Catalysts screen using BINOL derivative phosphite Au(I) complexes. Part 2.

Entry	*[L*AuCl]*	*ee (%)*	*Entry*	*[L*AuCl]*	*ee (%)*
1 **I-63**		36	4 **I-58m**		81[a]
2 **(*R*,*R*,*R*) I-29**		24	5 **I-58n**		74[b]
3 **(*R*,*R*,*S*) I-29**		0	6 **I-64**		60[c]

All Reactions were performed at 0 ºC and slowly warmed to room temperature over 2 h unless otherwise stated. In all cases, complete conversion was observed. Enantiomeric excess was measured by chiral HPLC. [a] 36 h, -25 ºC, $AgNTF_2$ used. [b] 3 days, room temperature. [c] 7 h, 0 ºC.

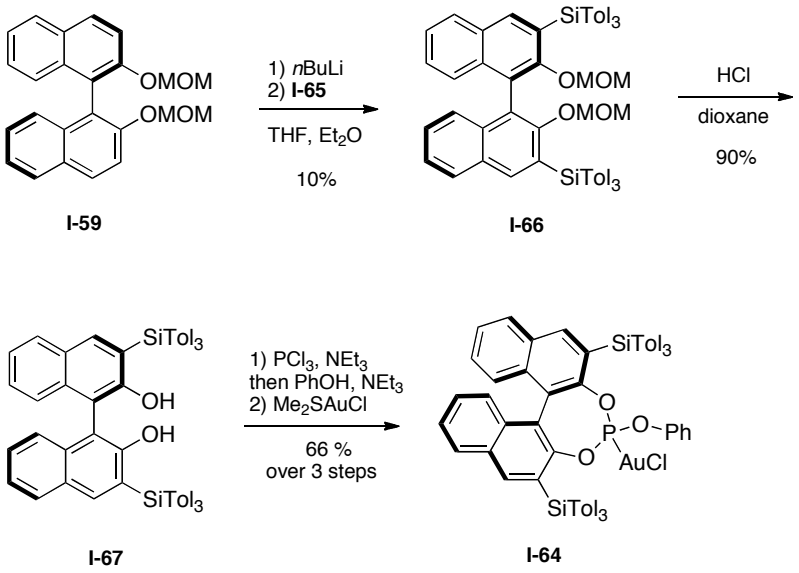
With the view to add more hindrance around the metal center (Figure 11) without decreasing the reactivity of the catalyst, an alternative approach was tried by slightly modifying the triphenylsilyl framework. Therefore, we assumed that adding a methyl to the *para*-position of the phenyl rings would have a beneficial effect on the

enantioselectivity. Tri-tolylsilyl chloride **I-65** was obtained from trichlorosilane in 2 steps and 65% overall yield using reported procedures (Scheme 15).[54,55]



Scheme 15. Synthesis of **I-65** from trichlorosilane

Protected BINOL derivative **I-66** was synthesized from **I-59** and **I-65** (Scheme 16).

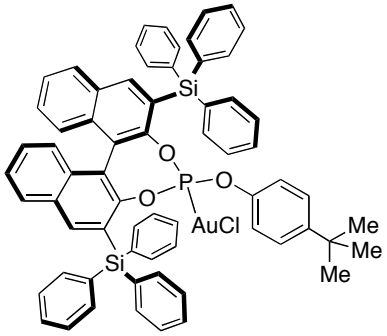


Scheme 16. Synthesis of Au(I) phosphite **I-64** from BINOL derivative **I-59**.

54. For the synthesis of triarylsilane, see: Prince, P. D.; Bearpark, M. J.; McGrady, G. S.; Steed, J. W. *Dalton Trans.* **2008**, 271-282.
55. For the conversion of triarylsilane in triarylsilyl chlroride, see: Varaprath, S.; Stutts, D. H. *J. Organomet. Chem.* **2007**, *692*, 1892-1897.

Catalyst **I-64** was synthesized from **I-66** in 3 steps and 66% overall yield using known procedures (*vide supra*). Disappointedly, catalyst **I-64** only afforded cycloadduct **I-14a** in a moderate 60% *ee* (Table 15, entry 6).

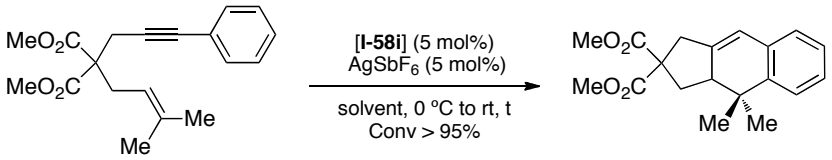
Regarding the high reactivity and the promising enantioselectivity obtained (i.e. 82% *ee*), chiral Au(I) phosphite with a *para*-*tert*-butyl phenol (Figure 14, **I-58i**) was selected as our best candidate for optimization studies.



I-58i

Figure 14. Au(I) complex **I-58i**.

Influence of the solvent on the reaction was investigated first with catalyst **I-58i**. As anticipated, the reaction was found to be solvent-dependent as enantiomeric excess vary from 63% to 82% *ee* (Table 16, entries 1-8). The use of toluene or dioxane led to no conversion (Table 16, entries 5 and 6) whether $MeNO_2$ or DCE gave moderate enantioselectivity with longer reaction times (Table 16, entries 3 and 6). Diethyl ether and acetone (acetone-d_6) were found to be suitable solvent for this reaction, providing good enantiomeric excess but longer reaction times were also required for completion (20 h to 24 h) (Table 16, entries 4 and 8). CH_2Cl_2 and $CDCl_3$ gave the best results with 82% *ee* and 79% *ee* respectively with short reaction times (Table 16, entries 1 and 2).



I-13a **I-14a**

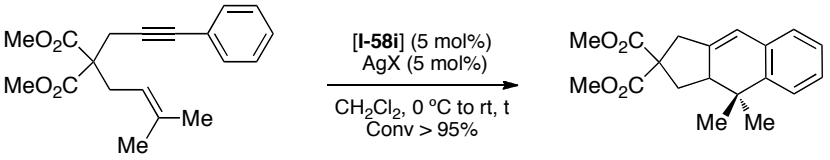
Table 16. Optimization studies: Influence of the solvent.

Entry	*Solvent*	*t*	*ee (%)*
1	CH_2Cl_2	2 h	82
2	$CDCl_3$	1 h	79
3	DCE	20 h	63
4	Et_2O	20 h	82
5	toluene	2 days	n.r.
6	$MeNO_2$	16 h	66
7	dioxane	1 day	n.r.
8	acetone-d_6	1 day	82

All Reactions were performed at 0 ºC and slowly warmed to room temperature until complete conversion. Enantiomeric excess was measured by chiral HPLC.

Variation of the silver salt did not lead to significant improvements with a range of values around 80% *ee* (Table 17, entries 1-6). No reaction occurred when AgOBz was

used to form the cationic Au(I) complex (Table 17, entry 3), as previously reported.[26] AgOTf and $AgNTf_2$ gave identical results to $AgSbF_6$ in terms of reactivity and enantioselectivity with 80% *ee* and 82% *ee* (Table 17, entries 2 and 5). Lower reactivity was observed when $AgPF_6$ was used, although **I-14a** could be formed in good enantioselectivity (72% *ee*) (Table 17, entry 4). Sodium salt $NaBAr_F$ afforded the product in high enantioselectivity but the reaction required longer reaction time to complete (Table 17, entry 6).



I-13a **I-14a**

Table 17. Optimization studies: Influence of the counterion.

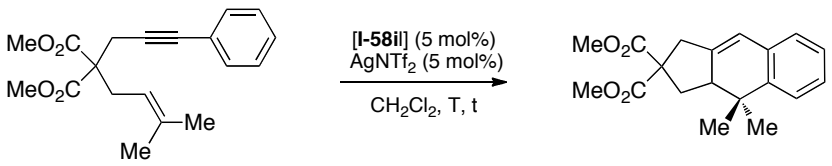
Entry	*AgX*	*t*	*ee (%)*
1	$AgSbF_6$	2 h	82
2	AgOTf	2 h	80
3	AgOBz	1 day	n.r.
4	$AgPF_6$	1 day	72
5	$AgNTf_2$	2 h	82
6	$NaBAr_F$	1 day	81

All Reactions were performed at 0 ºC and slowly warmed to room temperature until complete conversion was observed. Enantiomeric excess was measured by chiral HPLC.

26. (a) Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Chem. Eur. J.* **2009**, *15*, 1319-1323. (b) Chao, C.-M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, 6988-6990.

Better enantioselectivities were observed with $NaBAr_F$ rather than $AgNTf_2$ in the gold(I)-catalyzed ring expansion of allenylcyclopropanol, assuming an inherent background reaction by traces amount of $HNTf_2$.[28] In order to discard any role played by traces of $HNTf_2$ in the reaction, a control experiment was made using standard conditions. However, no traces of cycloadduct **I-14a** were observed when a large excess of $HNTf_2$ was mixed with **I-13a**.

$AgNTf_2$ was finally chosen as the silver salt instead of $AgSbF_6$ due to the ease to handle this reagent. Indeed, $AgNTf_2$ is relatively stable to air and allow a better reaction control by adding the exact amount of silver required to form the cationic gold species. Finally by lowering the temperature to -20 ºC, we obtained the cycloadduct **I-14a** in 88% *ee* with a reasonable reaction time (Table 18, entries 1-3). Measurement of the rotation angle gave $[\alpha]_D^{20}$= -25.0 ± 2.0 (*c* = 0.11, $CHCl_3$).[26] At lower temperature, no improvement in the enantioselectivity was observed (Table 18, entry 4).



I-13a **I-14a**

Table 18. Optimization studies: Influence of the temperature.

Entry	*T (ºC)*	*t*	*ee (%)*
1	0	2 h	82
2	-10	16 h	85

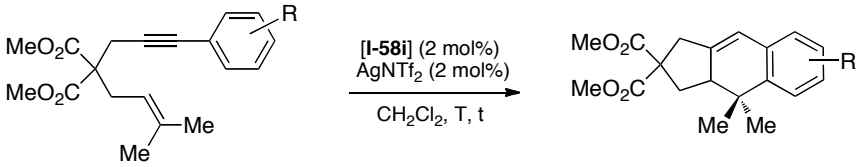
28. Kleinbeck, F.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 9178-9179.

26. Previously reported value was $[\alpha]_D^{20}$= +14.8 ($CHCl_3$, c = 0.93) for a reported 93% *ee*: Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Chem. Eur. J.* **2009**, *15*, 1319-1323.

Entry	*T (ºC)*	*t*	*ee (%)*
3	-20	16 h	88
4	-40	25 h	87

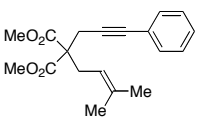
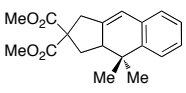
Reactions were run until complete conversion was observed. Enantiomeric excess was measured by chiral HPLC.

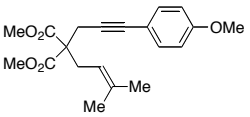
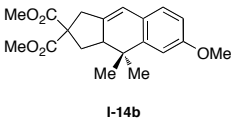
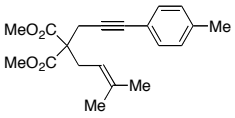
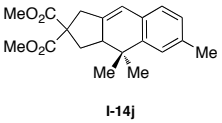
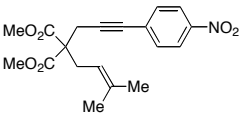
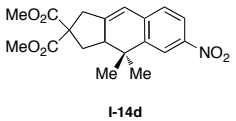
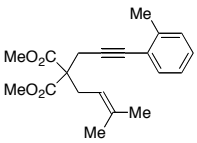
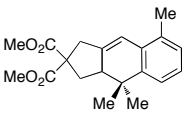
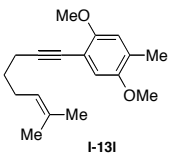
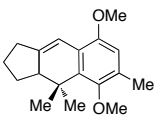
We then decided to evaluate the substrate scope under the optimized catalytic conditions. A series of aryl enyne with different substitution patterns were synthesized and tested (Table 19, entries 1-6). A methoxy group on the *para*-position afforded the corresponding cycloadduct **I-14b** in good enantioselectivity and good yield (86% *ee* and 85% yield) by running the reaction at -20 ºC over 30 h (Table 19, entry 2). Longer reaction time was required for the cyclization of an electron rich aromatic ring compared to the unsubstituted enyne (Table 19, entries 1 and 2). Good enantioselectivity was also obtained with enyne **I-13j** bearing a methyl group at the *para*-position (87% and 98% yield) at -20 ºC over 15 h (Table 19, entry 3). Cyclization with a *para*-nitro group on the phenyl ring gave the cycloadduct **I-14d** in 80% yield and 73% *ee* at 0 ºC (Table 19, entry 4). The reaction became sluggish at -20 ºC.



I-13 **I-14**

Table 19. Substrate scope of the enantioselective intramolecular [4+2] cycloaddition of arylenyne using catalyst **I-58i**.

Entry	*Substrate*	*Product*	*T (ºC)*	*t*	*Yield %*	*ee (%)*
1	 **I-13a**	 **I-14a**	- 20ºC	18 h	>95	88

Entry	*Substrate*	*Product*	*T (ºC)*	*t*	*Yield %*	*ee (%)*
2	 **I-13b**	 **I-14b**	- 20	30 h	85	86
3	 **I-13j**	 **I-14j**	-20	15 h	98	87
4	 **I-13d**	 **I-14d**	0[a]	15 h	80	73
5	 **I-13k**	 **I-14k**	- 20	30 h	70	79
6	 **I-13l**	 **I-14l**	0[a]	2 days	62	17

Enantiomeric excesses were measured by chiral HPLC. [a] No reaction observed at – 20 ºC after 12 h.

Substrates with *ortho*-substitutents were also studied. Arylenynes with a methyl group afforded the corresponding tricyclic compound **I-14k** in 70% yield and 79% *ee* at -20 ºC over 30 h (Table 19, entry 5).

In order to determine whether or not this catalyst could be successfully applied to the synthesis of pycnanthuquinones (Figure 8), model substrate with trisubstituted enyne **I-13l** was tried (Table 19, entry 6). Unfortunately, the desired cycloaduct **I-14l** was only obtained in 62% yield and 17% *ee* after 48 h. The reaction was very slow at -20 ºC.

C. Experimental Part

Towards an Enantioselctive Au(I)-Catalyzed Intramolecular [4+2] Cycloadditions of Arylalkynes

General Methods

Unless specified, all reactions were carried out at room temperature, under Ar, using magnetic stirring and in solvents dried using a Solvent Purification System (SPS). Analytical thin layer chromatography was carried out using TLC-aluminium sheets with 0.2 mm of silica gel (Merck GF234). Chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm). Commercial grade reagents and solvents were used without further purification. PCl_3 was distilled prior to use.[56]

NMR spectra were recorded at 23 ºC on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus. NMR chemical shifts (δ) are expressed in ppm. ^{1}H-NMR chemical shifts are referenced to TMS (in the case of $CDCl_3$) or to the solvent residual signal (in the case of other NMR solvents).[57] ^{13}C-NMR chemical shifts are referenced to the solvent signal. $^{31}P\{^1H\}$-NMR chemical shifts are referenced to an external standard (85% aqueous H_3PO_4). Optical rotation was measured on a Jasco P-1030 polarimeter. Chiral HPLC analyses were performed on a Waters system using a Chiralpak IA column (4.6x250 mm, 5μm), Chiralpak IB column (4.6x250 mm, 5μm) and Chiralpak IC column (4.6x250 mm, 5μm).

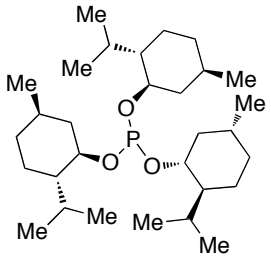
The following ligands were purchased from suppliers: (*R*)-**1**, (*R*)-**2**, (*R*)-**4**, (*R*)-BINOL, (*R*)-MOP, (*R*)-Monophos, (*R*,*R*,*R*)-(+)-(3,5-Dioxa-4-phosphacyclohepta[2,1-*a*:3,4-*a*′]dinaphthalen-4-yl)bis(1-phenylethyl)amine, (*R*,*S*,*S*)-(+)-(3,5-Dioxa-4-phosphacyclohepta[2,1-*a*:3,4-*a*′]dinaphthalen-4-yl)bis(1-phenylethyl)amine, (*R*,*R*)-*i*Pr-DuPhos, (*S*)-QuinoxP, (*S*)-ShiP, (*R*)-3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-bi-2-naphthol. Au(I) catalyst **BiP1** was purchased from suppliers.

56. Amarego, W. L. F.; Chai, C. L. L., *Purification of Laboratory Chemicals* **2003**, 5th edition. Butterworth-Heinemann.
57. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.

The corresponding Au(I) complexes [(*R*)-**1**-$(AuCl)_2$], [(*R*)-**2**-$(AuCl)_2$], **I-51**, **I-52**, (*R*,*R*,*R*)-**I-29**, (*R*,*S*,*S*)-**I-29** were prepared following reported procedures.[17,34,58]

Synthesis of Chiral Phosphite Ligands.

(-)-Menthol-derived monodentate phosphite I-68



To a solution of PCl_3 (0.87 mL, 0.010 mol) in toluene (15 mL), a solution of (-)-menthol (4.7 g, 0.030 mol) and NEt_3 (5.0 mL, 0.036 mol) in toluene (25 mL) was added dropwise at -20 ºC. The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was filtered off and the solvent was removed under *vacuo*. Purification by column chromatography on silica gel (toluene, Ar) provided the desired phosphite ligand **I-68** (3.05 g, 68%).

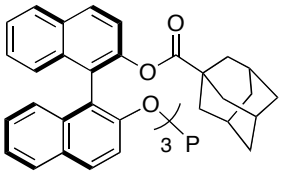
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.84 (ddd, J = 19.5, 10.5, 4.4 Hz, 3H), 2.21 (tdd, J = 10.4, 7.5, 2.9 Hz, 3H), 2.09 (dt, J = 9.0, 4.3 Hz, 3H), 1.68-1.59 (m, 6H), 1.45-1.32 (m, 3H), 1.30-1.22 (m, 3H), 1.11 (dd, J = 23.3, 12.2 Hz, 3H), 0.98 (ddd, J = 17.0, 14.2, 4.3 Hz, 3H), 0.89 (dd, J = 6.8, 1.4 Hz, 18H), 0.87-0.80 (m, 3H), 0.76 (d, J = 6.9 Hz, 9H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 150.1.

17. Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293-1300.

34. González, A. Z.; Toste, F. D. *Org. Lett.* **2009**, *12*, 200-203.

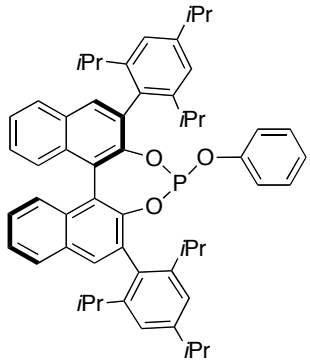
58. (a) Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721-7730. (b) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306-6316.

***C*$_3$-symmetric binol-derived monodentate phosphite I-69**



I-69 was synthesized from (*R*)-BINOL following a reported procedure.[35] ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.84 (d, *J* = 8.8 Hz, 3H), 7.71 (dd, *J* = 11.9, 8.2 Hz, 6H), 7.33-7.23 (m, 12H), 7.14 (t, *J* = 7.2 Hz, 3H), 7.00 (t, *J* = 7.6 Hz, 3H), 6.94 (d, *J* = 8.5 Hz, 3H), 6.66 (d, *J* = 8.4 Hz, 3H), 6.46 (d, *J* = 8.9 Hz, 3H), 1.71 (m, 9H), 1.53-1.50 (m, 9H), 1.39-1.36 (m, 12H), 1.23 (m, 15H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 137.2.

Binol-derived monodentate phosphite I-70



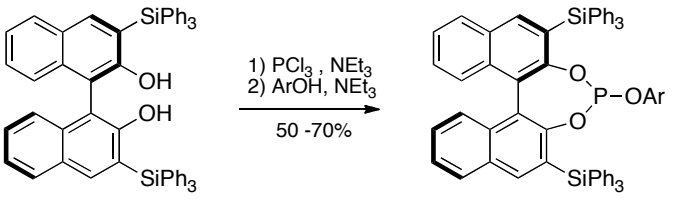
To a solution of (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-bi-2-naphthol (150 mg, 0.210 mmol) and Et_3N (0.21 ml, 0.45 mmol) in toluene (10 mL) was added PCl_3 (40 mg, 0.32 mmol) dropwise at 0 °C. The resulting mixture was stirred vigorously for 1 h and then at 80 °C for 1 h. The mixture was cooled to 0 °C, Et_3N (0,030 ml, 0,22 mmol) and phenol (22 mg, 0.23 mmol) were added. The resultant mixture was stirred at 0 °C for 1 h, then at room temperature for 1 h. The reaction mixture was filtered off and the solvent was removed under *vacuo*. Chromatographic purification (toluene, Ar) afforded **I-70** as a fluffy yellow solid (104 mg, 70%).

^{1}H-NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.95 (dd, *J* = 11.2, 8.4 Hz, 2H), 7.89 (s, 2H), 7.49 (ddd, *J* =10.9, 8.2, 6.98 Hz, 2H), 7.44-7.40 (m, 2H), 7.35-7.29 (m, 3H), 7.12-7.08 (m, 3H), 7.06-6.93 (m, 3H), 6.07 (d, *J* = 7.5 Hz, 2H), 3.01 (m, *J* = 7.0 Hz, 1H), 3.00 (m, *J* = 7.0 Hz, 1H), 2.91 (m, *J* = 6.6 Hz, 1H), 2.81 (m, *J* = 6.6 Hz, 1H), 2.73 (m, *J* = 6.6 Hz,

35. Reetz, M. T.; Guo, H.; Ma, J.-A.; Goddard, R.; Mynott, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 4136-4142.

1H), 2.60 (m, J = 6.6 Hz, 1H), 1.20-0.94 (m, 36H). $^{31}P\{^{1}H\}$-NMR (162 MHz, CD_2Cl_2): δ (ppm) = 140.4.

Phosphite complex I-62 – General methodology



I-61 **I-62**

In a typical procedure,[50] a solution of PCl_3 (42.7 mg, 374 µmol, 3.0 eq.) in THF (0.5 mL) was added dropwise to a solution of (*R*)-3,3'-bis(triphenylsilyl)-[1,1'-binaphthalene]-2,2'-diol[49] (**I-61,** 100 mg, 125 µmol, 1.0 eq.) in THF (0.5 mL) at –40 °C. After stirring at -40 °C for 10 min, a solution of NEt_3 (63.0 mg, 623 µmol, 5.0 eq.) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for another 2 h before being filtered through a Celite pad (rinsing with THF). The filtrate was concentrated under reduced pressure and the residue was treated with toluene (1 mL), evaporated and dried under *vacuo*. The obtained solid was redissolved in THF (2 mL) and treated with a solution of NEt_3 (63.0 mg, 623 µmol, 5.0 eq.) in THF (0.5 mL) at room temperature. A solution of the appropriate phenol or benzylic alcohol (249 µmol, 2.0 eq.) in THF (0.5 mL) was added dropwise and the resulting mixture was stirred for 2 h at room temperature. After evaporation of the volatiles under reduced pressure, the residue was purified by column chromatography on silica gel (toluene, Ar) to provide the desired phosphite ligand **I-62**.

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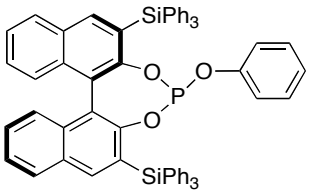
50. Albrow, V. E.; Blake, A. J.; Fryatt, R.; Wilson, C.; Woodward, S. *Eur. J. Org. Chem.* **2006**, 2549-2557.

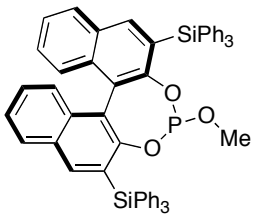
49. For the synthesis of BINOL derivative **I-61**, see: Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *128*, 84-86. and references therein.

(*R*)-Binol-derived monodentate phosphite I-62a



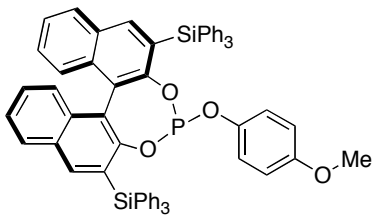
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = δ 8.07 (s, 1H), 7.93 (s, 1H), 7.83 (d, *J*= 8.3 Hz, 1H), 7.77 (d, *J*= 8.3 Hz, 1H), 7.59 (dt, *J*= 6.6, 1.7 Hz, 6 H), 7.54-7.52 (m, 6H), 7.34-7.31 (m, 12H), 7.25-7.21 (m, 12H), 6.82 (dd, *J*= 7.5, 7.1 Hz, 1H), 6.72 (t, *J*=7.8 Hz, 2H), 5.78 (d, *J*= 8.0 Hz, 2H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 150.5.

(*R*)-Binol-derived monodentate phosphite I-62b



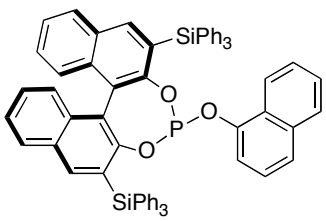
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.05 (s, 1H), 7.96 (s, 1H), 7.80-7.75 (dd, *J* = 7.7 Hz, 2H), 7.66–7.63 (m, 1H), 7.62-7.58 (m, 10H), 7.43-7.27 (m, 20H), 7.24-7.14 (m, 5H), 2.37-2.34 (d, *J* = 10.5Hz, 3H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 148.7.

(*R*)-Binol-derived monodentate phosphite I-62c



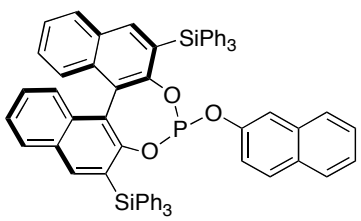
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.05 (s, 1H), 7.90 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.63–7.68 (m, 1H), 7.58 (dd, *J* = 8.0, 1,3 Hz, 6H), 7.52 (dd, *J* = 8.0, 1,3 Hz, 6H), 7.45–7.10 (m, 23H), 6.21 (d, *J*= 9.1, 2H), 5.68 (d, *J*= 8.7, 2H), 3.67 (s, 3H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 150.8.

(*R*)-Binol-derived monodentate phosphite I-62d



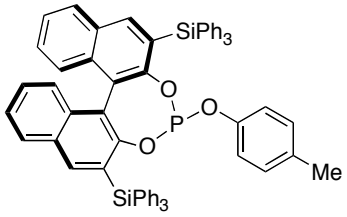
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.03 (s, 1H), 7.95 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.5 Hz, 6H), 7.45-7.28 (m, 14H), 7.20-7.08 (m, 13H), 7.00 (t, *J* = 7.7 Hz, 6H), 6.80 (dd, *J* = 15.4, 7.2 Hz, 2H), 5.76 (d, *J* = 7.5 Hz, 1H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 148.0.

(*R*)-Binol-derived monodentate phosphite I-62e



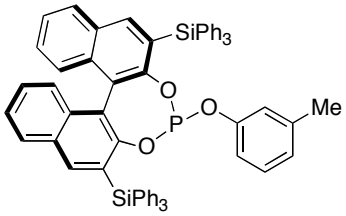
1H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.09 (s, 1H), 7.91 (s, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.71-7.63 (m, 2H), 7.60 (d, J = 6.7 Hz, 6H), 7.53 (d, J = 6.9 Hz, 6H), 7.42-7.13 (m, 26H), 7.03-7.00 (m, 1H), 6.19 (m, 1H), 5.94 (dd, J = 8.9, 2.3 Hz, 1H). $^{31}P\{^1H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 150.1.

(*R*)-Binol-derived monodentate phosphite I-62f



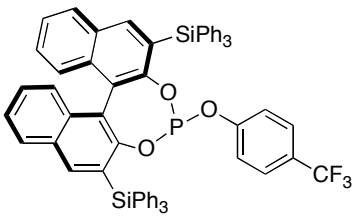
^1H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.06 (s, 1H), 7.90 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.57 (dd, *J* = 7.9, 1.2 Hz, 6H), 7.53 (dd, *J* = 7.8, 1.0 Hz, 6H), 7.42–7.37 (m, 2H), 7.36-7.29 (m, 8H), 7.26–7.19 (m, 14H), 6.49 (d, *J* = 8.4 Hz, 2H), 5.63 (d, *J* = 8.3 Hz, 2H), 2.15 (s, 3H). $^{31}P\{^1H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 150.8.

(*R*)-Binol-derived monodentate phosphite I-62g



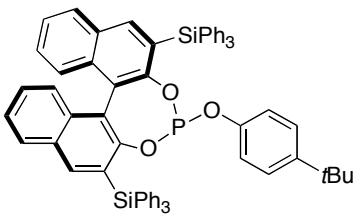
^1H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.06 (s, 1H), 7.90 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.68–7.65 (m, 1H), 7.58 (dd, *J* = 8.0, 1,3 Hz, 6H), 7.54 (dd, *J* = 8.0, 1,3 Hz, 6H), 7.43–7.38 (m, 2H), 7.37–7.28 (m, 10H), 7.24–7.19 (m, 11H), 6.62-6.56 (m, 2H), 5.59 (m, 2H), 1.90 (s, 3H). $^{31}P\{^1H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 150.8.

(*R*)-Binol-derived monodentate phosphite I-62h



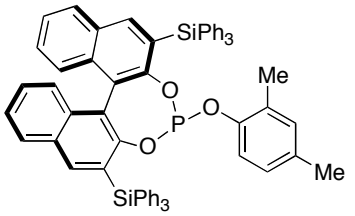
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.08 (s, 1H), 7.93 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.57 (dd, J = 8.1, 1.4 Hz, 6H), 7.52 (dd, J = 8.0, 1.3 Hz, 6H), 7.45-7.29 (m, 10H), 7.28-7.14 (m, 14H), 6.96 (d, J = 8.5 Hz, 2H), 5.83 (d, J = 8.7 Hz, 2H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 148.5.

(*R*)-Binol-derived monodentate phosphite I-62i



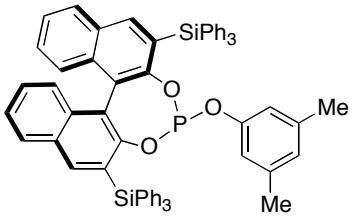
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.04 (s, 1H), 7.91 (s, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.57 (dd, J = 8.0, 1.3 Hz, 6H), 7.49 (dd, J = 7.9, 1.2 Hz, 6H), 7.42-7.29 (m, 12H), 7.24-7.19 (m, 12H), 6.68 (d, J = 8.7 Hz, 2H), 5.75 (d, J = 8.6 Hz, 2H), 1.21 (s, 9H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 150.4.

(*R*)-Binol-derived monodentate phosphite I-62j



^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.99 (s, 1H), 7.92 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 6.7 Hz, 6H), 7.43 (d, J = 6.9 Hz, 6H), 7.39–7.34 (m, 2H), 7.30–7.26 (m, 6H), 7.24-7.12 (m, 16H), 6.58 (s, 1H), 6.31 (d, J = 6.9 Hz, 1H), 5.55 (d, J = 8.1 Hz, 1H), 2.15 (s, 3H), 1.27 (s, 3H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 149.3.

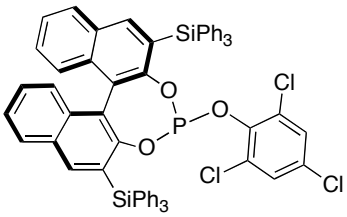
(*R*)-Binol-derived monodentate phosphite I-62k



^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.06 (s, 1H), 7.88 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.58 (dd, J = 7.9, 1.1 Hz, 6H), 7.55 (dd, J = 7.9, 1.0 Hz, 6H), 7.42-7.37 (m, 2H),

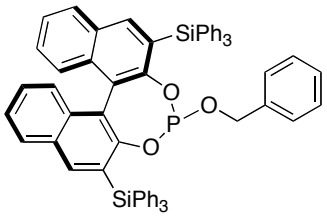
7.35-7.27 (m, 10H), 7.25-7.19 (m, 12H), 6.44 (s, 1H), 5.42 (s, 2H), 1.85 (s, 6H). $^{31}P\{^{1}H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 151.3.

(*R*)-Binol-derived monodentate phosphite I-62l



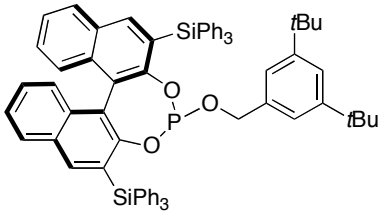
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.93 (s, 1H), 7.91 (s, 1H), 7.78 (d, J = 2.6 Hz, 1H), 7.76 (d, J = 2.5 Hz, 1H), 7.60–7.58 (m, 6H), 7.48–7.45 (m, 6H), 7.38–7.41 (m, 2H), 7.11–7.32 (m, 22H), 6.83 (s, 2H). $^{31}P\{^{1}H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 142.8.

(*R*)-Binol-derived monodentate phosphite I-62m



^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.06 (s, 1H), 7.93 (s, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.65–7.63 (m, 1H), 7.57–7.55 (m, 12H), 7.42–7.32 (m, 10H), 7.31–7.27 (m, 10H), 7.23–7.17 (m, 3H), 7.05 (t, J = 7.4 Hz, 1H), 6.88 (t, J = 7.6 Hz, 2H), 6.50 (d, J = 7.6 Hz, 2H), 3.60 (d, J = 8.5 Hz, 2H). $^{31}P\{^{1}H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 151.1.

(*R*)-Binol-derived monodentate phosphite I-62n

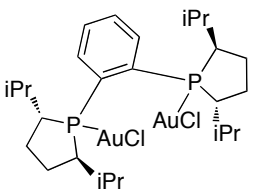


^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.04 (s, 1H), 7.97 (s, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.65-7.63 (m, 1H), 7.58 (dd, J = 8.0, 1.3 Hz, 6H), 7.51 (dd, J = 7.9, 1.2 Hz, 6H), 7.44-7.27 (m, 14H), 7.24–7.20 (m, 10H), 6.53 (d, J = 1.7 Hz, 2H), 3.87 (dd, J = 12.2, 6.6 Hz, 1H), 3.60 (dd, J = 12.1, 6.6 Hz, 1H), 1.18 (s, 18H). $^{31}P\{^{1}H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 147.2.

Synthesis of Chiral Au(I) Phosphite Complexes.

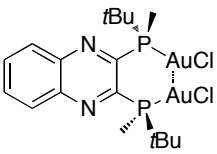
In a typical experiment, a solution of the desired ligand (46.3 µmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added dropwise to a suspension of $(Me)_2SAuCl$ (46.3 µmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C. The resulting clear solution was allowed to warm to room temperature and stirred for another 30 min. The solvent was removed to give the corresponding chiral Au(I) chloride phosphite complex as a white solid (46.3 µmol, quantitative).

(*R*,*R*)-DuPhOS-Au(I) chloride complex I-53



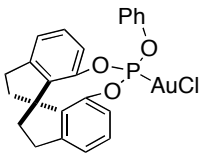
I-53 was synthesized using (*R*,*R*)-*i*Pr-DuPhos as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.89 (dtd, *J* = 8.7, 5.7, 3.4 Hz, 2H), 7.52-7.58 (m, 2H), 3.44 (tm, *J* = 9.1, 2.5 Hz, 2H), 2.60 (qd, *J* = 10.8, 5.6 Hz, 2H), 2.41-2.15 (m, 8H), 1.82 (qt, *J* = 13.2, 4.7 Hz, 2H), 1.65-1.55 (m, 2H), 1.15 (d, *J*= 6.7 Hz, 6H), 0.99 (d, *J*= 6.5 Hz, 6H), 0.81 (d, *J*= 6.7 Hz, 6H), 0.48 (d, *J*= 6.7 Hz, 6H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 40.6.

(*S*)-QUINOX-Au(I) chloride phosphite complex I-54



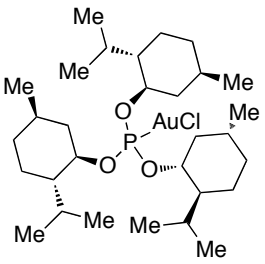
I-54 was synthesized using (*S*)-QuinoxP as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.21 (dd, *J* = 6.4, 3.4 Hz, 2H), 8.02 (dd, *J* = 6.5, 3.3 Hz, 2H), 2.2 (d, *J* =8.5 Hz, 6H), 1.43 (d, *J* = 17.3Hz, 18H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 32.2.

(*R*)-Ship Au(I) chloride phosphite complex I-55



I-55 was synthesized using (*S*)-ShiP as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.44 (t, *J* = 7.8 Hz, 2H), 7.36-7.28 (m, 2H), 7.25-7.22 (m, 4H), 7.19 (d, *J* = 8.1 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 2H), 3.24-3.01 (m, 2H), 2.95 (td, *J* = 15.9, 7.8 Hz, 2H), 2.35 (ddd, *J* = 11.8, 6.5, 4.3 Hz, 2H), 2.14-2.03 (m, 2H).

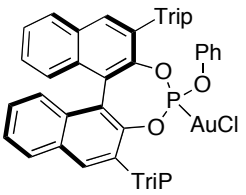
(-)-Menthol-derived Au(I) chloride phosphite complex I-56



I-56 was synthesized using phosphite **I-68** as a ligand.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.31-4.23 (m, 3H), 2.22-2.16 (m, 3H), 2.13 (qt, *J* = 7.0, 2.0 Hz, 3H), 1.70 (brs, 6H), 1.67 (brs, 3H), 1.45-1.35 (m, 6H), 1.18 (td, *J*=12.3, 11.0 Hz, 3H), 1.03 (qd, *J* = 13.1, 3.2 Hz, 3H), 0.93 (dd, *J* = 6.8, 2.9 Hz, 18H), 0.86 (d, *J* = 7.0 Hz, 9H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 116.4.

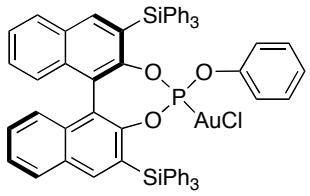
Au(I) chloride phosphite complex I-57



I-57 was synthesized using phosphite **I-70** as a ligand.

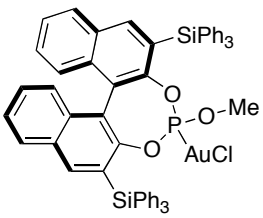
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.0 (d, *J* = 24.7 Hz, 2H), 7.97 (dd, *J* =14.5, 8.2 Hz, 2H), 7.59 (ddd, *J*= 8.0, 6.2, 1.8 Hz, 1H), 7.54 (ddd, *J*= 8.1, 6.8, 1.3 Hz, 1H), 7.42-7.37 (m, 3H), 7.33-7.26 (m, 2H), 7.21-7.19 (m, 1H), 7.16-7.14 (m, 1H), 7.08 (dd, *J* = 10.6, 1.6 Hz, 2H), 7.04-7.00 (m, 2H), 6.17 (dt, *J* = 7.2, 1.4 Hz, 2H), 2.99 (m, *J* = 6.8 Hz, 2H), 2.84 (m, *J* = 6.8 Hz, 2H), 2.61 (m, *J* = 6.8 Hz, 2H), 1.38 (d, *J* = 6.9 Hz, 6H), 1.32 (d, *J* = 6.8 Hz, 24H), 1.20 (d, *J* = 6.8 Hz, 6H). ^{31}P{^{1}H}-NMR (162 MHz, CD_2Cl_2): δ (ppm) = 123.9.

Au(I) chloride phosphite complex I-58a



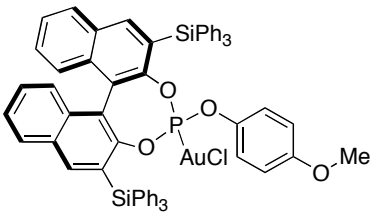
I-58a was synthesized using phosphite **I-62a** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = δ 8.18 (s, 1H), 8.08 (s, 1H), 7.89 (d, *J*= 8.3 Hz, 1H), 7.83 (d, *J*= 8.3 Hz, 1H), 7.59-7.56 (m, 6H), 7.51-7.48 (m, 6H), 7.39-7.30 (m, 12H), 7.26-7.22 (m, 12H), 7.03 (t, *J*= 7.7 Hz, 1H), 6.90 (t, *J*=7.7 Hz, 2H), 6.05 (d, *J*=8.2 Hz, 2H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 123.7.

Au(I) chloride phosphite complex I-58b



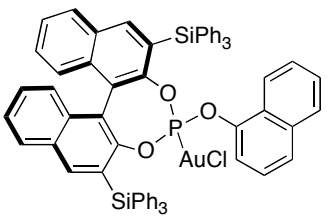
I-58b was synthesized using phosphite **I-62b** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.14 (s, 1H), 8.13 (s, 1H), 7.84 (s, 1H), 7.82 (s, 1H), 7.64-7.59 (m, 12H), 7.49-7.33 (m, 24H), 2.53 (d, J = 15.6 Hz, 3H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 130.5.

Au(I) chloride phosphite complex I-58c



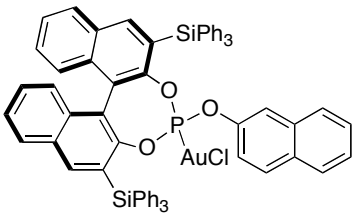
I-58c was synthesized using phosphite **I-62c** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.17 (s, 1H), 8.07 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.68-7.65 (m, 1H), 7.59-7.57 (m, 6H), 7.51-7.49 (m, 6H), 7.39-7.15 (m, 23H), 6.37 (d, J = 9.1 Hz, 2H), 5.93 (dd, J = 9.0, 1.4 Hz, 2H), 3.73 (s, 3H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 124.2.

Au(I) chloride phosphite complex I-58d



I-58d was synthesized using phosphite **I-62d** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.17 (s, 1H), 8.10 (s, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.57-7.47 (m, 3H), 7.52 (dd, J = 8.0, 1.4 Hz, 6H), 7.45-7.31 (m, 4H), 7.36 (dd, J = 8.1, 1.3 Hz, 6H), 7.28 (s, 1H), 7.25-7.21 (m, 3H), 7.18-7.06 (m, 10 H), 7.01-6.91 (m, 8 H), 6.25 (d, J = 8.6 Hz, 1H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 123.4

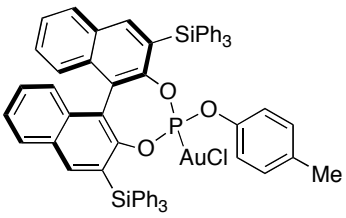
Au(I) chloride phosphite complex I-58e



I-58e was synthesized using phosphite **I-62e** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.16 (s, 1H), 8.08 (s, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.83

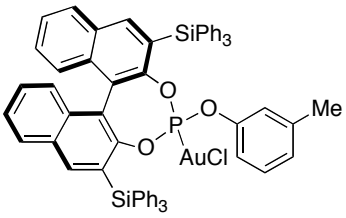
(d, J = 8.1 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.56-7.53 (m, 6H), 7.48-7.45 (m, 6H), 7.44-7.27 (m, 16H), 7.25-7.23 (m, 4H), 7.15-7.11 (m, 8H), 6.43 (t, J = 1.9 Hz, 1H), 6.22 (ddd, J = 8.9, 2.4, 0.8 Hz, 1H). $^{31}P\{^{1}H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 122.8.

Au(I) chloride phosphite complex I-58f



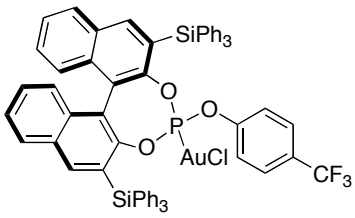
I-58f was synthesized using phosphite **I-62f** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.17 (s, 1H), 8.07 (s, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.57 (dd, J = 8.0, 1.4 Hz, 6H), 7.50 (dd, J = 8.0, 1.3 Hz, 6H), 7.50-7.45 (m, 2H), 7.40-7.28 (m, 15H), 7.25-7.18 (m, 7H), 6.67 (d, J = 8.6 Hz, 2H), 5.89 (dd, J = 8.5, 1.4 Hz, 2H), 2.24 (s, 3H). $^{31}P\{^{1}H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 123.8.

Au(I) chloride phosphite complex I-58g



I-58g was synthesized using phosphite **I-62g** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.16 (s, 1H), 8.08 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.68–7.65 (m, 1H), 7.56 (dd, J = 8.0, 1.4 Hz, 6H), 7.51 (dd, J = 8.0, 1.2 Hz, 6H), 7.48–7.27 (m, 16H), 7.25–7.21 (m, 7H), 6.82 (d, J = 7.4 Hz, 1H), 6.77 (t, J = 7.8 Hz, 1H), 5.87 (d, J = 7.8 Hz, 1H), 5.83 (s, 1H), 1.99 (s, 3H). $^{31}P\{^{1}H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 123.1.

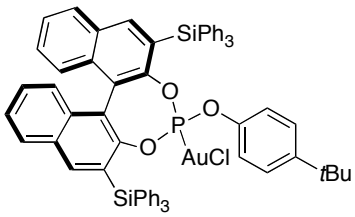
Au(I) chloride phosphite complex I-58h



I-58h was synthesized using phosphite **I-62h** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.18 (s, 1H), 8.08 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.57-7.55 (m, 6H), 7.52-7.47 (m, 8H), 7.39–7.28 (m, 15H), 7.25–7.20 (m, 7H), 7.14

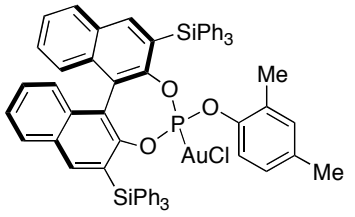
(d, J = 8.7 Hz, 2H), 6.11 (d, J = 8.5 Hz, 2H). $^{31}P\{^{1}H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 123.3.

Au(I) chloride phosphite complex I-58i



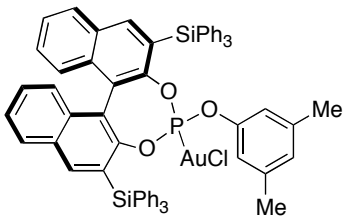
I-58i was synthesized using phosphite **I-62i** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.16 (s, 1H), 8.09 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.59-7.54 (m, 6H), 7.53-7.44 (m, 8H), 7.40–7.26 (m, 15H), 7.24-7.19 (m, 7H), 6.88 (d, J = 8.7 Hz, 2H), 6.03 (d, J = 8.5 Hz, 2H), 1.27 (s, 9H). $^{31}P\{^{1}H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 123.8.

Au(I) chloride phosphite complex I-58j



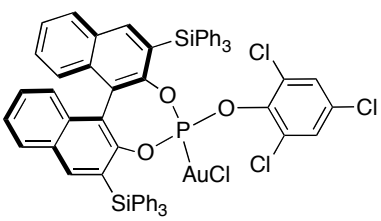
I-58j was synthesized using phosphite **I-62j** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.15 (s, 1H), 8.09 (s, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.59-7.42 (m, 14H), 7.40-7.20 (m, 16H), 7.19–7.13 (m, 6H), 6.70 (bs, 1H), 6.48 (dd, J = 8.6, 1.9 Hz, 1H), 6.00 (d, J = 8.2 Hz, 1H), 2.23 (s, 3H), 1.37 (s, 3H). $^{31}P\{^{1}H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 123.2.

Au(I) chloride phosphite complex I-58k



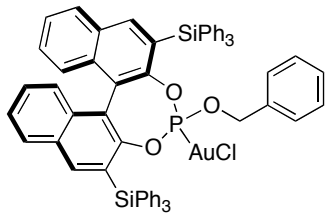
I-58k was synthesized using phosphite **I-62k** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.14 (s, 1H), 8.07 (s, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.58-7.45 (m, 14H), 7.40-7.19 (m, 22H), 6.63 (bs, 1H), 5.68 (bs, 2H), 1.94 (s, 6H). $^{31}P\{^{1}H\}$-NMR (162 MHz, $CDCl_3$): δ (ppm) = 122.6.

Au(I) chloride phosphite complex I-58l



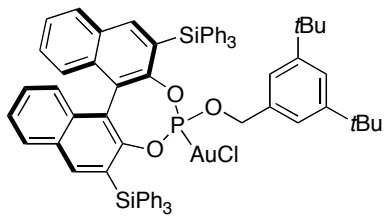
I-58l was synthesized using phosphite **I-62l** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.18 (s, 1H), 8.03 (s, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.64 (dd, J = 7.9, 1.4 Hz, 6H), 7.53-7.47 (m, 2H), 7.45 (dd, J = 8.0, 1.2 Hz, 6H), 7.39-7.14 (m, 22H), 6.89 (s, 2H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 124.1.

Au(I) chloride phosphite complex I-58m



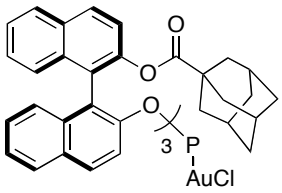
I-58m was synthesized using phosphite **I-62m** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.13 (d, J = 5.8 Hz, 2H), 7.86 (d, J = 7.7 Hz, 1H), 7.84 (d, J = 7.7 Hz, 1H), 7.66-7.63 (m, 1H), 7.60 (dd, J = 8.0, 1.3 Hz, 6H), 7.49 (dd, J = 8.0, 1.3 Hz, 8H), 7.41-7.32 (m, 10H), 7.29 (dd, J = 7.6, 2.4 Hz, 10H), 7.25-7.18 (m, 2H), 7.14 (t, J = 7.5 Hz, 2H), 6.68 (d, J = 7.2 Hz, 2H), 3.94 (dd, J = 11.8, 9.0 Hz, 1H), 3.70 (dd, J = 11.9, 7.5 Hz, 1H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 126.8.

Au(I) chloride phosphite complex I-58n



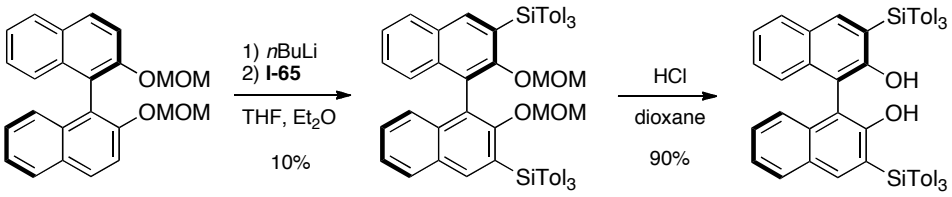
I-58n was synthesized using phosphite **I-62n** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.13 (d, J = 6.2 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 7.67-7.64 (m, 1H), 7.59 (dd, J = 8.0, 1.3 Hz, 6H), 7.48 (dd, J = 8.0, 1.3 Hz, 6H), 7.52-7.45 (m, 2H), 7.39-7.31 (m, 11H), 7.30-7.26 (m, 5H), 7.25-7.18 (m, 6H), 6.61 (d, J = 1.8 Hz, 2H), 3.93 (dd, J = 11.3, 8.4 Hz, 1H), 3.78 (dd, J = 11.4, 6.9 Hz, 1H), 1.20 (s, 18H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 125.6.

Au(I) chloride phosphite complex I-63



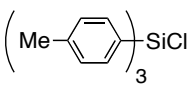
I-63 was synthesized using phosphite **I-69** as a ligand. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.01 (d, J = 8.9 Hz, 3H), 7.88 (d, J = 8.2 Hz, 3H), 7.75 (d, J = 8.2 Hz, 3H), 7.43-7.37 (m, 9H), 7.25-7.18 (m, 6H), 7.15 (d, J = 9.0 Hz, 3H), 6.98 (dd, J = 8.5, 1.6 Hz, 6H), 6.36 (d, J = 9.0 Hz, 3H), 1.76 (m, 9H), 1.57-1.56 (m, 12H), 1.44-1.41 (m, 9H), 1.28 (brs, 15H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 112.0.

Au(I) chloride phosphite complex I-64



I-59 **I-66** **I-67**

Tritolylsilyl chloride I-65



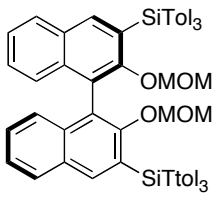
To a stirred solution of TCCA (1.4 g, 6.1 mmol) in CH_2Cl_2, (*para*-tolyl)$_3$SiH[54] (5.02 g, 16.6 mmol) was added dropwise at a rate to maintain a steady reflux of the solvent. After the addition was over, the mixture was heated at reflux and monitored by GC-MS until the reaction was completed. The mixture was filtered off over celite and solvents were removed under reduced pressure to yield **I-65** as a white solid used directly in the next step without purification.

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.52 (d, J = 8.0 Hz, 6H), 7.21 (dd, J = 8.1, 0.5 Hz, 6H), 2.37 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ (ppm) = 141.4 (C), 135.9 (CH),

54. Prince, P. D.; Bearpark, M. J.; McGrady, G. S.; Steed, J. W. *Dalton Trans.* **2008**, 271-282.

130.4 (C), 129.5 (CH), 22.3 (CH_3).

(*R*)-2-(methoxymethoxy)-1-(2-(methoxymethoxy)-3-(tritolylsilyl)naphthalen-1-yl)-3-(triphenylsilyl)naphthalene I-66



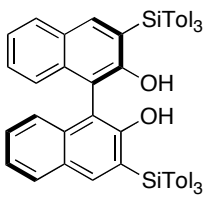
MOM protected (*R*)-BINOL **I-59** can be purchased directly or synthesized in quantitative yield following the procedure described by Kobayashi.[59] Following a reported procedure,[49] **I-59** (1.0 g, 2.6 mmol) was dissolved in Et_2O (50 mL) followed by dropwise addition of *n*BuLi (2.5 M in hexane, 2.9 mL, 7.2 mmol) over 10 min at room temperature. The resulting suspension was stirred at room temperature for 2 h. The mixture was cooled to 0 ˚C and THF (20 mL) was added. After a further 20 min at 0 ˚C a solution of **I-65** (2.249 g, 6.675 mmol) in THF (10 mL) was added. The reaction mixture was warmed to room temperature and stirred for 48 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$ and solvents were evaporated under reduced pressure to yield the crude product as viscous yellow oil. The product was purified by silica flash column chromatography (40:1 to 20:1 hexanes/EtOAc) to yield product **I-66** as a white solid (160 mg, 12.2% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.89 (s, 2H), 7.71-7.68 (m, 2H), 7.58 (d, J = 7.9 Hz, 12H), 7.36–7.29 (m, 6H), 7.16 (d, J = 7.6 Hz, 12H), 3.82 (d, J = 5.1 Hz, 2H), 3.75 (d, J = 5.1 Hz, 2H), 2.37 (s, 18H), 2.26 (s, 6H).

59. Kobayashi, S.; Kusakabe, K.-i.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220-4221.

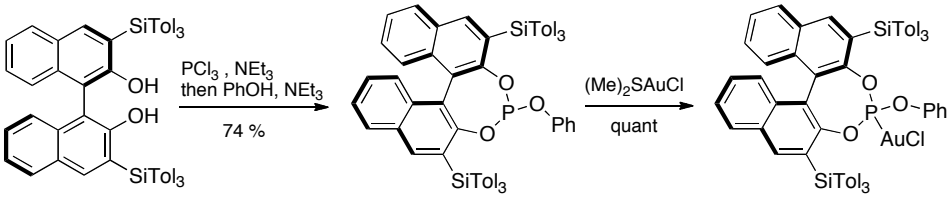
49. Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *128*, 84-86.

(*R*)-1-(2-hydroxy-3-(triphenylsilyl)naphthalen-1-yl)-3-(triphenylsilyl)naphthalen-2-ol I-67



Concentrated HCl (0.05 mL) was added to a solution of MOM protected binol **I-66** (319 mg, 0,327 mmol) in dioxane (3.5 mL). The resulting solution was heated to 70 ˚C for 24 h. The reaction mixture was cooled to room temperature and quenched by addition of a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted twice with EtOAc and washed with water, then brine. The combined organics were dried over Na_2SO_4, filtered and concentrated to yield the crude product **I-67** as a white brownish solid directly used in the next step (300 mg, > 99% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.95-7.87 (m, 2H), 7.74-7.68 (m, 2H), 7.57 (d, J = 7.9 Hz, 4H), 7.53 (d, J = 7.9 Hz, 8H), 7.37–7.22 (m, 6H), 7.17 (d, J = 7.7 Hz, 12H), 2.37 (s, 18H).



I-67 **I-71** **I-64**

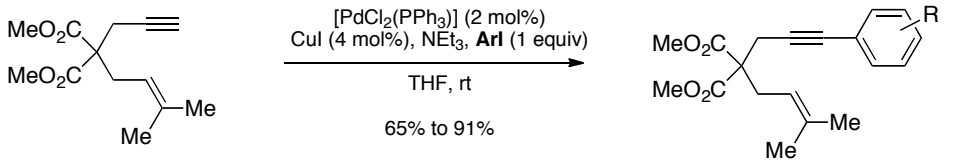
Phosphite **I-71** was prepared from **I-67** according to the general procedure. The residue was purified by flash column chromatography on silica gel (toluene, Ar) to give **I-71** as white powder that was directly used in the next step (93 mg, 74% yield).

Au(I) chloride phosphite complex I-64

Following the general procedure**,** phosphite **I-71** (59 mg, 58 µmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a suspension of $(Me)_2SAuCl$ (18.0 mg, 64.0 µmol) in CH_2Cl_2 (0.5 mL) at 0 °C. The resulting clear solution was allowed to warm to room temperature and stirred for another 30 min. The solvent was evaporated to give the chiral Au(I) phosphite complex **I-64** as a white solid (69 mg, 96% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.17 (s, 1H), 8.08 (s, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.55-7.50 (m, 2H), 7.46 (d, J = 7.9 Hz, 6H), 7.38 (d, J = 7.9 Hz, 6H), 7.35-7.29 (m, 2H), 7.17-.13 (m, 3H), 7.09 (d, J = 7.6 Hz, 6H), 7.03 (d, J = 7.6 Hz, 6H), 6.90 (t, J = 7.9 Hz, 2H), 6.04 (d, J = 8.6 Hz, 2H), 2.29 (s, 18H). ^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$): δ (ppm) = 123.6.

Synthesis of substituted aryl enynes

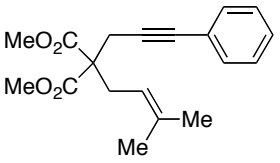


I-72 **I-13**

In a typical procedure, NEt_3 (0.85 mL, 8.4 mmol) was added dropwise to a mixture of the appropriate aryl **ArI** (2.73 mmol), $[PdCl_2(PPh_3)_2]$ (29.5 mg, 42.0 µmol), CuI (16.0 mg, 84.0 µmol) in THF (4 mL) at room temperature. A solution of dimethyl 2-(3-methylbut-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate[60] (**I-72**) (500 mg, 2.10 mmol) in THF (1 mL) was added and the whole was stirred at room temperature until complete conversion. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution and the aqueous phase was extracted twice with Et_2O. The combined organic fractions were dried over Na_2SO_4 and concentrated in *vacuo*. Chromatographic purification of the crude material (hexanes/Et_2O) provided the desired aryl-susbtituted enyne **I-13** (65% to 91% yield).

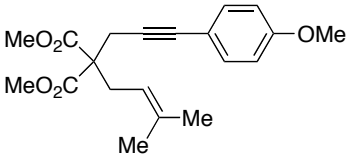
60. Muñoz, M.; Méndez, M.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Synthesis* **2003**, 2898-2902.

2-(3-Methyl-but-2-enyl)-2-(3-phenyl-prop-2-ynyl)-malonic acid dimethyl ester I-13a



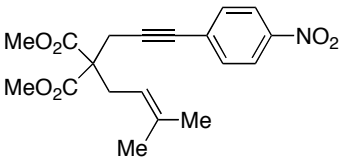
I-13a was synthesized according to the general procedure using iodobenzene (557 mg, 2.73 mmol). Obtained as a clear oil after purification (585 mg, 89% yield). Analytical data are in agreement with those reported.[36,37]

2-[3-(4-Methoxy-phenyl)-prop-2-ynyl]-2-(3-methyl-but-2-enyl)-malonic acid dimethyl ester I-13b



I-13b was synthesized according to the general procedure using 4-methoxy-iodobenzene (638 mg, 2.73 mmol). Obtained as a clear oil after purification (470 mg, 65% yield). Analytical data are in agreement with those reported.[36,37]

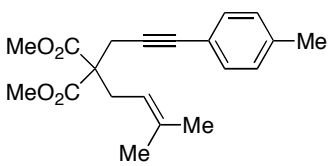
2-(3-Methyl-but-2-enyl)-2-[3-(4-nitro-phenyl)-prop-2-ynyl]-malonic acid dimethyl ester I-13d



I-13d was synthesized according to the general procedure using 4-nitro-iodobenzene (523 mg, 2.10 mmol). Obtained as a clear oil after purification (691 mg, 91% yield). Analytical data are in agreement with those reported.[37]

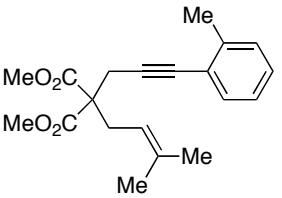
36. Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178-6179.
37. Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *130*, 269-279.

Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(3-(p-tolyl)prop-2-yn-1-yl)malonate I-13j



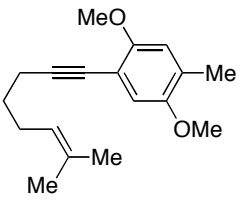
I-13j was synthesized according to the general procedure using 4-methyl-iodobenzene (595 mg, 2.73 mmol). Obtained as a clear oil after purification (475 mg, 69% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.25 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 7.9 Hz, 2H), 4.95 (t, J = 7.7 Hz, 1H), 3.74 (s, 6H), 2.98 (s, 2H), 2.84 (d, J = 7.7 Hz, 2H), 2.33 (s, 3H), 1.71 (s, 3H), 1.67 (s, 3H).

2-(3-Methyl-but-2-enyl)-2-(3-*o*-tolyl-prop-2-ynyl)-malonic acid dimethyl ester I-13k



I-13k was synthesized according to the general procedure using 2-methyl-iodobenzene (595 mg, 2.73 mmol). Obtained as a clear oil after purification (493 mg, 72% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.33 (d, J = 7.5 Hz, 1H), 7.20-7.06 (m, 3H), 4.97 (t, J = 7.7 Hz, 1H), 3.75 (s, 6H), 3.05 (s, 2H), 2.85 (d, J = 7.7 Hz, 2H), 2.37 (s, 3H), 1.72 (s, 3H), 1.66 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ (ppm) = 171.3 (CO), 140.7 (C), 137.5 (C), 132.7 (CH), 130.0 (CH), 128.6 (CH), 126.1 (CH), 123.7 (C), 117.8 (CH), 89.2 (C), 82.8 (C), 58.2 (C), 53.3 (CH_3), 31.6 (CH_2), 26.8 (CH_2), 24.3 (CH_3), 21.4 (CH_3), 18.7 (CH_3).

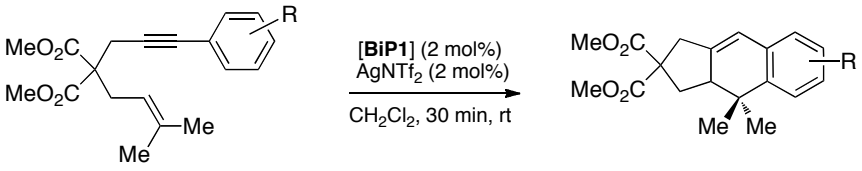
1,4-Dimethoxy-2-methyl-5-(7-methyloct-6-en-1-yn-1-yl)benzene I-13l



I-13l was synthesized according to the general procedure using 4-bromo-2,5-dimethoxytoluene (630 mg, 2.73 mmol). Obtained as a yellow oil after purification (400 mg, 70% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.73 (d, J = 3.1 Hz, 1H), 6.65 (d, J = 3.0 Hz, 1H), 5.14 (t, J = 7.2 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 2.45 (t, J = 7.1 Hz, 2H), 2.23 (s, 3H), 2.16 (q, J = 7.3 Hz, 2H), 1.70 (s, 3H), 1.63 (s, 3H), 1.68-1.63 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 155.6 (C), 154.1 (C), 133.1 (C), 132.8 (C), 124.3 (CH), 118.6 (C), 117.5 (CH), 115.5 (CH), 94.9 (C), 77.6 (C),

61.2 (CH_3), 56.2 (CH_3), 29.6 (CH_2), 27.9 (CH_2), 26.4 (CH_2), 19.8 (CH_3), 18.4 (CH_3), 17.0 (CH_3).

Gold-Catalyzed [4+2] Cycloaddition: Synthesis of the Racemic Substrates

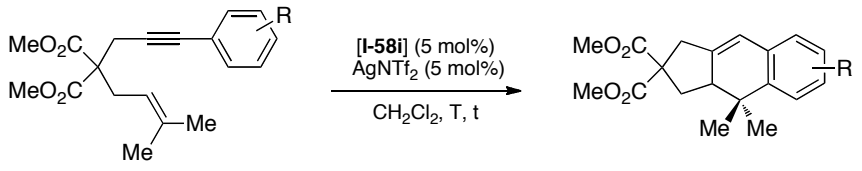


I-13 **I-14**

Racemic cycloadducts **I-14** were synthesized from **I-13** using the following procedure:

To a solution of aryl enyne **I-13** (1 equiv) in CH_2Cl_2 (0.1 M), **BiP1** (0.02 equiv) was added in one portion at room temperature. The mixture was stirred for 30 min and the reaction was stopped by adding a few drop of a solution of NEt_3 in hexane (0.1 M). The solids were removed by filtration over silica. Evaporation of the solvent and chromatographic purification on silica (hexanes/EtOAc) provided the title compound in quantitative yield.

Enantioselective Gold-Catalyzed [4+2] Cycloaddition

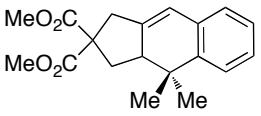


I-13 **I-14**

In a typical experiment, chiral gold(I) complex **I-58i** (5 mol%) and $AgNTf_2$ (5 mol%) were weighed in a glove box. CH_2Cl_2 (0.008 M) was added and the resulting solution was stirred for 10 min at 0 °C and further 10 min at room temperature. The obtained

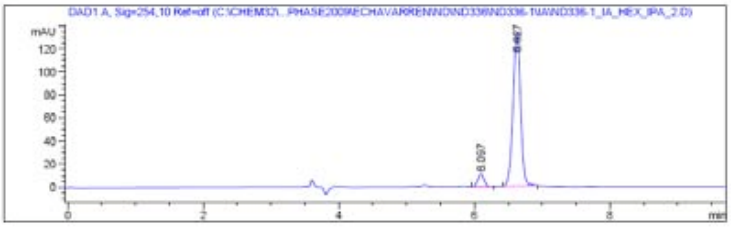
catalyst solution was cooled to the indicated temperature followed by dropwise addition of a solution of the desired enyne **I-13** (1.0 equiv) in CH_2Cl_2 (0.2 M) over 10 min. After complete addition, stirring was continued at the indicated temperature until the starting material was consumed. After quenching with a solution of NEt_3 in hexane (0.1 M), the solids were removed by filtration over silica. Evaporation of the solvent and chromatographic purification on silica (hexanes/EtOAc) provided the title compound **I-14**. Enantiomeric excess was determined by chiral HPLC.

Dimethyl 4,4-dimethyl-3a,4-dihydro-1*H*-cyclopenta[*b*]naphthalene-2,2(3*H*)-dicarboxylate I-14a



I-14a was synthesized from **I-13a** according to the general procedure after stirring at -20 ºC for 18 h (126 mg, 98% yield). Analytical data are in agreement with those reported.[36] $[\alpha]_D^{20}$ = -25.0 ± 2.0 (*c* = 0.1065, $CHCl_3$). Enantiomeric excess: 88% *ee* (Chiralpak IA 250x4.6mm, 5µm, Hex/IPA 98:2, 1 mL/min).

Sample Info : Chiralpak IA250x4.6mm, 5µm
HEX / IPA 98:2
1 mL/min
2mg/mL (DCM)



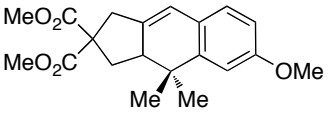
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,10 Ref=off

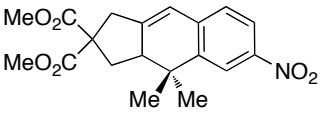
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.097	BB	0.0996	69.22163	10.60395	6.2756
2	6.627	BB	0.1186	1033.80090	133.07730	93.7244
Totals :				1103.02253	143.76125	

Dimethyl 6-methoxy-4,4-dimethyl-3a,4-dihydro-1*H*-cyclopenta[*b*]naphthalene-2,2(3*H*)-dicarboxylate I-14b



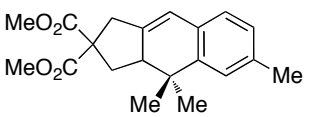
I-14b was synthesized from **I-13b** according to the general procedure after stirring at -20 ºC for 30 h (120 mg, 85% yield). Analytical data are in agreement with those reported.[37] Enantiomeric excess: 86% *ee* (Chiralpak IC 250x4.6mm, 5µm, Hex/THF 98:2, 1 mL/min).

Dimethyl 4,4-dimethyl-6-nitro-3a,4-dihydro-1*H*-cyclopenta[*b*]naphthalene-2,2(3*H*)-dicarboxylate I-14d



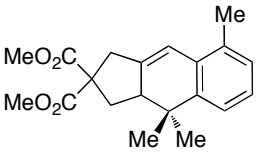
I-14d was synthesized from **I-13d** according to the general procedure after stirring at 0 ºC for 15 h (118 mg, 80% yield). Analytical data are in agreement with those reported.[37] Enantiomeric excess: 73% *ee* (Chiralpak IB 250x4.6mm, 5µm, Hex/IPA 96:4, 1 mL/min).

Dimethyl 4,4,6-trimethyl-3a,4-dihydro-1*H*-cyclopenta[*b*]naphthalene-2,2(3*H*)-dicarboxylate I-13j



I-14j was synthesized from **I-13j** according to the general procedure after stirring at -20 ºC for 15 h (134 mg, 98% yield). Analytical data are in agreement with those reported. Enantiomeric excess: 87% *ee* (Chiralpak IC 250x4.6mm, 5µm, Hex/IPA 99:1, 1 mL/min).

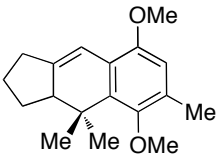
Dimethyl 4,4,8-trimethyl-3a,4-dihydro-1*H*-cyclopenta[*b*]naphthalene-2,2(3*H*)-dicarboxylate I-14k



I-14k was synthesized from **I-13k** according to the general procedure after stirring at -20 ºC for 30 h (93 mg, 70% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.15 (d, J = 7.6 Hz,

1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 6.57-6.54 (m, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.32 (d, *J* = 19.2 Hz, 1H), 3.01 (dt, *J* = 17.9, 3 Hz, 1H), 2.70-2.55 (m, 2H), 2.32 (s, 3H), 2.14 (t, *J* = 12 Hz, 1H), 1.40 (s, 3H), 0.91 (s, 3H). Enantiomeric excess: 79% *ee* (Chiralpak IC 250x4.6mm, 5µm, Hex/IPA 99:1, 1 mL/min).

5,8-Dimethoxy 4,4,6-trimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*b*]naphthalene I-14l



I-14l was synthesized from **I-13l** according to the general procedure after stirring at 0 ºC for 48 h (52 mg, 62% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.54 (s, 1H), 6.52 (dd, *J* = 4.8, 2.3 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 2.64-2.59 (m, 1H), 2.53-2.48 (m, 1H), 2.43-2.35 (m, 1H), 2.25 (s, 3H), 1.95-1.82 (m, 2H), 1.60 (s, 3H), 1.57-1.53 (m, 2H), 0.93 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ (ppm) = 155.0 (C), 148.8 (C), 148.1 (C), 131.4 (C), 130.3 (C), 129.4 (C), 113.5 (CH), 112.7 (CH), 61.6 (CH), 56.5 (CH_3), 52.2 (CH_3), 38.4 (CH_2), 33.0 (CH_2), 28.4 (CH_2), 27.7 (C), 25.5 (CH_3), 20.1 (CH_3), 16.6 (CH_3). Enantiomeric excess: 17% *ee* (Chiralpak IC 250x4.6mm, 5µm, Hex/THF 99:1, 0.5 mL/min).

II. Total Synthesis of Englerin A and B

A. Introduction

1. Isolation and Characterization

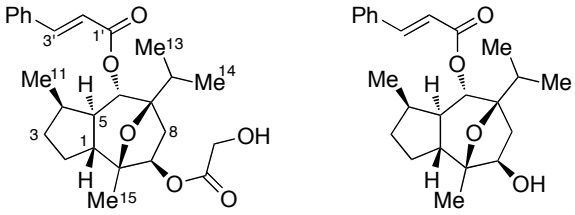
Kidney cancer affects an estimated 63000 individuals in Europe yearly and is a major cause of morbidity and mortality in adults.[61] Currently approved drugs such as bevacizumab, sunitinib and sorafenib offer benefit to patients with metastatic renal cancer but do not produce complete responses, require long-term administration for continued disease control, and have serious adverse side effects.[62] Thus, the search for new agents, which display specific activity against renal cancers, is of great interest.

An extensive study to identify natural product extracts that exhibited a preferential selectivity toward renal tumor cells was carried out in 2008.[63] The extract of *Phyllanthus engleri* was chosen because of its excellent selectivity and potency, relative to others extracts, against the renal panel (Figure 15).

Figure 15. *Phyllanthus engleri.*

61. Ferlay, J.; Autier, P.; Boniol, M.; Heanue, M.; Colombet, M.; Boyle, P. *Ann. Oncol.* **2007,** *18*, 581-592.
62. Atkins, M. B.; Ernstoff, M. S.; Figlin, R. A.; Flaherty, K. T.; George, D. J.; Kaelin, W. G.; Kwon, E. D.; Libermann, T. A.; Linehan, W. M.; McDermott, D. F.; Ochoa, A. C.; Pantuck, A. J.; Rini, B. I.; Rosen, M. A.; Sosman, J. A.; Sukhatme, V. P.; Vieweg, J. W.; Wood, C. G.; King, L. *Clin. Cancer Res.* **2007,** *13*, 667s-670s.
63. Ratnayake, R.; Covell, D.; Ransom, T. T.; Gustafson, K. R.; Beutler, J. A. *Org. Lett.* **2008,** *11*, 57-60.

This plant is found in East Africa, particularly in Tanzania and Zimbabwe, and has not been subjected to chemical study in recent years. Two new guaiane-type sesquiterpernes (terpenes that consist of three isoprene units), englerins A **II-1** and B **II-2** (Figure 16) were isolated from the stem bark of *Phyllanthus engleri*.



(-)-englerin A (-)-englerin B

Figure 16. (-)-Englerin A **II-1** and (-)-englerin B **II-2**.

These two compounds were fully characterized by mass spectrometry and NMR studies, but only the relative configuration was assigned.

2. Biological Activity

(-)-Englerin A **II-1** demonstrated excellent selectivity for the renal cancer cell line panel, with 5 of 8 renal lines having GI_{50} values below 20 nM (GI_{50} refers to the concentration required to reach 50% of growth inhibition). The low activity and selectivity of the structural analogue englerin B **II-2** suggests that substitution at the C9 position by the glycolate ester may be important for the observed potency and selectivity (Figure 16). It is well-known that glycolic acid, an important metabolite of ethylene glycol, causes acute renal toxicity in mammals,[64] but this fragment alone cannot account for the renal selectivity of **II-1** considering the low activity of other natural products containing a similar glycolate moiety.[65] In addition, structure-activity relationship studies of a series of synthetic analogues support the importance of the glycolic acid residue at the C9 position.[66,67,68]

3. Reported Syntheses

The design of competitive methodologies for chemical synthesis is often driven by natural products with unique structure or highly specific biological activity. In this regard, englerin A **II-1** has attracted considerable attention from the community of synthetic chemists because of the selective and low nanomolar inhibitory activity

64. (a) Carney, E. W.; Freshour, N. L.; Dittenber, D. A.; Dryzga, M. D. *Toxicol. Sci.* **1999,** *50*, 117-126. (b) Bove, K. E. *Amer. J. Clin. Pathol.* **1966**, 45, 46.
65. Paull, K. D.; Shoemaker, R. H.; Hodes, L.; Monks, A.; Scudiero, D. A.; Rubinstein, L.; Plowman, J.; Boyd, M. R. *J. Natl. Cancer Inst.* **1989,** *81*, 1088-1092.
66. Chan, K. P.; Chen, D. Y. K. *ChemMedChem* **2011**, *6*, 420-423.
67. Nicolaou, K. C.; Kang, Q.; Ng, S. Y.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2010,** *132*, 8219-8222.
68. Radtke, L.; Willot, M.; Sun, H.; Ziegler, S.; Sauerland, S.; Strohmann, C.; Fröhlich, R.; Habenberger, P.; Waldmann, H.; Christmann, M. *Angew. Chem. Int. Ed.* **2011**, DOI: 10.1002/anie.201007790.

mentioned above, as well as its challenging structure which features seven contiguous stereocenters, including two quaternary centers (Figure 16).[69]

In the following section are reported the syntheses of englerin A published to date by other research groups. The synthesis we achieved in our laboratory[70] will be discussed along with the one made by Ma and co-workers[71] in the next chapter. Both syntheses relied on the same approach and they were published as back-to-back papers in 2010.

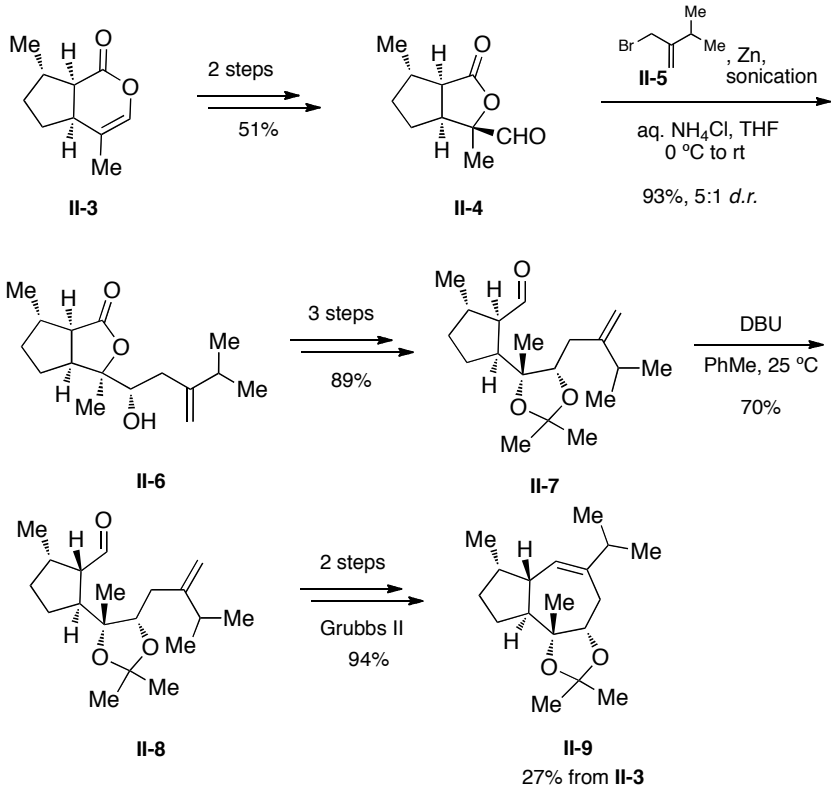
a) Biomimetic Approach- First Synthesis of Englerin A.

Less than a year after the isolation of (-)-englerin A and B by Beutler and co-workers, the first total synthesis of the (+)-englerin A (**II-12**) was completed, thereby establishing the previously unknown absolute configuration of the natural product.[72]

The synthesis started with an epoxylactone rearrangement to afford **II-4** in two steps and an overall yield of 51% from the monoterpene *cis,trans*-nepetalactone **II-3** (Scheme 17). Despite the necessity of a late stage epimerization at the α-position to the ester, this compound, commercially available in diastereomerically pure form, gave the desired epoxylactone with the best yield. Treatment of **II-4** with the allyl bromide **II-5** in a Barbier-type reaction with zinc gave the desired homoallylic alcohol **II-6** in 93% yield and a 5:1 *d.r.*. Reduction of **II-6** into the corresponding triol and acetalization of the vicinal hydroxyl group were followed by IBX oxidation of the primary alcohol to give aldehyde **II-7** in three steps and 89% overall yield. The desired epimer **II-8** was smoothly obtained in 70% yield by treating **II-7** with DBU at room temperature. Wittig olefination of aldehyde **II-8** led to the acyclic diene that was submitted to olefin metathesis with Grubbs II catalyst to give key intermediate **II-9**. At that point, 5

69. Willot, M.; Christmann, M. *Nature Chem.* **2010,** *2*, 519-520.
70. Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519.
71. Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 3513-3516.
72. Willot, M.; Radtke, L.; Könning, D.; Fröhlich, R.; Gessner, V. H.; Strohmann, C.; Christmann, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 9105-9108.

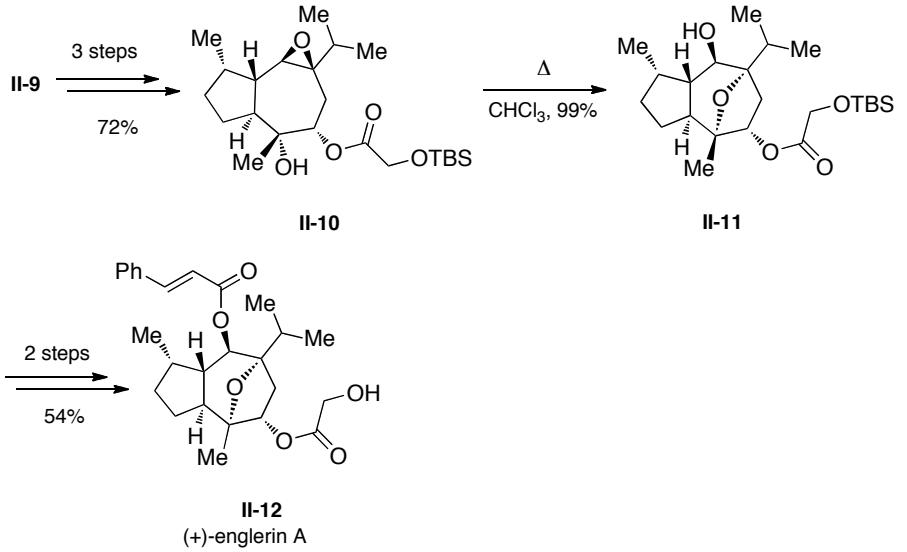
stereocenters were established from the three stereocenters originally present in the starting material. Guaiane **II-9** was obtained in 9 steps and 27% overall yield from **II-3**.



Scheme 17. Synthesis of cyclic acetal **II-9**.

After deprotection of the cyclic acetal **II-9**, the secondary alcohol was converted to the ester with (*tert*-butyldimethylsiloxy)acetyl chloride (Scheme 18). Subsequent epoxidation of the olefin using *m*CPBA afforded the desired epoxide **II-10** with moderate selectivity in 72% yield over 3 steps (2.3:1 *d.r.*). Following their proposal based on a biomimetic pathway, they successfully observed the quantitative conversion of epoxide **II-10** into the corresponding intermediate **II-11** *via* a transannular epoxide opening when the mixture was heated. The natural product (+)-englerin A (**II-12**) was finally obtained in two steps and 54% overall yield by converting **II-11** into the

cinnamate ester under Yamaguchi conditions and removing the TBS protecting group at the glycolate moiety.



Scheme 18. Completion of the synthesis of (+)-englerin A (**II-12**) from **II-9**.

The spectroscopic data matched with those reported by Beutler and co-workers, but the optical rotation observed ($[\alpha]_D^{20}$ = +51 (c = 0.58, MeOH)) was opposite to the one found in the natural product ($[\alpha]_D^{20}$ = -63 (c = 0.13, MeOH)). Thanks to this pioneer work on the synthesis of (+)-englerin A, the correct absolute configuration was established, thereby opening the door to other syntheses.[68]

68. During the writing of this manuscript, a total synthesis of (-)-englerin A was reported based on a similar strategy, see: Radtke, L.; Willot, M.; Sun, H.; Ziegler, S.; Sauerland, S.; Strohmann, C.; Fröhlich, R.; Habenberger, P.; Waldmann, H.; Christmann, M. *Angew. Chem. Int. Ed.* **2011**, DOI: 10.1002/anie.201007790.

b) [5+2] Cycloaddition approach.

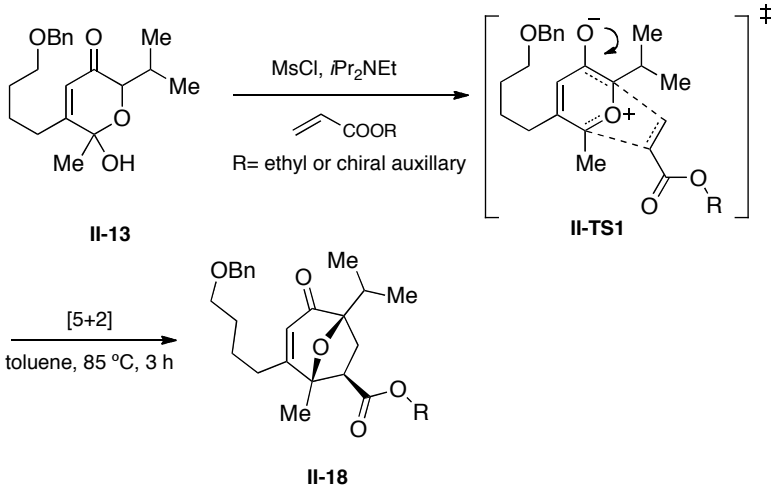
In 2010, a total synthesis of (-)-englerin A **II-1** was published using a [5+2] cycloaddition reaction to cast the seven-membered oxo-bicyclic key intermediate in both racemic and optically active forms.[67] The synthesis of englerin B **II-2** was also reported (Figure 16) and several structural analogues were made in order to investigate their biological activities towards a selected panel of cancer cell lines.

The key transformation consisted in the formation of a reactive 3-oxidopyrylium ylide species from cyclohexenone **II-13** to afford **II-18** by an intermolecular [5+2] cycloaddition with an acrylate derivative, containing a chiral auxiliary in the case of an enantioselective synthesis. Three new stereocenters would be obtained in only one step (Scheme 19).[73,74]

67. Nicolaou, K. C.; Kang, Q.; Ng, S. Y.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2010,** *132*, 8219-8222.

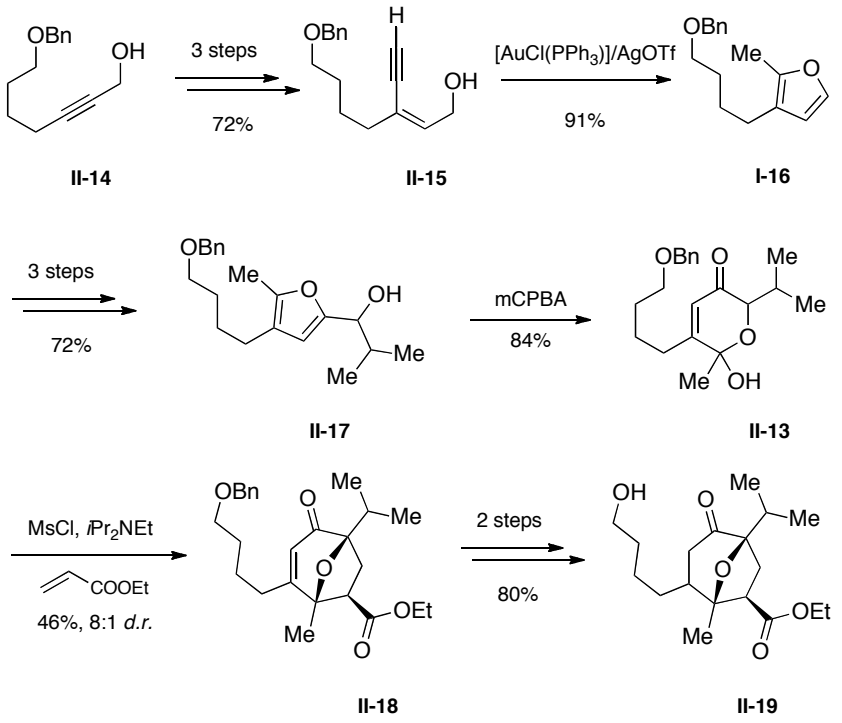
73. For an example of intermolecular [5+2] cycloaddition, see: Delgado, A.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2002,** *4*, 3091-3094.

74. For selected synthetic applications of Achmatowitcz oxidation and subsequent 1,3-dipolar cycloadditions of oxidopyrylium dipoles, see: (a) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997,** *119*, 7897-7898. (b) Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006,** *8*, 5901-5904. and references therein.



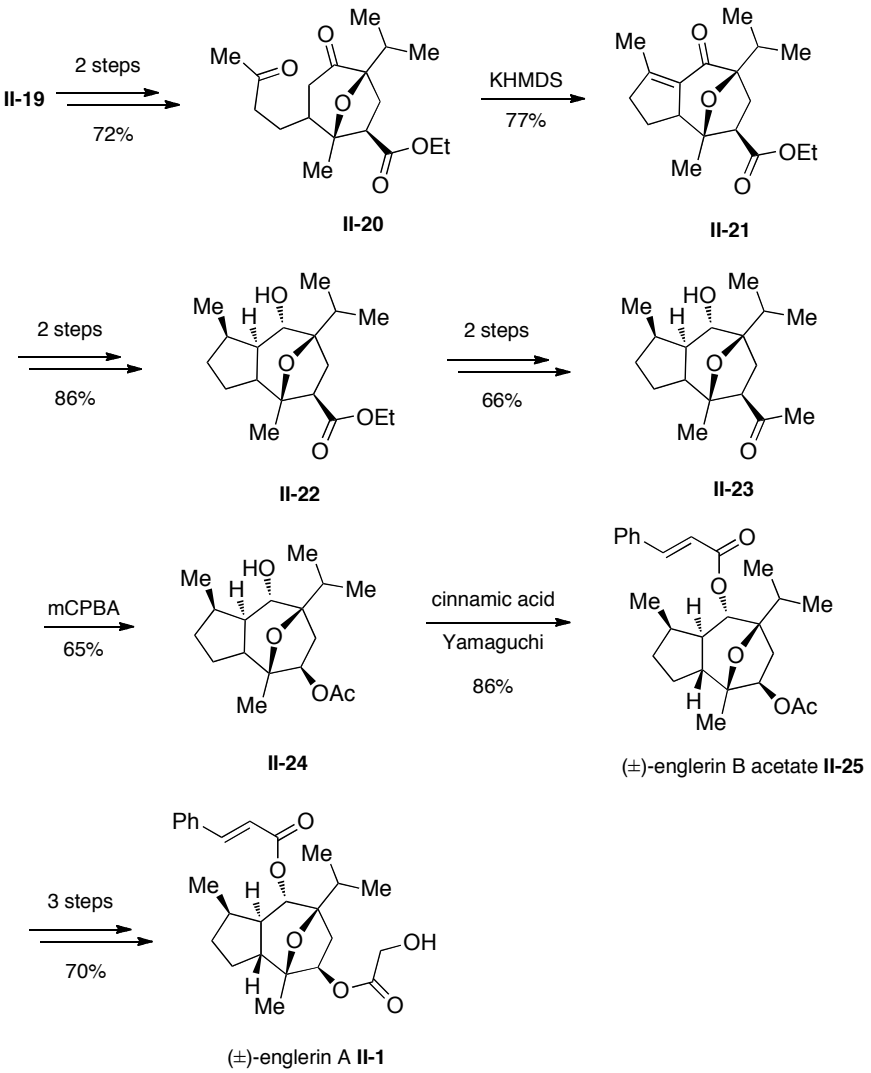
Scheme 19. Intermolecular [5+2] cycloaddition.

Synthesis of key intermediate **II-13** was achieved through a series of transformation from **II-14**, synthesized in two steps from 5-hexyn-1-ol (Scheme 20). It featured a gold(I)-catalyzed ring closure reaction to generate furan system **II-16** from **II-15** in 91% yield and an Achmatowicz rearrangement from hydroxy furan **II-17** into the desired cyclohexenone **II-13** in 84% yield. With the optimized conditions, a [5+2] cycloaddition between **II-13** and ethyl acrylate delivered bicyclic product **II-18** in a moderate 46% yield but with good selectivity as a 8:1 *d.r.* of a separable mixture. Sequential exposure of enone **II-18** to catalytic hydrogenation conditions resulted in reduction of the olefinic bond and cleavage of the benzyl ether to give hydroxy ketone **II-19** in 2 steps and 80% overall yield (Scheme 20).



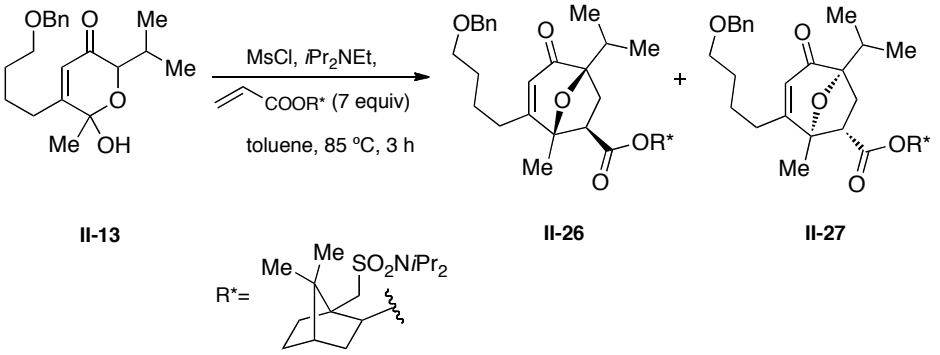
Scheme 20. Synthesis of hydroxy-ketone **II-19**.

The five-membered ring of the englerin core was settled in three steps with a Grieco elimination and a Wacker oxidation to afford methyl ketone **II-20** in 72% overall yield, followed by an aldol condensation using KHMDS at low temperature to give compound **II-21** in 77% yield (Scheme 21). Stereoselective reduction from the less hindered face of enone **II-21** under Luche conditions and stereoselective hydrogenation using Crabtree's catalyst (0.3 equiv, H_2 (1 atm)) afforded tricyclic system **II-22** in 86% overall yield. Methyl ketone **II-23** was obtained in two steps from **II-22** in 66% overall yield and was submitted to a Baeyer-Villiger oxidation in order to introduce a masked hydroxyl group in compound **II-24** (65% yield). Simple protection of **II-24** with cinnamic acid under Yamaguchi esterification conditions afforded (±)-englerin B acetate **II-25**, from which the acetate group was removed to give (±)-englerin B **II-2**. (±)-Englerin A **II-1** could be synthesized in a further three steps.



Scheme 21. Completion of the synthesis of (±)-englerin A **II-1**.

An asymmetric version of the intermolecular [5+2] cycloaddition was also developed in order to achieve an enantioselective formal total synthesis of (-)-englerin A. For that purpose, a chiral acrylate derivative based on the Oppolzer camphor sulfonamide was used. A separable mixture of two diastereosisomers **II-26** and **II-27** was obtained in 30% yield (2:1 *d.r.*). **II-26** was converted into the enantiopure (-)-**II-18** *via* a series of transformation on the ester moiety. (-)-**II-18** would give a formal total synthesis of (-)-englerin A **II-1**.



Scheme 22. Asymmetric intermolecular [5+2] cycloaddition.

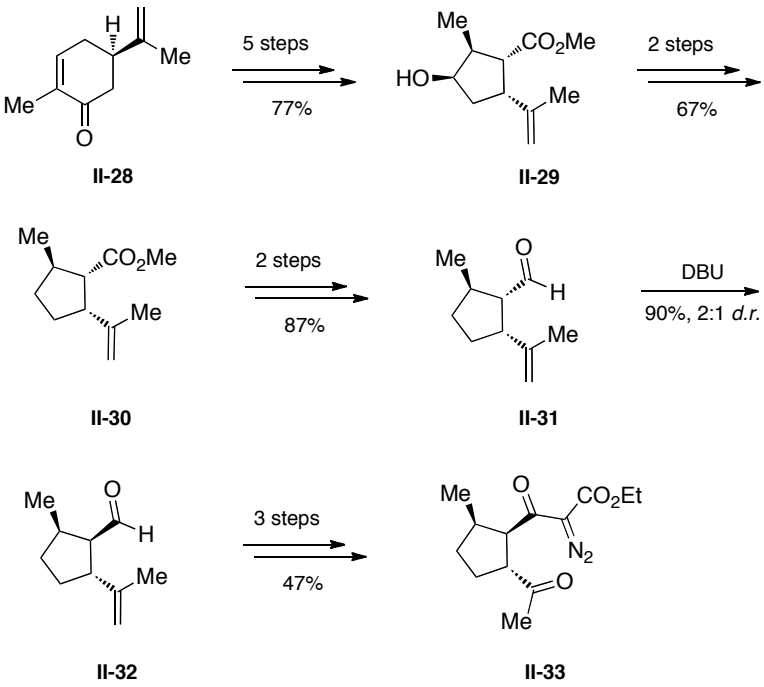
The synthesis required a total of 23 steps to isolate (±) englerin A in about 2% overall yield and 26 steps to reach the natural enantiomer (-)-englerin A with less than 1% overall yield. The yield and the selectivity of the intermolecular [5+2] cycloaddition are not high, making the key step the major limitation of the synthesis. In addition, the biological evaluations of the synthesized englerins are based on racemic forms and only provide useful structure-activity relationship. This study confirms the importance of the glycolic acid residue for the biological activity.

c) Rhodium(II)-catalyzed cycloaddition strategy.

The transition metal catalyzed reaction of α-diazo carbonyl compounds has found numerous applications in organic synthesis, and its use in either heterocyclic or carbocyclic ring formation is well precedented. Many examples of natural product syntheses have been reported to date relying on a rhodium(II)-catalyzed 1,3-dipolar cycloaddition with an alkene or an alkyne as described in the synthesis of zaragozic acid.[75]

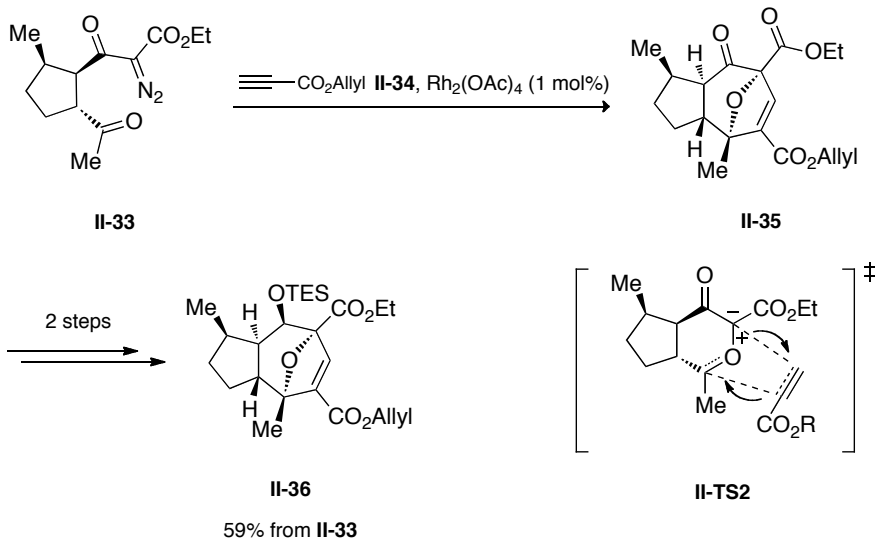
This elegant strategy was chosen to directly access in one step to the skeleton of (-)-englerin A.[76] The synthesis started with the transformation of the commercially available (*R*)-(-)-carvone **II-28** in a 5 steps sequence relying on the epoxidation of the enone, the regioselective epoxide opening, and a Favorskii rearrangement to finally give the cyclopentane intermediate **II-29** in 77% overall yield (Scheme 23). The hydroxyl group was removed with the Barton-McCombie protocol yielding the corresponding ester **II-30** in 67% yield over 2 steps. Aldehyde **II-31**, obtained from reduction and selective oxidation of **II-30** in 87% yield, was epimerized to give **II-32** in 64% yield along with aldehyde **II-31** (90%, 2:1 *d.r.*). At that point, three of the seven stereocenters were introduced starting from (*R*)-(-)-carvone in 10 steps and a 26% overall yield, although no carbon atoms have been added during this series of transformations. Subsequent ozonolysis and reaction with ethyldiazoacetate in the presence of a catalytic amount of tin(II) chloride gave **II-33** as a single isomer in 3 steps and 47% overall yield.

75. For selected synthetic applications, see: Nakamura, S.; Hirata, Y.; Kurosaki, T.; Anada, M.; Kataoka, O.; Kitagaki, S.; Hashimoto, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 5351-5355. (b) Kim, C. H.; Jang, K. P.; Choi, S. Y.; Chung, Y. K.; Lee, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 4009-4011.(c) Dauben, W. G.; Dinges, J.; Smith, T. C. *J. Org. Chem.* **1993,** *58*, 7635-7637.
76. Navickas, V.; Ushakov, D. B.; Maier, M. E.; Ströbele, M.; Meyer, H. J. *Org. Lett.* **2010,** *12*, 3418-3421.



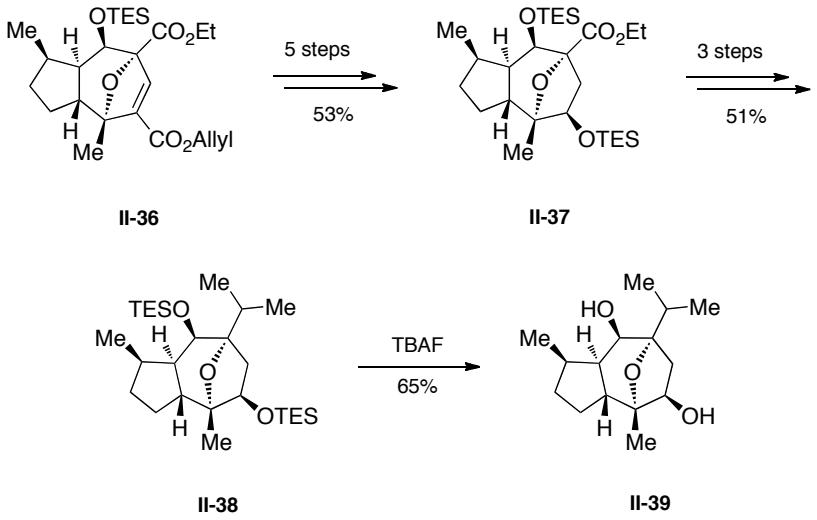
Scheme 23. Synthesis of diazo intermediate **II-33**.

Synthesis of the oxygen bridge intermediate **II-35** as a single isomer was achieved in very high yield from **II-33** using catalytic amount of $Rh_2(OAc)_4$ and allylester **II-34** (Scheme 24). Diazo intermediate **II-33** gave a carbonyl ylide that could react *in situ* with allyl acetate **II-34** *via* a 1,3-dipolar cycloaddition (e.g., **II-TS2**). The product **II-35** was immediately converted to the corresponding TES protected alcohol **II-36** as a single isomer in order to avoid any epimerization observed with the ketone **II-35** (84% over 3 steps).



Scheme 24. Synthesis of tricyclic intermediate **II-36**.

Unfortunately, the cyloaddition reaction gave product **II-35** with the wrong facial selectivity. Lacking structural information about the tricylic product **II-36**, the authors pursued their synthesis with the hope to get structural evidence later on. Further functionalization of the seven-membered ring resulted in a long series of transformations to access to the guaianolide **II-38** (Scheme 25). After removal of the allyl ester group with the Wilkinson catalyst, compound **II-36** was submitted to a Curtius rearrangement followed by hydrolysis to afford the corresponding ketone, which was stereoselectively reduced and converted into double TES protected intermediate **II-37** in five steps (53% overall yield from **II-36**). The ester group of **II-37** was then transformed to an isopropyl group in three steps and 51% overall yield leading to key guaianolide intermediate **II-38**. At that stage, X-ray structure analysis of diol **II-39** indicated a wrong facial selectivity during the 1,3-dipolar cycloaddition reaction.



Scheme 25. Synthesis of tricyclic diol **II-39**.

Despite of calculations showing a half chair conformation of the six-membered carbonyl ylide intermediate, the facial selectivity observed could not be fully rationalized. A pyramidalization of the reacting centers during the 1,3-dipolar cycloaddition was proposed.

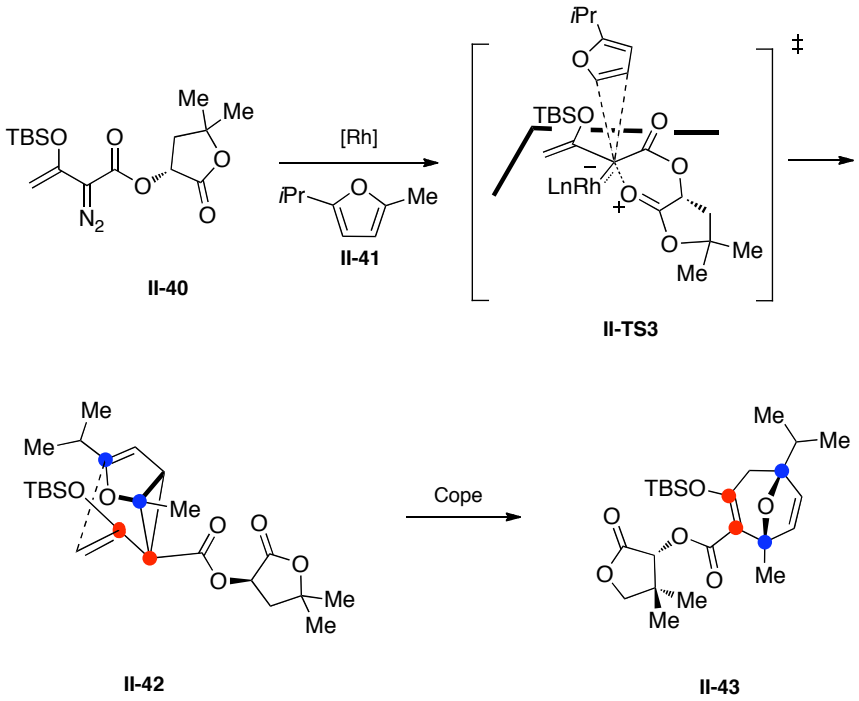
This synthesis, also based on cycloaddition reaction, is attractive. However, it suffers from limitations, especially with the intermolecular [2+3] cycloaddition that gave the wrong diastereoisomer.

d) Rhodium(II)-catalyzed cycloaddition strategy- Another approach.

Shortly after this publication, an alternative transformation also using rhodium as a catalyst, was reported to build the tricyclic scaffold and leading to an enantioselective formal synthesis of (-)-englerin A **II-1**.[77]

77. Xu, J.; Caro-Diaz, E. J. E.; Theodorakis, E. A. *Org. Lett.* **2010,** *12*, 3708-3711.

The key oxo-bicyclic intermediate was synthesized using a rhodium(II)-catalyzed ring formation between furan **II-41** and chiral diazo ester **II-40** to afford cyclopropane **II-42** (Scheme 26).[78] The asymmetric induction was rationalized by an interaction between the chiral auxiliary and the carbenoid as depicted in **II-TS3**. In the next step, **II-42** underwent a Cope cyclization to yield oxa-bicyclic compound **II-43**.

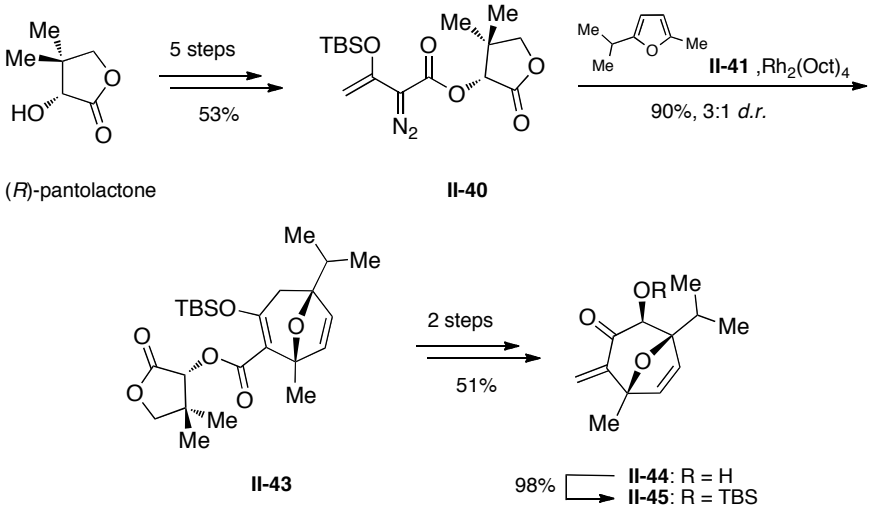


Scheme 26. Rhodium(II)-catalyzed cycloaddition between furan **II-41** and chiral diazo ester **II-40**. Methyl group of **II-41** has been omitted in **II-TS3** for clarity.

The synthesis started with the preparation of diazo ester **II-40**, following a reported procedure in 3 steps from (*R*)-pantolactone (Scheme 27). Its coupling partner, furan **II-**

78. For a seminal work on the rhodium-catalyzed [4+3] cycloaddition reactions, see: Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996,** *118*, 10774-10782.

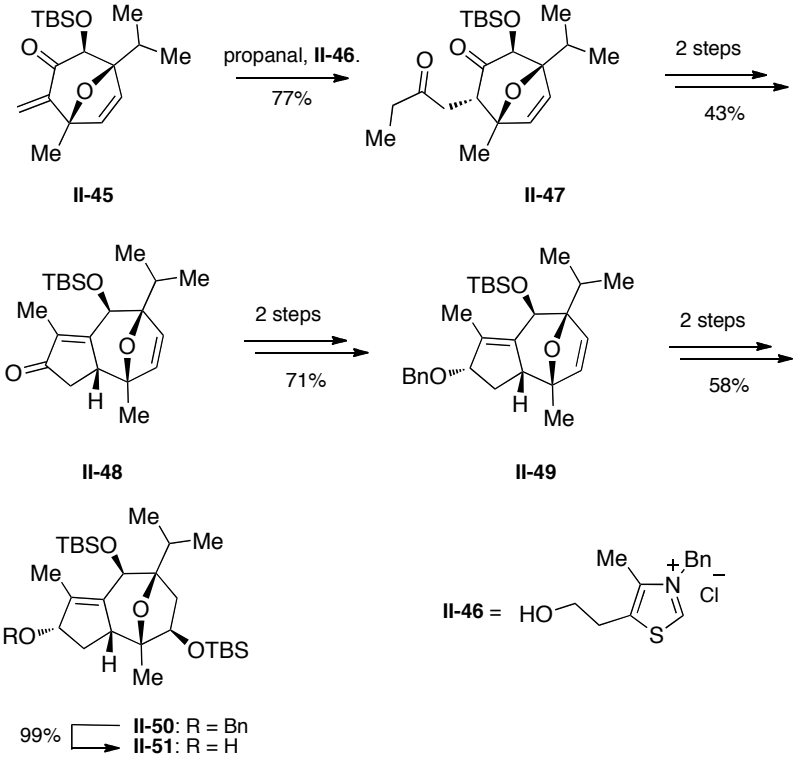
41, was obtained in 3 steps and 52% overall yield from commercially available 2-methyl furan. These two compounds are readily available in gram scale. Reaction between furan **II-41** and diazo ester **II-40** with a catalytic amount of Rh(II) gave the oxo-tricylcic intermediate **II-43** as a separable mixture in excellent yield (90% yield) but with moderate diastereoselectivity (3:1 *d.r.*). Lowering the temperature or the catalyst loading did not afford better results. α-Hydroxyl enone **II-44** was readily obtained in 51% overall yield after a reduction of **II-43** with DIBAL-H and a Lewis acid induced rearrangement, followed by a Rubottom oxidation with high chemoselectivity. Hydroxyl enone **II-44** was then quantitatively converted into TBS protected enone **II-45**.



Scheme 27. Synthesis of TBS protected enone **II-45**.

The next steps of the synthesis involved the elaboration of the five membered ring of the tricyclic englerin core (Scheme 28). Enone **II-45** was submitted to a 1,4-addition with propanal catalyzed by thiazolium salt **II-46** to afford diketone **II-47** as a single diastereoisomer in good yield (77% yield). Treatement of **II-47** with NaHMDS followed by heating in NaOMe/MeOH only provide **II-48** with 43% yield over two steps under optimised conditions. Reduction of **II-48** and subsequent protection with benzylbromide afforded **II-49** in 71% yield. A regio- and stereoselective hydroboration of the olefin followed by TBS protection afforded the corresponding bis protected TBS ether **II-50** in

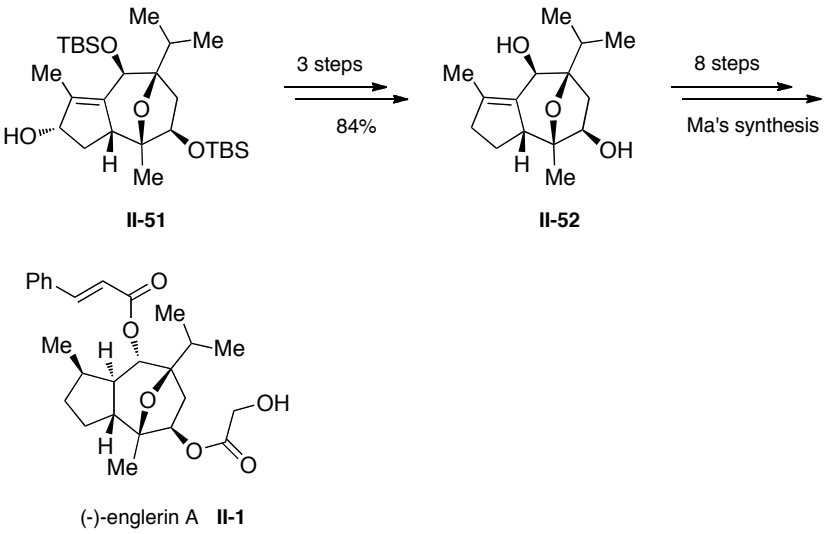
58% overall yield.



Scheme 28. Synthesis of tricyclic intermediate **II-51**.

The benzyl group was removed in order to liberate a free hydroxyl group in compound **II-51**. This alcohol was assumed to act as a directing group for the hydrogenation of the tetrasubstituted double bond. Unfortunately, no reaction occurred even under high pressure (up to 130 bar) and different catalysts. Alcohol **II-51** was finally converted in three steps and 84% overall yield into diol **II-52** (Scheme 29), a common intermediate to Ma's synthesis (Scheme 48).[71] (-)-Englerin A **II-1** was obtained in a formal total synthesis in eight steps from diol **II-52**.

71. Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 3513-3516.



Scheme 29. Obtention of tricyclic diol **II-52** and formal total synthesis of (-)-englerin A.

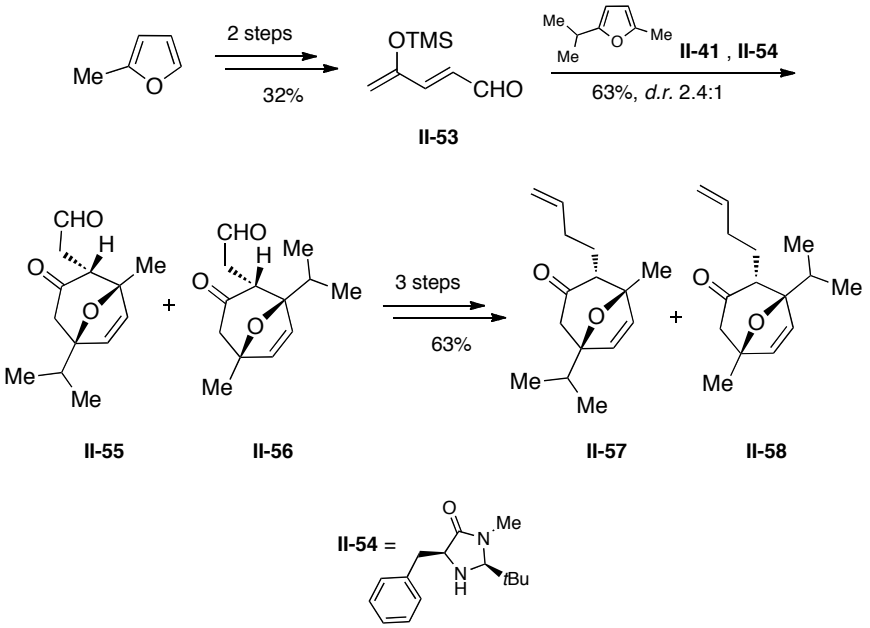
Theodorakis and co-workers developed an elegant metal-catalyzed strategy towards the synthesis of common guaiane-type tricylic skeleton. However, this approach suffers from major limitations with a low diastereoisomeric ratio (3:1 *d.r.*) in the cycloaddition reaction and a total number of 28 steps from commercially available (*R*)-pantolactone to access to (-)-englerin A **II-1** (less than 1% overall yield). Indeed the guaiane-type tricylic sesquiterpene skeleton **II-48** was readily obtained in 12 steps and 6% overall yield (80% per step in average), but access to the final product required a further 15 steps including oxidation/reduction reactions and inversion of stereocenters.

e) Organocatalyzed [4+3] cycloaddition approach towards the guaiane-type framework.

Recently,[79] a novel approach towards the synthesis of the guaiane-type tricyclic core *via*

79. Sun, B.-F.; Wang, C.-L.; Ding, R.; Xu, J.-Y.; Lin, G.-Q. *Tetrahedron Lett.* **2010,** *52*, 2155-2158.

an organocatalyzed [4+3] cycloaddition reaction was reported.[80] Dienal **II-53** was readily obtained in multigram scale from 2-methylfuran in two steps and 32% overall yield (Scheme 30).



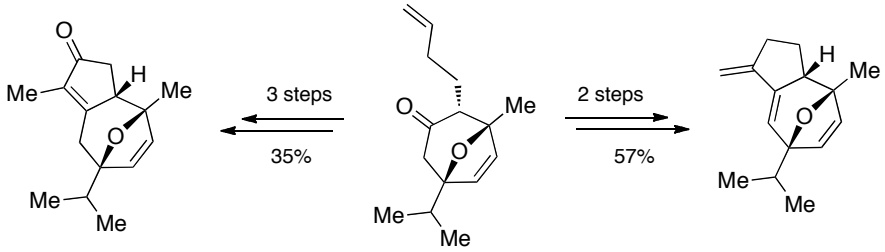
Scheme 30. Synthesis of dienes **II-57** and **II-58**.

Reaction of **II-53** with furan **II-41** and McMillan's catalyst **II-54** provided a mixture of diastereoisomers **II-55** and **II-56** in 63% yield (2.4:1 *d.r.*) and good enantioselectivity (respectively 67% *ee* and 82% *ee*). Aldehydes **II-55** and **II-56** were converted into a separable mixture of dienes **II-57** and **II-58** in 63% overall yield over three steps.

An intramolecular Heck reaction delivered the corresponding tricyclic key intermediate **II-59** From **II-57** in 57% yield (Scheme 31). Ketone **II-60** could also be obtained *via* an

80. For a seminal work on the asymmetric organocatalysis of the [4+3] cycloaddition reaction, see: Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003,** *125*, 2058-2059.

aldol condensation in 35% overall yield in three steps.



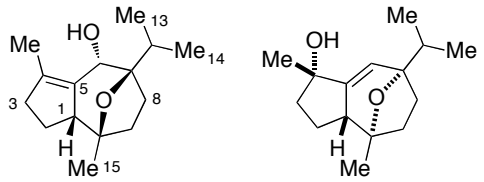
II-60 **II-57** **II-59**

Scheme 31. Synthesis of triene **II-59** and enone **II-60**.

4. Stereoselective Gold-Catalyzed Cycloaddition of Ketoenynes and Synthesis of (+)-Orientalol F

An impressive number of cascade reactions based on biomimetic approaches have been reported to date since the seminal work of Robinson on the synthesis of tropinone in 1917.[81] However, the ability to mimic biological pathways in creating complex polycyclic scaffolds from simple acyclic starting material is still today a major challenge in the chemical synthesis of terpenes.[69]

New gold(I)-catalyzed cascade reactions of enynes have been recently developed in our group by taking advantage of the highly reactive cyclopropyl Au(I) carbene intermediates towards a large scope of nucleophiles.[82] Our group published in 2009 the synthesis of guaiane sesquiterpene (+)-orientalol F (**II-61**) and (±)-pubinernoid B (**II-62**), by a novel approach (Figure 17).[83]

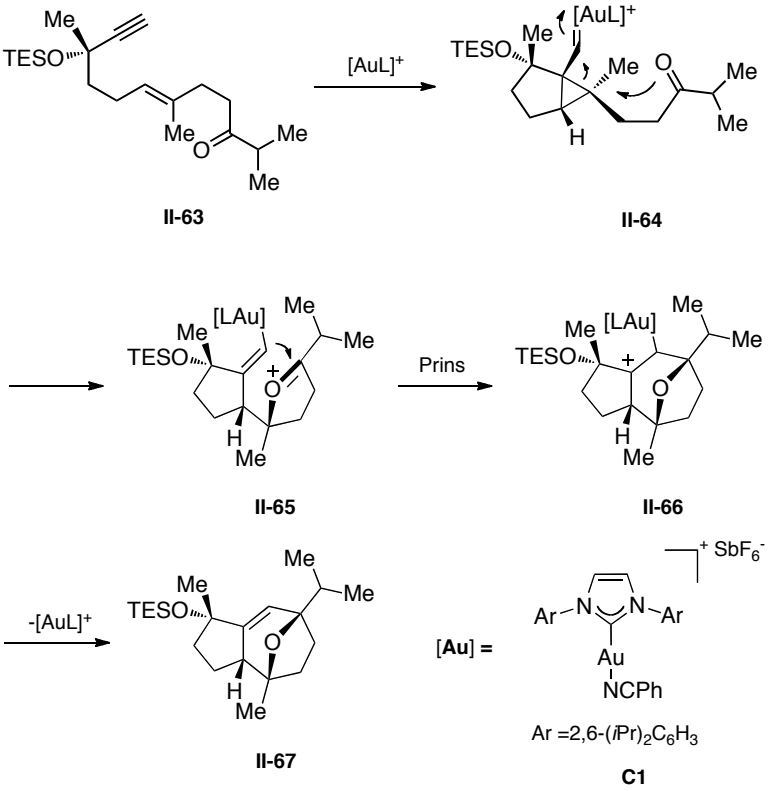


(+)-orientalol F **II-61** (±)-pubinernoid B **II-62**

Figure 17. (+)-orientalol F and (±)-pubinernoid B

81. For a review on cascade reactions in total synthesis of natural products, see: Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186.
69. Willot, M.; Christmann, M. *Nature Chem.* **2010,** *2*, 519-520.
82. For reviews on gold(I)-catalyzed transformations with alkynes, see: (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333-346. (b) Echavarren, A.; Jiménez-Núñez, E. *Top. Catal.* **2010,** *53*, 924-930.
83. Jiménez-Núñez, E.; Molawi, K.; Echavarren, A. M. *Chem. Commun.* **2009**, 7327-7329.

A gold(I)-catalyzed formal [2+2+2] alkyne/alkene/carbonyl cycloaddition[84] allowed to readily access to the guaiane-type tricyclic skeleton **II-67** from an acyclic substrate **II-63** (Scheme 32).



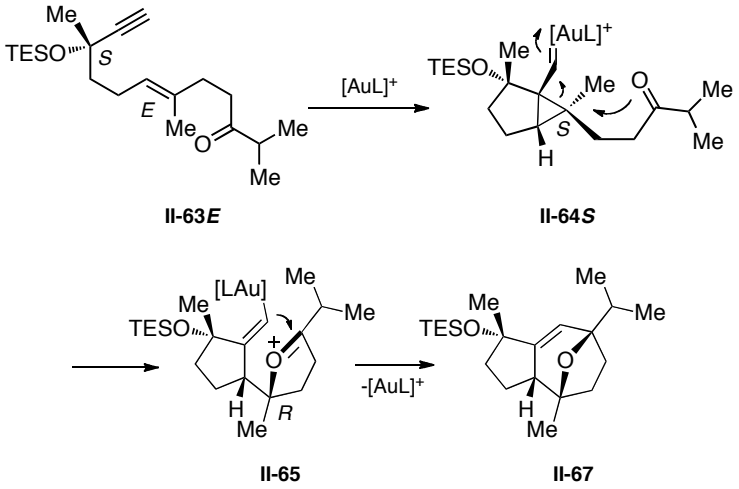
Scheme 32. Mechanistic rationale for the gold(I)-catalyzed [2+2+2] alkyne/alkene/carbonyl cycloaddition of ketoenyne **II-63**.

After screening of reaction conditions, best results were obtained using gold(I) carbene **C1** as a catalyst and a TES protecting group on the propargylic alcohol of ketoenyne **II-**

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

63. The cascade reaction proceeded *via* cyclopropyl gold(I) carbene **II-64** followed by an attack from the carbonyl group, acting as an internal nucleophile, to give oxonium cation **II-65**. Subsequent Prins-type reaction[85] afforded **II-66** that underwent a proto-demetalation to form tricyclic key intermediate **II-67**.

The configuration of the propargylic chiral center in **II-63** controls the configuration of the newly formed stereocenter C1 (see numbering in Figure 17) during the cyclization through intermediate **II-64*S*** in which the OTES group is *anti* to the C1-H of the cyclopropyl ring and the Au(I) carbene (Scheme 33). This hypothesis was supported by DFT calculations and experiments using a model substrate.[83]

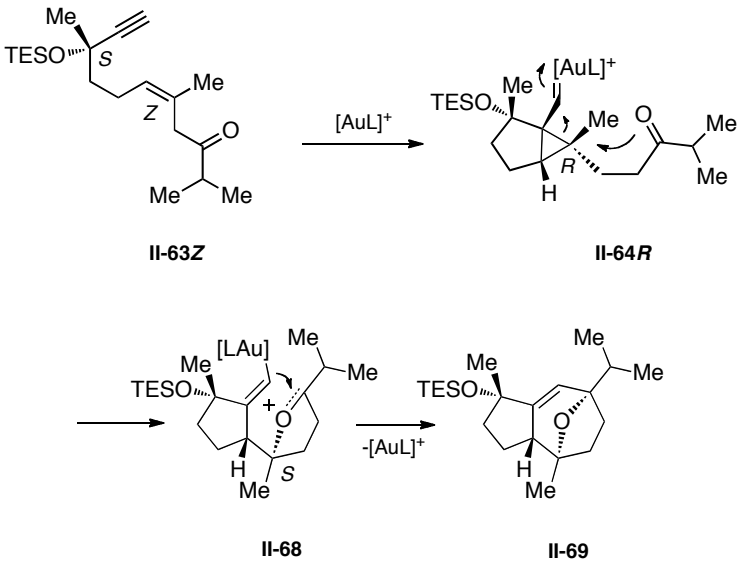


Scheme 33. Mechanistic rationale for the synthesis of **II-67** from **II-63*E***

85. For reviews on Prins and ene reactions, see: (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952,** *51*, 505-555. (b) Snider, B. B. *Acc. Chem. Res.* **1980,** *13*, 426-432. (c) Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006,** *128*, 13640-13648.

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

The geometry of the internal alkene was also crucial by controlling the configuration of the oxo-bridge framework (Scheme 33). Indeed, a substrate with an *E* double bond (**II-63*E***) afforded the oxo-bridge of the tricyclic framework *anti*-oriented to the TES protected propargylic alcohol. Conversely, a substrate with a Z double bond (**II-63*Z***) led to a *syn*-orientation (Scheme 34).

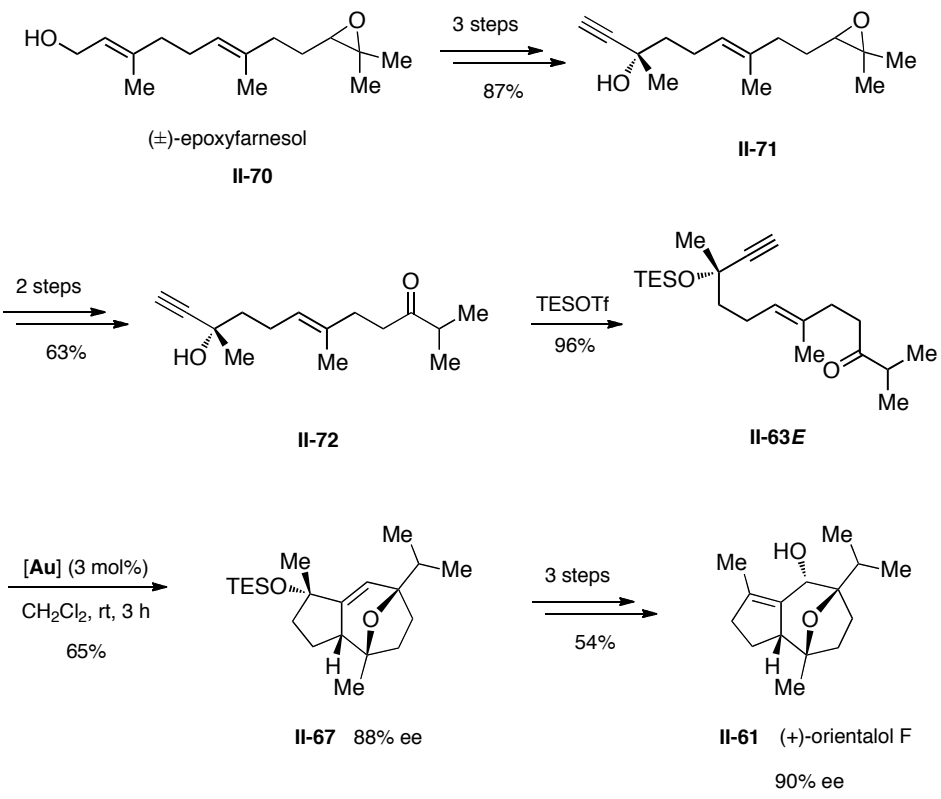


Scheme 34. Mechanistic rationale for the synthesis of **II-69** from **II-63*Z***

As a general rule to rationalize the stereoinduction from the substrate in the cyclization reaction, propargylic stereocenter of **II-63** controls the configuration at C1 and the configuration at C7 and C10 are set by the internal double (Figure 18).

Figure 18. Stereoinduction model in the gold(I)-catalyzed [2+2+2] alkyne/alkene/carbonyl cycloaddition of enyne.

The synthesis started from commercially available (±)-epoxyfarnesol **II-70** that was submitted to a Sharpless epoxidation, followed by a chlorination of the corresponding epoxy-alcohol and an elimination to furnished propargylic alcohol **II-71** in 87% overall yield (Scheme 35). Propargylic alcohol **II-71** was converted into ketoenyne **II-72** in 63% overall yield through a regioselective reduction of the epoxide with $NaBH_3CN$ and $BF_3.Et_2O$ followed by DMP oxidation. Protection of propargylic alcohol **II-72** with TESOTf yielded **II-63*E***. Then, cyclization of **II-63*E*** with Au(I) catalyst **C1** afforded tricyclic intermediate **II-67** in 65% yield. (+)-Orientalol F **II-61** was obtained in 54% yield and 88% *ee* over two steps after deprotection of the TES protecting group with TBAF and a 1,3-migration of the corresponding allylic alcohol in a two steps procedure.



Scheme 35. Synthesis of (+)-orientalol F.

Retention of the enantiomeric excess between enyne **II-63*E*** and cycloadduct **II-67** proved that no racemization *via* a carbocation occurred during the gold(I)-catalyzed cyclization process.

B. Results

The synthesis of (-)-englerin A we achieved in our laboratory is very similar to the one proposed by Ma and co-workers.[70,71] Both syntheses relied on a gold(I)-catalyzed cycloaddition of a linear ketoenyne to generate the tricyclic core of (-)-englerin A **II-1**. After detailed description of our synthesis, we will comment on that reported by Ma.

1. Gold(I)-Catalyzed Cascade Reaction Strategy

Based on the successful strategy applied in the synthesis of (+)-orientalol F, we planned to use a similar gold(I)-catalyzed domino reaction for the synthesis of englerin A **II-1** and englerin B **II-2**. From the stereoinduction model we proposed (Figure 18), stereocenter at C1 of (-)-englerin A **II-1** could be built by using ketoenyne **II-73** containing a protected propargylic alcohol with the *S* configuration at C4 (Figure 19). The absolute configuration of the protected allylic alcohol at C9 would be directly defined from the natural product (i.e. *R* configuration).

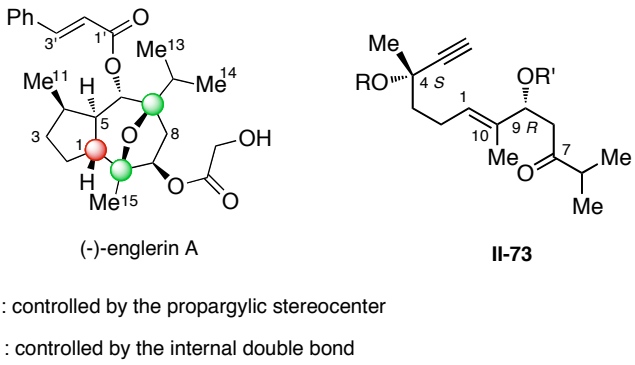
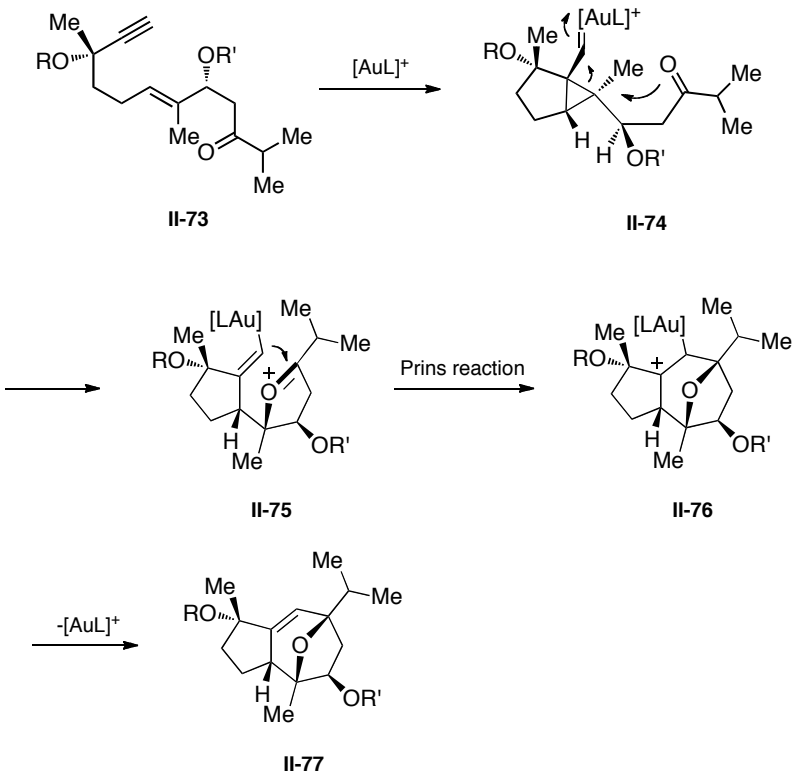


Figure 19. Design of ketoenyne **II-73** using stereoinduction model (Figure 18)

70. Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519.
71. Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 3513-3516.

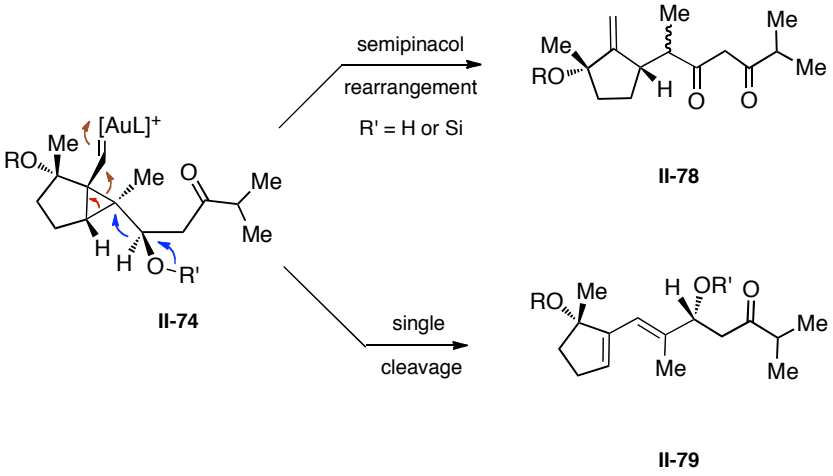
Similarly, stereocenters at C7 and C10 of the oxo-bridge of the tricyclic core would require an *E* double bond.

With ketoenyne **II-73** in hands, the gold(I)-catalyzed cyclization is assumed to proceed as follow (Scheme 36). Coordination of the Au(I) catalyst to the alkyne leads to cyclopropyl Au(I) carbene intermediate **II-74**. Accordingly, the carbonyl group acts as an internal nucleophile in **II-74** to form the electrophilic oxonium intermediate **II-75**, which undergoes a Prins-type reaction with the alkenyl metal to give **II-76**. Direct elimination of the gold metal by proto-demetalation would form tricyclic compound **II-77**.



Scheme 36. Mechanistic rationale for the gold(I)-catalyzed [2+2+2] alkyne/alkene/carbonyl cycloaddition of ketoenyne **II-73**.

However, the allylic OR' group could confer additional lability to substrate **II-73** in the presence of Lewis acidic Au(I) catalyst. The OR' group could also interfere with the carbonyl group in the opening of intermediate **II-74**. Thus, a semipinacol-type rearrangement could lead to an earlier termination of the cyclization process and give ketone **II-78** (Scheme 37). In addition, intermediate **II-74** could undergo a single cleavage rearrangement leading to compound **II-79**. Elimination of R'OH and retroaldol reaction could also lead to decomposition pathways.

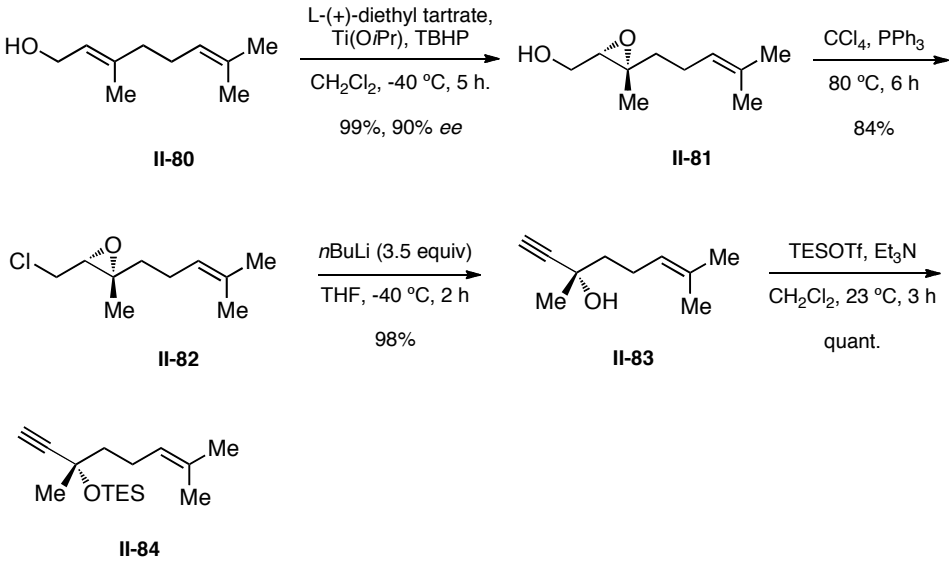


Scheme 37. Possible side termination processes in the gold(I)-catalyzed [2+2+2] alkyne/alkene/carbonyl cycloaddition.

The synthesis started with the preparation of known enyne **II-83** following a reported procedure.[86] Sharpless asymmetric epoxidation[87] of commercially available geraniol **II-80** afforded **II-81** in 99% yield and 90 % *ee*. Substitution of the primary alcohol by a

86. Mohapatra, D. K.; Pramanik, C.; Chorghade, M. S.; Gurjar, M. K. *Eur. J. Org. Chem.* **2007**, 5059-5063.
87. Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987,** *109*, 5765-5780.

chlorine atom using Appel reaction conditions[88] yielded epoxy-chloride **II-82** in 84% yield. Subsequent reaction with *n*BuLi (3.5 equiv) gave propargylic alcohol **II-83** in 98% yield and protection with TESOTf afforded the corresponding protected enyne **II-84** in quantitative yield.

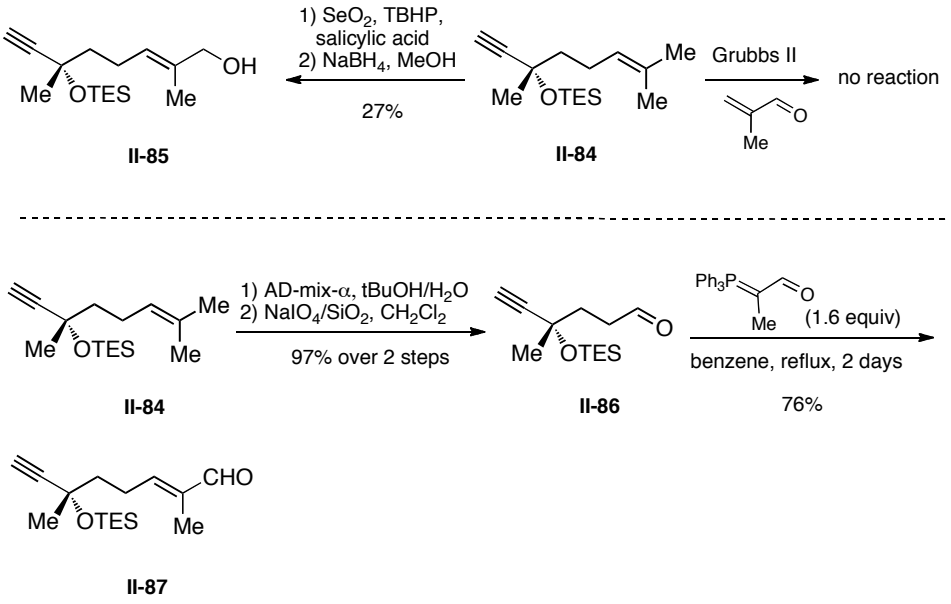


Scheme 38. Synthesis of enyne **II-84**.

In order to obtain aldehyde **II-87** from **II-84** in a minimum number of steps, several methodologies were tried (Scheme 39). Allylic oxidation was considered first as the most straightforward approach, but reaction of **II-84** with a mixture of SeO_2, salicylic acid and TBHP gave alcohol **II-85** in low yield (27%) after reductive work-up with $NaBH_4$.[89] Replacing the TES protecting group by a benzyl-protecting group did not

88. Appel, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 801-811.
89. Larsson, M.; Nguyen, B.-V.; Högberg, H.-E.; Hedenström, E. *Eur. J. Org. Chem.* **2001**, 353-363.

improve the yield of the reaction (20%). Metathesis olefination of **II-84** with methacrolein and Grubbs II catalyst gave no reaction under different conditions (room temperature or under microwave heating).



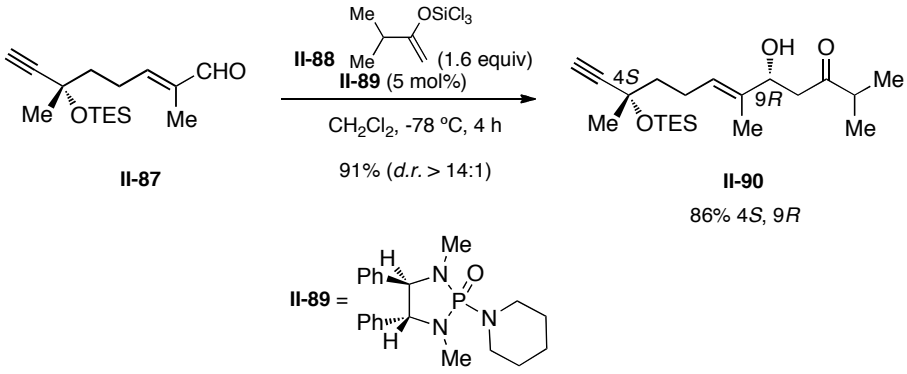
Scheme 39. Synthesis of aldehyde **II-87**.

Aldehyde **II-87** was finally obtained in three steps and 73% overall yield from **II-84** by oxidative cleavage using a two-step procedure[90,91] and subsequent olefination reaction of **II-86** with 2-(triphenylphosphoranylidene)propionaldehyde. ^{1}H-NMR of **II-87** only showed the presence of the *E* isomer. Oxidative cleavage by ozonolysis and subsequent olefination of **II-86** gave lower yield (i.e. 43% yield over two steps).

90. Hamon, D. P. G.; Tuck, K. L.; Christie, H. S. *Tetrahedron* **2001,** *57*, 9499-9508.

91. Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem*. **1997,** *62*, 2622-2624.

A stereoselective Denmark aldol reaction[92] of **II-87** with trichlorosilyl enol ether **II-88** in the presence of chiral phosphoramidite **II-89** afforded β-hydroxy ketone **II-90** in 91% yield (Scheme 40). Analysis of both (*R*)- and (*S*)-Mosher esters of **II-90** showed that the aldol reaction had proceeded with very high diastereoselectivity (i.e. *d.r.* > 14:1).



Scheme 40. Synthesis of *β*-hydroxy ketoenyne **II-90**.

This route is amenable to scale-up and hydroxy ketoenyne **II-90** was synthesized from **II-80** in 55% overall yield and 8 steps.

With substrate **II-90** in hands, we screened different conditions for the gold(I)-catalyzed cyclization (Table 20, entries 1-8). After testing a number of protected derivatives of aldol **II-90** and different catalysts, we found that the best results were obtained by using the unprotected substrate and gold catalyst **C1** (Table 20, entry 3). Lowering the catalyst loading gave diminished yield (Table 20, entries 4 and 5).

92. Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000,** *122*, 8837-8847.

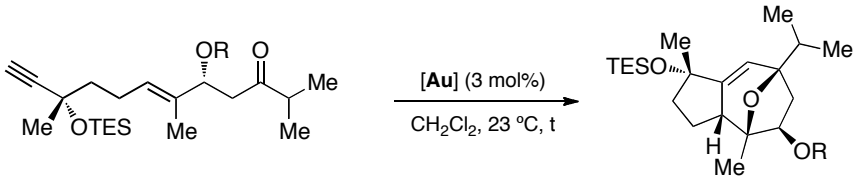
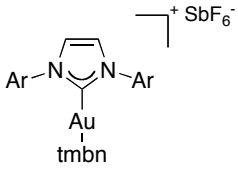


Table 20. Gold(I)-catalyzed cyclization of enynes: Screening of conditions.

Entry	*Substrate*	*R*	*t (h)*	*[Au]*	*Product (% yield)*
1	**II-92**	TES	12	**C1**	66
2	**II-93**	TIPS	12	**C1**	68
3	**II-90**	H	5	**C1**	58
4[a]	**II-90**	H	15	**C1**	35
5[b]	**II-90**	H	12	**C1**	10
6	**II-90**	H	15	**C2**	messy
7	**II-90**	H	15	**BiP1**	messy
8	**II-90**	H	15	**TriP**	messy

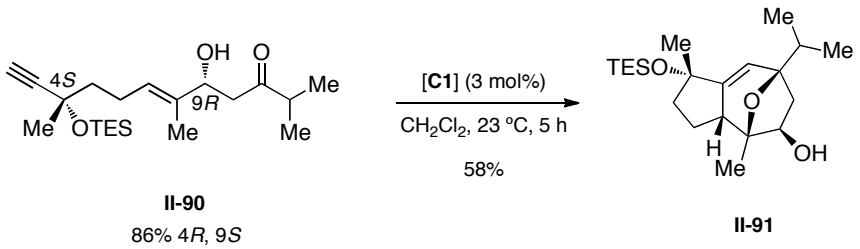
[a] with 1 mol% catalyst. [b] with 0.5 mol% catalyst.



Ar =2,4,6-$(Me)_3C_6H_2$

C2

Under these conditions, oxo-tricyclic derivative **II-91** was obtained as a single diastereoisomer in 58% yield, which corresponds to a 67% yield based on the major 4*S*, 9*R* stereoisomer of *β*-hydroxy ketoenyne **II-90** (Scheme 41).

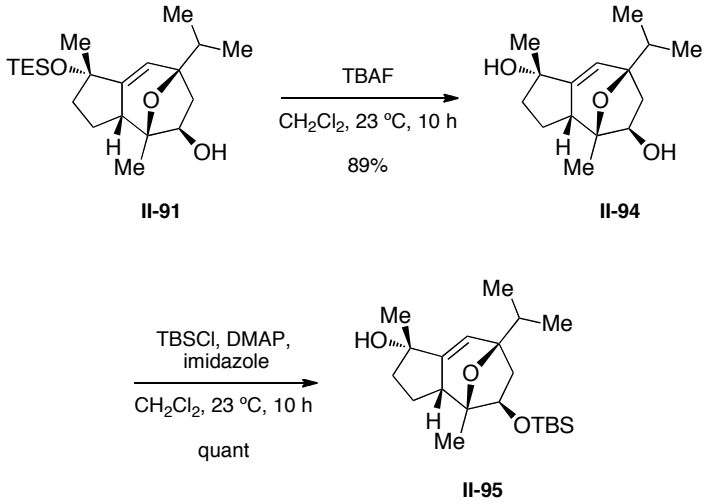


II-90
86% 4*R*, 9*S*

II-91

Scheme 41. Gold(I)-catalyzed cyclization of **II-90** into **II-91**.

TES protecting group of tricyclic intermediate **II-91** was removed with TBAF to give diol **II-94** in 89% yield, followed by selective protection of the secondary alcohol with TBSCl to afford **II-95** in a quantitative yield (Scheme 42).



II-91 **II-94**

II-95

Scheme 42. Synthesis of **II-95**.

X-ray structure analysis of **II-94** confirmed the desired isomer was obtained (Figure 20).

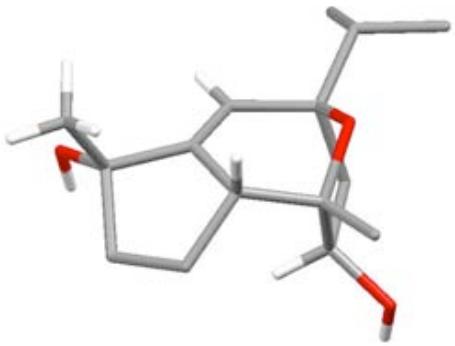
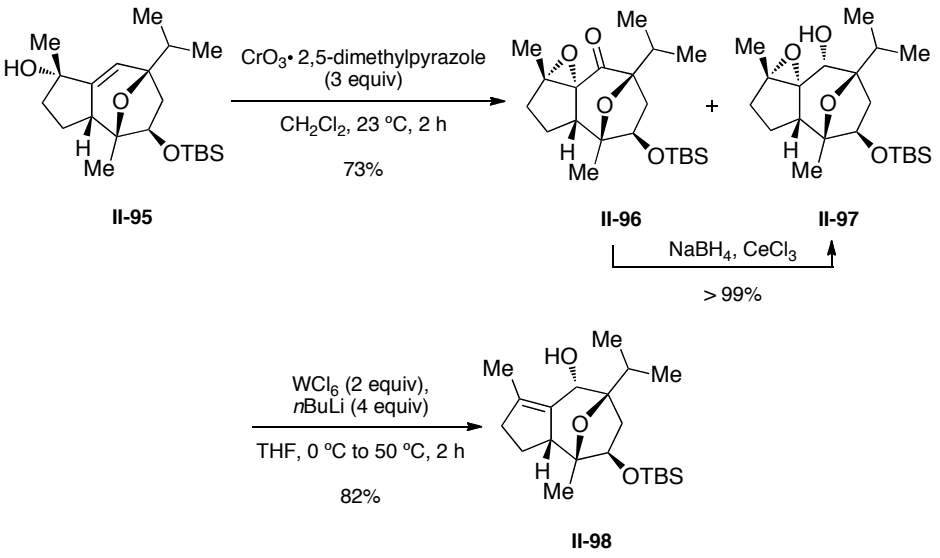


Figure 20. X-Ray crystal structure of diol **II-94.**

In addition, measurement of the enantiomeric excess of **II-95** by chiral HPLC analysis showed a high enantiomeric excess (> 99% ee) that clearly demonstrated both a diastereomeric and an enantiomeric enrichment *via* the gold(I)-catalyzed cyclization. The cyclization was assumed to proceed through a match case with a preference for diastereoisomers with the *SR* and *RS* configurations, explaining the formation of **II-91** as a single isomer.

The isomerization of **II-95** to **II-98** was performed in two steps by an oxidation/reduction protocol (Scheme 43).[83,93] Treatment of **II-95** with CrO_3 and 2,5-dimethylpyrazole[94] gave epoxy alcohol **II-97** in 73% yield. When the reaction was carried out with Collins reagent, **II-97** was obtained in a similar yield (71%) along with the corresponding epoxy ketone **II-96** (17%). Reduction of **II-96** with $NaBH_4$ and $CeCl_3$ yielded **II-97** quantitatively.

83. Jiménez-Núñez, E.; Molawi, K.; Echavarren, A. M. *Chem. Commun.* **2009**, 7327-7329.
93. Sundararaman, P.; Herz, W. *J. Org. Chem.* **1977,** *42*, 813-819.
94. Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978,** *43*, 2057-2059.



Scheme 43. Synthesis of **II-98**

Reduction of **II-97** with WCl_6 and *n*BuLi[95] gave the desired allylic alcohol **II-98** in 82% yield.

Oxidative rearrangement of **II-95** using $TEMPO^+BF_4^-$[96] or $TEMPO/NaIO_4/SiO_2$[97] failed and the use of Parikh-Doering conditions[98] was not successful either. Metal-catalyzed allylic rearrangement with $ReO_3(OSiPh_3)$ or $ReO_3(OMe)$ also failed.[99]

The hydrogenation of the tetrasubstituted olefin was particularly challenging (Scheme 44).

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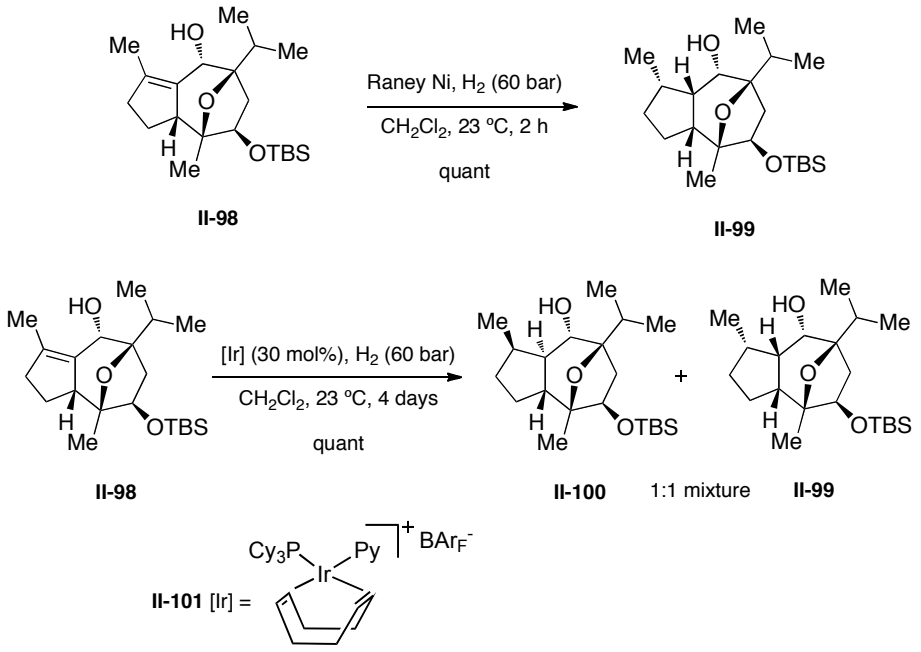
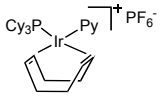
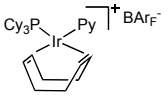
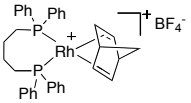
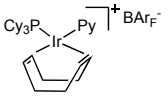
95. Umbreit, M.A.; Sharpless, K.B., *Org. Synth*. **1981**, *60*, 29-32.
96. Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *J. Org. Chem.* **2008,** *73*, 4750-4752.
97. Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *Org. Lett.* **2008,** *10*, 4715-4718.
98. Larson, K. K.; Sarpong, R. *J. Am. Chem. Soc.* **2009,** *131*, 13244-13245.
99. Morrill, C.; Beutner, G. L.; Grubbs, R. H. *J. Org. Chem*. **2006**, *71*, 7813-7825. and references therein.

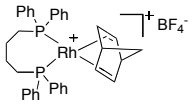
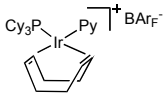
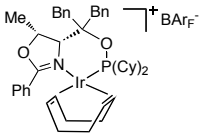
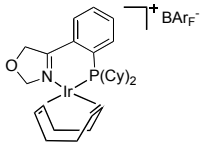
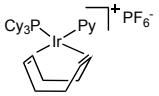


Scheme 44. Hydrogenation of **II-98** in **II-100**.

Catalytic hydrogenation of **II-98** with H_2/Raney Ni or Pd/C yielded alcohol **II-99** as a single disatereoisomer (Table 21, entries 1 and 2). As predicted, hydrogen transfer occurred from the less hindered face of the molecule.

Table 21. Hydrogenation study of substrate **II-98**. Screening of conditions.

Entry	*Catalyst*	*Product (%)*	*Entry*	*Catalyst*	*Product*
1	Pd/C	**II-99** (70)	7		n.r.
2	Raney Ni	**II-99** (98)	8		**II-100** : **II-99** (> 95%, 1:1)
3		n.r.	9[a]		n.r.

Entry	*Catalyst*	*Product (%)*	*Entry*	*Catalyst*	*Product*
4[a]		n.r.	10[b]		messy
5		messy	11		messy
6		n.r.			

All reactions were carried out in CH_2Cl_2 for 24 h at room temperature under H_2 (60 bar). [a] NaH added. [b] $B(OMe)_3$ added.

To overcome the steric bias of this olefin, our strategy relied on the use of a highly active catalyst towards substituted olefins associated to a directing effect from the free hydroxyl group in C6. Several Rh(I) and Ir(I) catalysts were tried but only messy reactions were obtained (Table 21, entries 5 and 11) or no reaction at all (Table 21, entries 3-4 and 6-7). The breakthrough came by using Pfaltz Ir(I) catalyst[100] **II-101** that afforded a separable 1:1 mixture of **II-100** and **II-99** with complete conversion of substrate **II-98** (Scheme 44 and Table 21, entry 8). Addition of NaH or $B(OMe)_3$[101] gave respectively starting material and a messy reaction (Table 21, entries 9 and 10).

100. Wüstenberg, B.; Pfaltz, A. *Adv. Synth. Catal.* **2008,** *350*, 174-178.

101. Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 1467-1470.

Structure of the key intermediate **II-100** was confirmed by X-ray analysis (Figure 21).

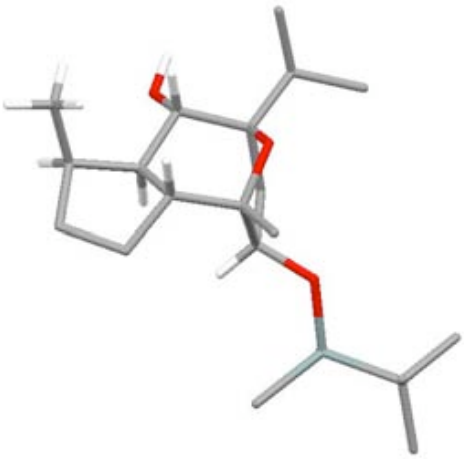
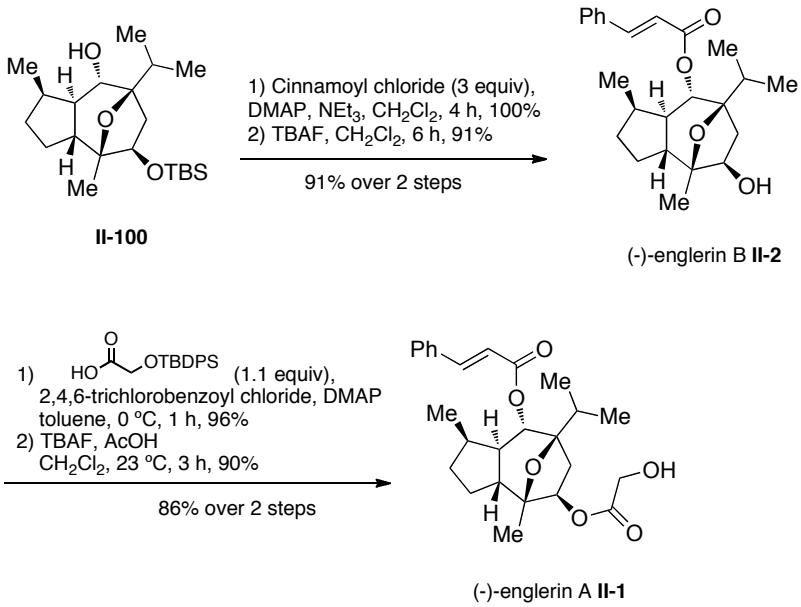


Figure 21. X-Ray crystal structure of **II-100**.

Esterification of the secondary alcohol of **II-100** with cinnamoyl chloride and removal of the TBS protecting group with TBAF led to (-)-englerin B **II-2** in two steps and 91% overall yield (Scheme 45). Synthesis of (-)-englerin A **II-1** was achieved in a further two steps by treatment with TBDPS-protected glycolic acid under Yamaguchi conditions,[102] followed by deprotection using TBAF buffered with acetic acid (86 % overall yield). The use of acetic was essential to buffer the TBAF solution, which caused the cleavage of the glycolate moiety.

102. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem, Soc. Jpn.* **1979**, *52*, 1989-1993.



Scheme 45. Synthesis of (-)-englerin A and (-)-englerin B.

The ^{1}H and ^{13}C NMR spectra[103] and the optical rotations of synthetic (-)-englerin A **II-1** and (-)-englerin B **II-2** matched with those reported in the literature (Table 22).

Table 22. Comparison of the optical rotations between synthetic and natural (-)-englerin A and (-)-englerin B.

$[\alpha]_D^{20}$	(-)-englerin A	(-)-englerin B
synthetic	-58.7±2.5 (*c* = 0.52, MeOH)	-29.8±1.7 (*c* = 0.17, MeOH)

103. For a comparison of the NMR shifts between synthetic and natural englerins, see the experimental part at the end of this chapter.

$[\alpha]_D^{20}$	(-)-englerin A	(-)-englerin B
Natural[63]	-63 (*c* = 0.13, MeOH)	-32 (*c* = 0.17, MeOH)

The total synthesis of (-)-englerin A was achieved in 18 steps and 7% overall yield from geraniol. Although the synthesis is suffering from poor selectivity in the hydrogenation step (i.e. 1:1 *d.r.*), the synthesis of the oxotricyclic core was stereoselective and provided the key intermediate **II-100** with very high enantioselectivity (> 99% *ee*).

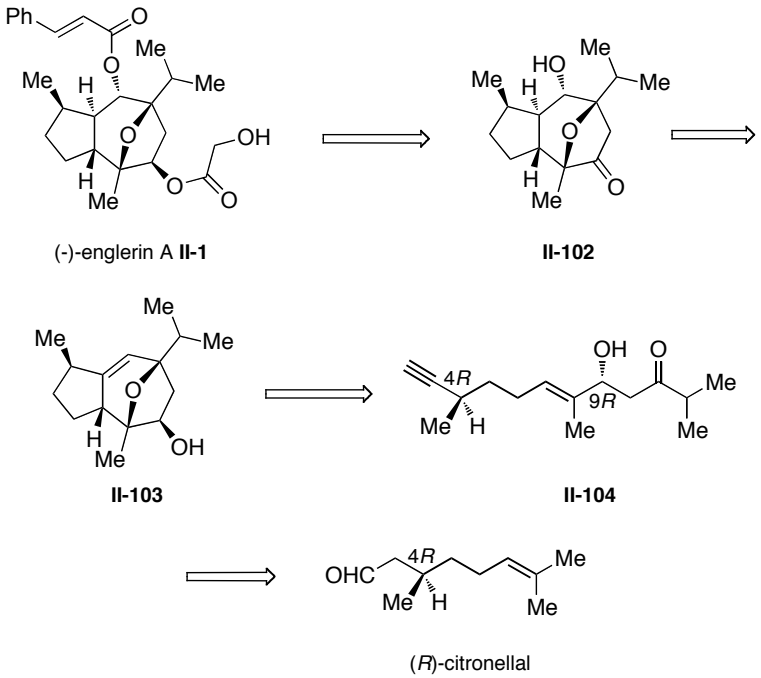
63. Ratnayake, R.; Covell, D.; Ransom, T. T.; Gustafson, K. R.; Beutler, J. A. *Org. Lett.* **2008,** *11*, 57-60.

2. Gold(I)-catalyzed Cascade Reaction: a second approach. Description and Comparison

As mentioned earlier, another synthesis of (-)-englerin A was published by Ma and co-workers.[71] Similarly to our strategy, the oxotricyclic core of (-)-englerin A was obtained by a gold(I)-catalyzed [2+2+2] cyclization reaction. The synthesis only differed in the choice of the cyclization precursor and the nature of the gold(I) catalyst.

In a retrosynthetic analysis, (-)-englerin A **II-1** would be obtained from ketone **II-102** by introducing two ester groups at a late stage (Scheme 46). Ketone **II-102** would be synthesized after successive functional-group manipulations from oxo-tricyclic intermediate **II-103**, that would be delivered by a gold(I)-catalyzed [2+2+2] cyclization from ketoenyne **II-104**. Finally, enyne **II-104** would be prepared from commercially available (*R*)-citronellal.

71. Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 3513-3516.

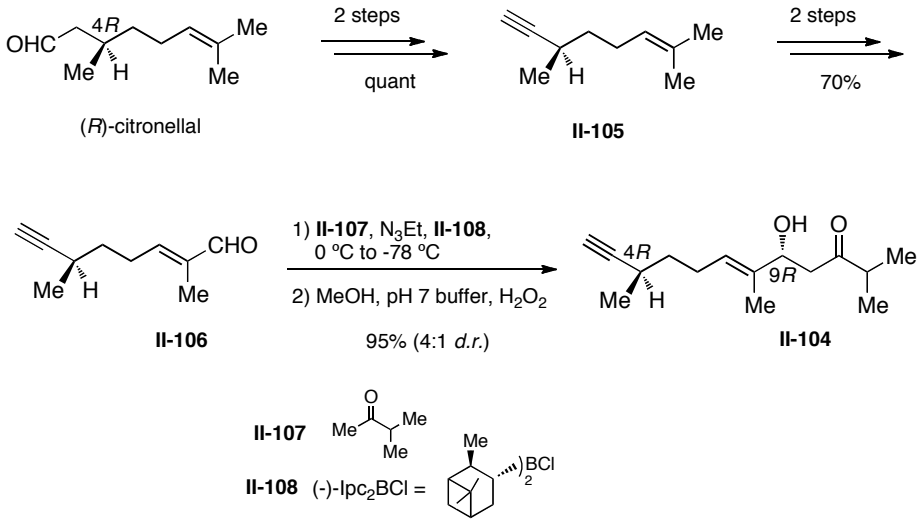


Scheme 46. Retrosynthetic analysis.

The gold(I)-catalyzed cyclization would give access to five of the seven stereocenters (i.e. intermediate **II-102**) present in the final compound. Last but not least, this approach would rely on a protecting-group-free synthesis by adding functionality as late as possible in the synthesis.

The synthesis started with the preparation of the cyclization precursor **II-104** in 5 steps and 66% yield (Scheme 47). (*R*)-Citronellal was transformed into the corresponding alkyne **II-105** in 2 steps and quantitative yields. Allylic oxidation of **II-105** using TBHP/SeO_2 produced the desired aldehyde **II-106** in 32% yield along with the corresponding alcohol (i.e. 41%), which could be converted into **II-106** after oxidation with IBX in 95% yield.

A similar approach relying on allylic oxidation of **II-84** with SeO_2 was also attempted during our synthesis (Scheme 39). However, the moderate yields we obtained, forced us to consider alternative routes. Finally, we were pleased to find that oxidative cleavage could also afford the desired aldehyde **II-87** in a similar yield (73%) over 3 steps.



Scheme 47. Synthesis of β-hydroxy ketone **II-104**

Boron-mediated enantioselective aldol reaction[104] of aldehyde **II-106** with enolate **II-107** and borane derivative **II-108** provided β-hydroxy ketone **II-104** in 95% yield, but with a moderate selectivity (4:1 *d.r.*).

With ketoenyne **II-104** in hand, a series of different protected derivatives were synthesized and tested in the gold(I)-catalyzed cyclization (Table 23, entries 1-7). In all the cases, cycloadduct **II-110** was obtained with moderate to good yield with catalyst AuCl or $[AuCl(PPh)_3]/AgSbF_6$ (Table 23, entries 1-5). However, the authors found that the free alcohol delivered the oxo-tricyclic product **II-109** as a single diastereoisomer in 48% yield using AuCl as the catalyst (Table 23, entry 6). Further attempt to improve the yield with $[AuCl(PPh)_3]/AgSbF_6$ gave unsatisfactory result (Table 23, entry 7).

104. Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994,** *116*, 11287-11314.

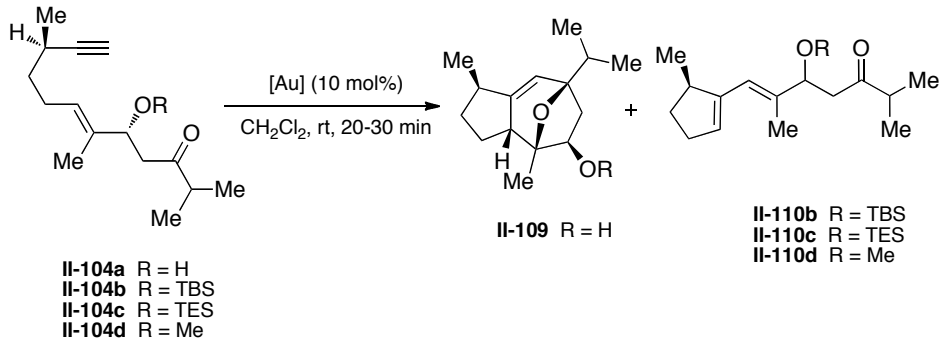
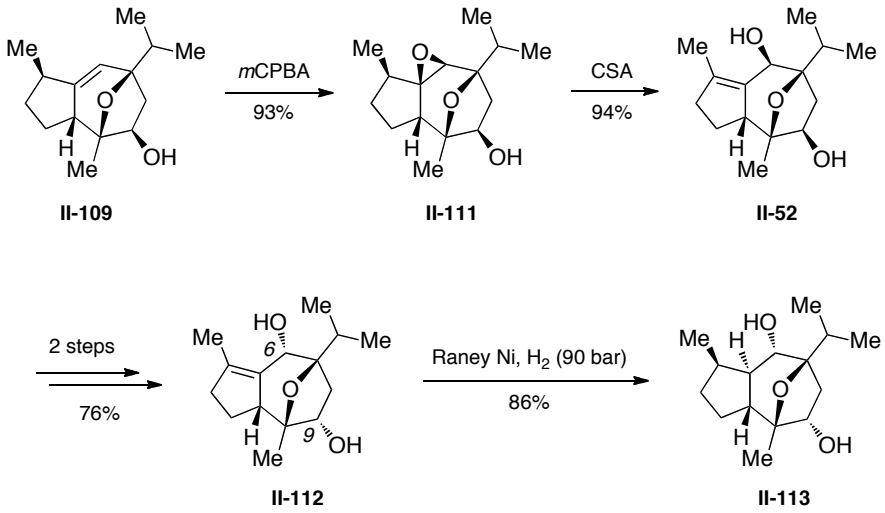


Table 23. Gold(I)-catalyzed cyclization of enynes **II-104**. Screening of conditions.

Entry	*R*	*Substrate*	*[Au]*	*Product (%)*
1	TBS	**II-104b**	AuCl	**II-110b** (80)
2	TBS	**II-104b**	$[AuCl(PPh)_3]/AgSbF_6$	**II-110b** (40)
3	TES	**II-104c**	AuCl	**II-110c** (90)
4	Me	**II-104d**	AuCl	n.r.
5	Me	**II-104d**	$[AuCl(PPh)_3]/AgSbF_6$	**II-110d** (10)
6	H	**II-104a**	AuCl	**II-109** (48)
7	H	**II-104a**	$[AuCl(PPh)_3]/AgSbF_6$	**II-109** (20)

To rationalize these results, a steric effect from the protecting groups was assumed by preventing the internal attack from the carbonyl group. Instead, the cyclopropyl Au(I) carbene gave exclusively monocyclic product **II-110** from a single cleavage rearrangement (Scheme 37, intermediate **II-79**).

The *trans*-fused ring of (-)-englerin A was built from oxotricyclic **II-109** by a series of oxidation/reduction sequences (Scheme 48). Stereoselective epoxidation with *m*CPBA afforded the corresponding epoxy alcohol **II-111** in 93% yield and subsequent reaction with camphor sulfonic acid provided the diol **II-52** in 94% yield. Attempts to protect **II-52** with silyl ethers and to hydrogenate the tetrasubstituted alkene failed. To overcome this challenging issue, a group-directed hydrogenation was envisaged instead.[105] Accordingly, **II-52** was converted into diol **II-112** with both hydroxyl groups pointing in the opposite direction to the oxo-bridge using a two steps sequence featuring a TPAP oxidation and a reduction with $NaBH_4$. Finally, diol **II-112** could be selectively hydrogenated into **II-113** in 86% yield at 75 ºC and high pressure (90 bar) with Raney Ni.



II-109 **II-111** **II-52**

II-112 **II-113**

Scheme 48. Synthesis of diol **II-113**.

Based on our experience in the hydrogenantion reaction of **II-98**, it is very unlikely that the free hydroxyl group in C6 could direct the hydrogenation of **II-112**. Indeed with

105. Sehgal, R. K.; Koenigsberger, R. U.; Howard, T. J. *J. Org. Chem.* **1975,** *40*, 3073-3078.

similar substrate **II-98**, hydrogenation using Raney Ni as a catalyst only afforded the wrong diastereoisomer **II-99** in quantitative yield (Scheme 44). In addition, analysis of substrate **II-112** showed the hydroxyl group in a *syn*-periplanar orientation with respect to the substituted alkene (Figure 22). Thus in our opinion, the high diastereoselectivity observed with compound **II-113** could be rationalized as a result of a directing effect from the hydroxyl group in C9.

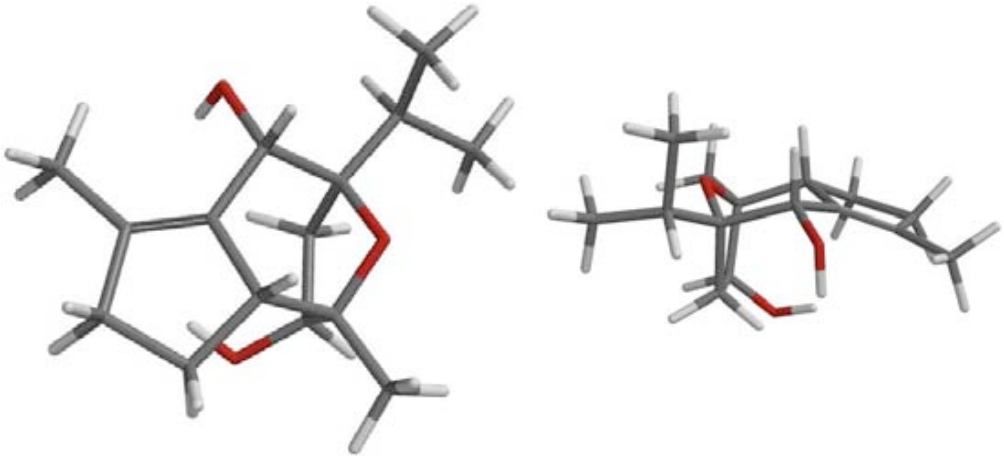
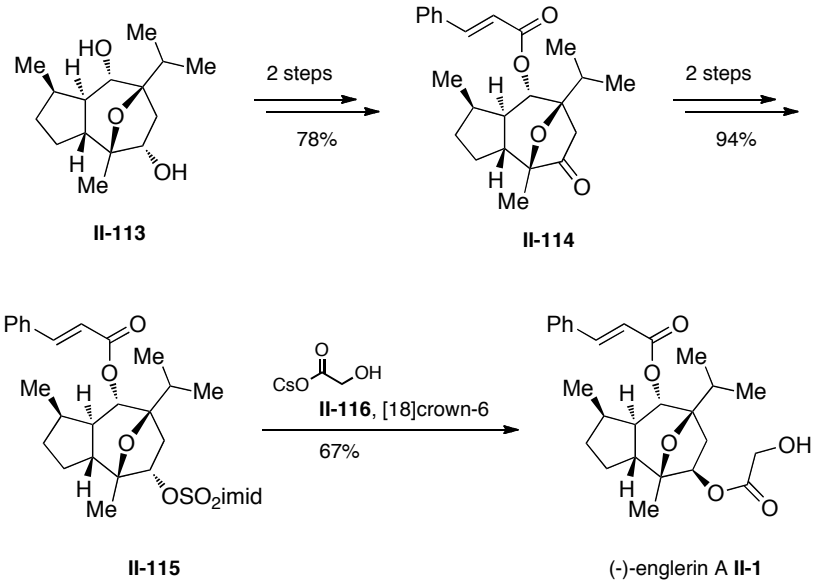


Figure 22. Two views of the calculated minimum energy conformation of **II-113**.[106]

Completion of the synthesis required an extra inversion of the hydroxyl group at C9 and the introduction of two ester groups (Scheme 49). Accordingly, diol **II-113** was transformed in ketone **II-114** by selective oxidation with DMP of the less hindered hydroxyl group in C9 followed by protection with cinnamic acid under Yamaguchi conditions in 78% overall yield. Reduction of **II-114** with $NaBH_4$ followed by treatment with $(imid)_2SO_2$ and LiHMDS provided sulfonylation product **II-115**.

106. Calculated minimum energy conformation using Spartan 10 (B3LYP, 6-31G*).



Scheme 49. Completion of the synthesis of (-)-englerin A.

(-)-Englerin A **II-1** was obtained in one step and 67% yield by heating **II-115** with the corresponding cesium salt of **II-116**.[107]

Analytical data of synthetic and natural (-)-englerin A matched with those reported in the literature although a lower optical rotation value was obtained (synthetic product $[\alpha]_D^{20} = -47$ (c = 0.55, MeOH)). This low enantiomeric purity was attributed to the starting material (*R*)-citronellal used in the beginning of the synthesis (77% *ee*).

The total synthesis of (-)-englerin A **II-1** was finally achieved in 15 steps and 8% overall yield from (*R*)-citronellal. No protecting groups were required during the synthesis, although an oxidation/reduction strategy was used instead to mask a hydroxyl group.

107. Vatèle, J.-M.; Hanessian, S. *Tetrahedron* **1996,** *52*, 10557-10568.

C. Experimental Part

Total Synthesis of Englerin A and B

General Methods

All reactions were carried out under Ar unless otherwise specified, using magnetic stirring and in solvents dried with a Solvent Purification System (SPS) or using standard procedures.[56] The rest of the reagents were used directly as provided from the commercial sources. Analytical thin layer chromatography was carried out using TLC aluminium sheets with 0.2 mm of silica gel (Merk GF_{234}). Flash chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm).

NMR spectra were recorded at 23 ºC on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus. NMR chemical shifts (δ) are expressed in ppm. ^{1}H-NMR chemical shifts are referenced to TMS (in the case of $CDCl_3$) or to the solvent residual signal (in the case of other NMR solvents).[57] ^{13}C-NMR chemical shifts are referenced to the solvent signal. ESI mass spectra were recorded on a Waters LCT Premier spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter. Chiral HPLC analysis was performed on a Waters system using a Chrialpak IA column (4.6x250 mm) or a Chrialpak IC column (4.6x250 mm). Melting points were determined using a Büchi melting point apparatus.

Catalysts **C1**, **C2** and **TriP** were synthesized according to literature procedures.[58]

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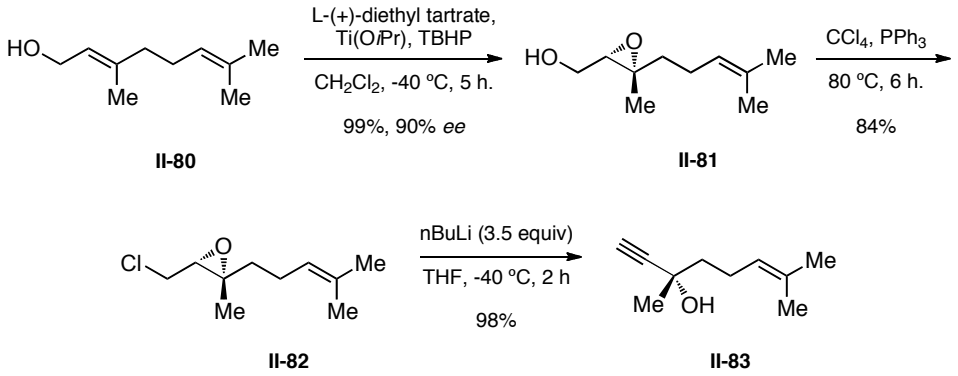
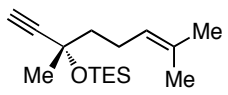
56. Amarego, W. L. F.; Chai, C. L. L., *Purification of Laboratory Chemicals* **2003**, 5th edition. Butterworth-Heinemann.
57. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997,** *62*, 7512-7515.
58. (a) Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008,** *73*, 7721-7730. (b) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007,** *63*, 6306-6316.

(*S*)-3,7-Dimethyloct-6-en-1-yn-3-ol II-83



(*S*)-3,7-dimethyloct-6-en-1-yn-3-ol **II-83** was synthesized in three steps according to the procedure of D. K. Mohapatra *et al.*[86] with an overall yield of 81% and an *e.r.* of 95:5

(*S*)-(3,7-Dimethyloct-6-en-1-yn-3-yloxy)triethylsilane II-84



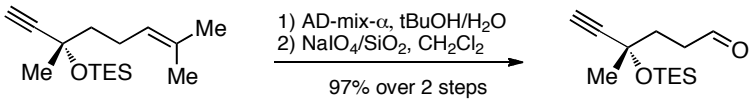
TES triflate (7.1 mL, 8.3 g, 31 mmol) was added dropwise to a solution of (*S*)-3,7-dimethyloct-6-en-1-yn-3-ol **II-83** (4.0 g, 26 mmol) and NEt_3 (6.6 mL, 4.8 g, 47 mmol) in CH_2Cl_2 (40 mL) at 0 ºC. The mixture was stirred for 3 h at room temperature before being quenched with sat. aq. NH_4Cl solution. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Chromatographic purification (hexanes) of the crude material yielded the corresponding silyl ether **II-84** as a colorless oil (7.0 g, 100%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ (ppm) = 5.13 (tq, J = 7.2, 1.4 Hz, 1H), 2.40 (s, 1H), 2.23-2.10 (m, 2H), 1.68 (s, 3H), 1.66-1.58 (m, 2H), 1.62 (s, 3H), 1.46 (s, 3H), 0.97 (t, J = 7.9 Hz, 9H), 0.70-0.65 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 131.7 (C), 124.2 (CH), 88.4 (C), 71.8 (CH), 68.9 (C), 45.3 (CH_2), 31.0 (CH_3), 25.8 (CH_3), 23.5

86. Mohapatra, D. K.; Pramanik, C.; Chorghade, M. S.; Gurjar, M. K. *Eur. J. Org. Chem.* **2007**, 5059-5063.

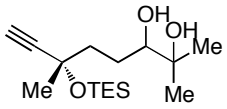
(CH_2), 17.7 (CH_3), 7.1 (3xCH_3), 6.2 (3xCH_2). GC-MS, m/z (%): 266 (M^+, 6), 251 (22), 183 (27), 119 (100), 103 (76), 75 (55).

(*S*)-4-Methyl-4-(triethylsilyloxy)hex-5-ynal II-86



II-84 **II-86**

(6*S*)-2,6-Dimethyl-6-(triethylsilyloxy)oct-7-yne-2,3-diol[90]

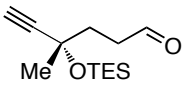


A solution of **II-84** (10.0 g, 37.5 mmol) in *tert*-BuOH (10 mL) was added to a stirred solution of AD-mix-α (52.6 g) and methanesulfonamide (3.57 g, 37.5 mmol) in *tert*-BuOH (130 mL) and water (130 mL) at 0 ºC. After stirring the solution over night at room temperature Na_2SO_3 (50 g) was added at 0 ºC followed by further stirring for 3 h. The mixture was extracted with EtOAc, the combined organic phases were washed with aq. KOH (2M) and dried over Na_2SO_4. Evaporation of the solvents yielded the pure diol as a light yellow oil (11.3 g, 100%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.40 (dq, J = 10.4, 2.1 Hz, 1H), 2.49 (d, J = 4.4 Hz, 1H, OH), 2.42 (s, 1H), 2.05 (br, 1H, OH), 1.97-1.90 (m, 1H), 1.80-1.70 (m, 2H), 1.53-1.44 (m, 1H), 1.50 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 0.97 (t, J = 7.6 Hz, 9H), 0.70-0.65 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 87.9 (C), 78.5 (CH), 73.2 (C), 72.3 (CH), 69.3 (C), 42.4 (CH_2), 31.2 (CH_3), 27.0 (CH_2), 26.9 (CH_3), 23.4 (CH_3), 7.1 (3xCH_3), 6.1 (3xCH_2). HRMS-ESI calcd for $C_{16}H_{32}O_3SiNa$ (M+Na)$^+$: 323.2013; found: 323.2015.

90. Hamon, D. P. G.; Tuck, K. L.; Christie, H. S. *Tetrahedron* **2001,** *57*, 9499-9508.

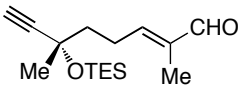
(*S*)-4-Methyl-4-(triethylsilyloxy)hex-5-ynal II-86



To a vigorously stirred suspension of SiO_2-supported $NaIO_4$[91] (0.680 mmol/g, 96.0 g, 65.3 mmol) in CH_2Cl_2 (1 L) was added a solution of the previous diol (10.26 g, 34.15 mmol) in CH_2Cl_2 (100 mL) within 10 min. After stirring the mixture over night at room temperature the solids were filtered off over celite. Evaporation of the solvents yielded pure aldehyde **II-86** as a light yellow oil (8.16 g, 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.80 (t, J = 1.6 Hz, 1H), 2.73-2.57 (m, 2H), 2.43 (s, 1H), 2.05-1.93 (m, 2H), 1.50 (s, 3H), 0.96 (t, J = 7.9 Hz, 9H), 0.71-0.64 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 202.5 (CH), 87.4 (C), 72.5 (CH), 68.4 (C), 39.8 (CH_2), 37.8 (CH_2), 31.0 (CH_3), 7.1 (3xCH_3), 6.1 (3xCH_2). HRMS-ESI calcd for $C_{13}H_{24}O_2SiNa$ (M+Na)$^+$: 263.1438; found: 263.1435.

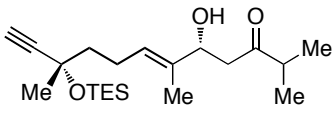
(*S*,*E*)-2,6-Dimethyl-6-(triethylsilyloxy)oct-2-en-7-ynal II-87



2-(triphenylphosphoranylidene)-propionaldehyde (15.57 g, 48.92 mmol) was added to a solution of **II-86** (9.048 g, 37.63 mmol) in benzene (260 mL). The suspension was refluxed for 15 h during which the ylide dissolved. ^{1}H-NMR spectroscopy of an aliquot showed 30% of remaining starting material. After addition of another 0.3 equiv of the ylide (3.600 g, 11.32 mmol) the mixture was refluxed for 24 h. The solution was then concentrated, hexane (250 mL) was added, the solids were filtered off over celite, and the solvents were evaporated. Chromatographic purification (30:1 to 10:1 hexanes/Et_2O) of the crude material yielded aldehyde **II-87** as a colorless oil (8.070 g, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.40 (s, 1H), 6.55 (td, J = 7.4, 1.0 Hz, 1H), 2.65-2.50 (m, 2H), 2.46 (s, 1H), 1.82-1.78 (m, 2H), 1.77 (s, 3H), 1.51 (s, 3H), 0.97 (t, J = 7.9 Hz, 9H), 0.72-0.66 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 195.4 (CH), 154.8 (CH), 139.5 (C), 87.6 (C), 72.5 (CH), 68.7 (C), 43.7 (CH_2), 31.1 (CH_3), 24.7 (CH_2), 9.2 (CH_3), 7.1 (3xCH_3), 6.2 (3xCH_2). HRMS-ESI calcd for $C_{16}H_{28}O_2SiNa$ (M+Na)$^+$: 303.1751; found: 303.1754.

(5*R*,10*S*,*E*)-5-Hydroxy-2,6,10-trimethyl-10-(triethylsilyloxy)dodec-6-en-11-yn-3-one II-90

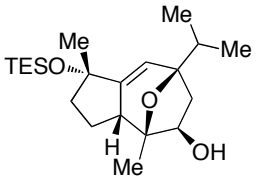


Following a reported procedure,[92] trichloro(3-methylbut-1-en-2-yloxy)silane **II-88** (1.88g, 8.56 mmol) was added quickly to a solution of phosphoramide catalyst **II-89** (132 mg, 0.357 mmol) in CH_2Cl_2 (7 mL) at -78 ºC. After the quick addition of a cold solution (-78 ºC) of (*S,E*)-2,6-dimethyl-6-(triethylsilyloxy)oct-2-en-7-ynal (**II-87**, 2.00g, 7.13 mmol) in CH_2Cl_2 (7 mL) the mixture was stirred for 4 h at -78 ºC. It was then quickly poured into a cold (0 ºC) sat. aq. $NaHCO_3$ solution and the slurry was vigorously stirred for 15 min. After filtration through a pad of celite the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and solvents were evaporated. Chromatographic purification (10:1 hexanes/EtOAc) of the crude material yielded the aldol product as a colorless oil (2.39 g, 91%). Formation of both *R*- and *S*-Mosher esters of **II-90** showed that the aldol reaction had proceeded with a *d.r.* >14:1 (see spectra p 184).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.48 (t, J = 7.2, 1H), 4.44 (dd, J = 8.9, 3.0 Hz, 1H), 2.99 (d, J = 2.5 Hz, 1H), 2.73-2.56 (m, 3H), 2.41 (s, 1H), 2.30-2.13 (m, 2H), 1.72-1.59 (m, 2H), 1.65 (s, 3H), 1.46 (s, 3H), 1.11 (d, J = 7.0 Hz, 6H), 0.96 (t, J = 7.9 Hz, 9H), 0.71-0.65 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 215.9 (C), 135.9 (C), 126.2 (CH), 88.2 (C), 73.1 (CH), 72.0 (CH), 68.9 (C), 45.5 (CH_2), 44.9 (CH_2), 41.7 (CH), 31.1 (CH_3), 23.0 (CH_2), 18.13 (CH_3), 18.11 (CH_3), 12.2 (CH_3), 7.2 (3xCH_3), 6.2 (3xCH_2). HRMS-ESI calcd for $C_{21}H_{38}O_3SiNa$ (M+Na)$^+$: 389.2482; found: 389.2462.

92. Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000,** *122*, 8837-8847.

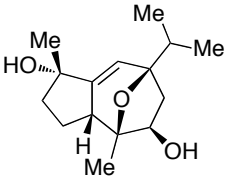
(1*S*,3a*R*,4*S*,5*R*,7*R*)-7-Isopropyl-1,4-dimethyl-1-((triethylsilyl)oxy)-1,2,3,3a,4,5,6,7-octahydro-4,7-epoxyazulen-5-ol II-91



Gold(I) catalyst **C1** (11.7 mg, 0.0127 mmol) was added at room temperature to a solution of **II-90** (155 mg, 0.423 mmol) in CH_2Cl_2 (5 mL) containing 4 Å molecular sieves. After stirring the mixture for 5 h the reaction was stopped by the addition of NEt_3 (0.1 mL). Filtration over SiO_2 and evaporation of the solvent followed by chromatographic purification (3:1 hexanes/Et_2O) of the crude material yielded the product **II-91** as a colorless oil and a single diastereoisomer (90 mg, 58%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.60 (d, J = 2.8 Hz, 1H), 4.13 (t, J = 6.6 Hz, 1H), 2.78-2.73 (m, 1H), 2.47 (dd, J = 11.8, 7.5 Hz, 1H), 1.89 (hept, J = 6.8 Hz, 1H), 1.81-1.66 (m, 3H), 1.52 (dd, J = 11.8, 5.8 Hz, 1H), 1.47-1.39 (m, 1H), 1.30 (s, 3H), 1.29 (s, 3H), 0.97 (d, J = 7.0 Hz, 6H), 0.95 (t, J = 7.6 Hz, 9H), 0.61-0.55 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 148.2 (C), 118.3 (CH), 84.9 (C), 83.6 (C), 79.4 (C), 74.1 (CH), 50.7 (CH_2), 47.6 (CH), 40.9 (CH_2), 34.1 (CH), 28.6 (CH_3), 22.7 (CH_2), 20.3 (CH_3), 17.8 (2xCH_3), 7.2 (3xCH_3), 6.9 (3xCH_2). The structure assignment of this compound was confirmed by 2D COSY, HSQC, HMBC and NOESY spectra. HRMS-ESI calcd for $C_{21}H_{38}O_3SiNa$ $(M+Na)^+$: 389.2482; found: 389.2485.

(1*S*,3a*R*,4*S*,5*R*,7*R*)-7-Isopropyl-1,4-dimethyl-1,2,3,3a,4,5,6,7-octahydro-4,7-epoxyazulene-1,5-diol II-94

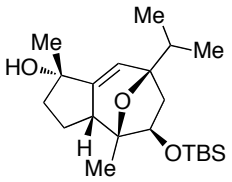


A TBAF solution (1.0 M in THF, 1.47 mL, 1.47 mmol) was added to a solution of tricycle **II-91** (450 mg, 1.23 mmol) in THF (10 mL) at 0 ºC. After stirring the mixture at room temperature for 10 h the reaction was stopped by addition of a sat. aq. NH_4Cl solution followed by extractive work up with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and the solvents were evaporated. Chromatographic purification (1:1 hexanes/EtOAc) of the crude material yielded diol **II-94** as a solid (275 mg, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.73 (d, J = 2.8 Hz, 1H), 4.16 (dd, J = 6.4, 6.0 Hz, 1H), 2.80-2.75 (m, 1H), 2.47 (dd, J = 12.0, 7.5 Hz, 1H), 1.91 (hept, J = 6.9 Hz, 1H),

1.83-1.69 (m, 5H), 1.55 (dd, J = 12.0, 5.8 Hz, 1H), 1.47-1.39 (m, 1H), 1.36 (s, 3H), 1.32 (s, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 149.0 (C), 119.6 (CH), 84.7 (C), 83.4 (C), 77.5 (C), 73.6 (CH), 50.7 (CH_2), 50.2 (CH), 41.1 (CH_2), 34.1 (CH), 28.0 (CH_3), 23.6 (CH_2), 20.4 (CH_3), 17.8 (CH_3), 17.7 (CH_3). The structure assignment of this compound was confirmed by 2D COSY, HSQC, HMBC and NOESY spectra and X-ray diffraction. HRMS-ESI calcd for $C_{15}H_{24}O_3Na$ $(M+Na)^+$: 275.1618; found: 275.1630.

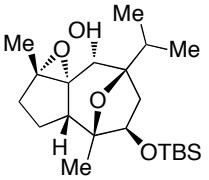
(1*S*,3a*R*,4*S*,5*R*,7*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-7-isopropyl-1,4-dimethyl-1,2,3,3a,4,5,6,7-octahydro-4,7-epoxyazulen-1-ol II-95



TBSCl (846 mg, 5.62 mmol) was added to a solution of diol **II-94** (1.09 g, 4.32 mmol), DMAP (53 mg, 0.43 mmol) and imidazole (882 mg, 13.0 mmol) in CH_2Cl_2 (40 mL). After stirring the mixture for 10 h at room temperature it was washed with aq. HCl (1 M). The aqueous phase was extracted with Et_2O, the combined organic layers were dried over Na_2SO_4 and solvents were evaporated. Chromatographic purification (5:1 hexanes/EtOAc) of the crude material yielded product **II-95** as a colorless oil (1.58 g, 100%). Chiral HPLC analysis at this stage of the synthesis revealed an *e.r.* of 99.6:0.4.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.70 (d, J = 2.7 Hz, 1H), 4.12 (dd, J = 6.9, 6.0 Hz, 1H), 2.78-2.73 (m, 1H), 2.31 (dd, J = 11.6, 7.3 Hz, 1H), 1.90 (hept, J = 6.8 Hz, 1H), 1.79-1.70 (m, 3H), 1.55 (dd, J = 11.6, 5.6 Hz, 1H), 1.40-1.37 (m, 1H), 1.34 (s, 3H), 1.25 (s, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 149.0 (C), 119.5 (CH), 85.2 (C), 83.5 (C), 77.5 (C), 73.5 (CH), 51.1 (CH_2), 50.3 (CH), 41.2 (CH_2), 34.2 (CH), 28.1 (CH_3), 25.9 (3xCH_3), 23.6 (CH_2), 20.9 (CH_3), 18.1 (C), 17.9 (CH_3), 17.8 (CH_3), -4.4 (CH_3), -4.8 (CH_3). The structure assignment of this compound was confirmed by 2D COSY, HSQC, HMBC and NOESY spectra. HRMS-ESI calcd for $C_{21}H_{38}O_3SiNa$ $(M+Na)^+$: 389.2482; found: 389.2480.

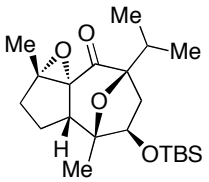
(1a*S*,3a*S*,4*S*,5*R*,7*R*,8*R*,8a*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-7-isopropyl-1a,4-dimethyloctahydro-1aH-4,7-epoxyazuleno[1,8*a*-*b*]oxiren-8-ol II-97



Method A: 3,5-dimethylpyrazole (39 mg, 0.41 mmol) was added to a suspension of CrO_3 (41 mg, 0.41 mmol) in CH_2Cl_2 (1.2 mL) at room temperature. After stirring the mixture for 15 min a dark red solution had formed. A solution of allyl alcohol **II-95** (50 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) was added at once and the mixture was stirred for 2 h. After stopping the reaction by dilution with Et_2O (10 mL) the suspension was filtered through a pad of Celite and the solvents were evaporated. Chromatographic purification (20:1 hexanes/EtOAc) of the crude material yielded epoxy alcohol **II-97** as a colorless oil (38 mg, 73%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.27 (dd, J = 7.3, 2.4 Hz, 1H), 4.04 (dd, J = 10.2, 1.2 Hz, 1H), 2.53 (dd, J = 13.9, 7.3 Hz, 1H), 2.18 (d, J = 10.2 Hz, 1H), 2.00 (hept, J = 6.9 Hz, 1H), 1.93-1.86 (m, 2H), 1.58 (dt, J = 14.0, 1.8 Hz, 1H), 1.54-1.42 (m, 2H), 1.50 (s, 3H), 1.16 (s, 3H), 1.063 (d, J = 7.0 Hz, 3H), 1.059 (d, J = 6.8 Hz, 3H), 1.03-0.99 (m, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 86.5 (C), 86.0 (C), 72.8 (CH), 71.2 (C), 67.0 (CH), 65.3 (C), 49.5 (CH), 41.5 (CH_2), 33.1 (CH), 32.9 (CH_2), 25.9 (3xCH_3), 20.2 (CH_2), 19.4 (CH_3), 18.3 (CH_3), 18.2 (C), 17.4 (CH_3), 15.3 (CH_3), -4.5 (CH_3), -4.9 (CH_3). The structure assignment of this compound was confirmed by 2D COSY, HSQC, HMBC and NOESY spectra. HRMS-ESI calcd for $C_{21}H_{38}O_4SiNa$ (M+Na)$^+$: 405.2432; found: 405.2428.

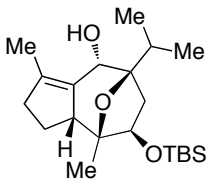
Method B: CrO_3 (164 mg, 1.64 mmol) was added to a solution of pyridine (264 μL, 259 mg, 3.27 mmol) in CH_2Cl_2 (4 mL) at 0 ºC. While warming the mixture to room temperature a dark red solution formed. A solution of allyl alcohol **II-95** (100 mg, 0.273 mmol) in CH_2Cl_2 (2 mL) was added at once and the mixture was stirred for 1 h at room temperature. Then the suspension was filtered through SiO_2 and the solvents were evaporated. Chromatographic purification (30:1 to 15:1 hexanes/EtOAc) of the crude material yielded the epoxy alcohol **II-97** (74 mg, 71%) and the corresponding epoxy ketone **II-96** (18 mg, 17%) as colorless oils.



^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.55 (dd, J = 7.4, 2.8 Hz, 1H), 2.63 (dd, J = 14.2, 7.4 Hz, 1H), 2.25 (d, J = 11.4, 7.0 Hz, 1H), 2.18 (hept, J = 6.8 Hz, 1H), 1.91-1.86 (m, 2H), 1.64 (s, 3H), 1.58-1.43 (m, 2H), 1.26 (s, 3H), 1.18-1.08 (m, 1H), 1.00 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 203.1 (C), 91.1 (C), 87.7 (C), 72.5 (CH), 68.0 (C), 66.6 (C), 52.0 (CH), 43.3 (CH_2), 33.1 (CH), 32.0 (CH_2), 25.9 (3xCH_3), 19.4 (CH_3), 19.1 (CH_2), 18.2 (C), 18.0 (CH_3), 16.9 (CH_3), 15.3 (CH_3), -4.5 (CH_3), -4.9 (CH_3). The structure assignment of this compound was confirmed by 2D COSY, HSQC, HMBC and NOESY spectra. HRMS-ESI calcd for $C_{21}H_{36}O_4SiNa$ (M+Na)$^+$: 403.2275; found: 403.2273.

$NaBH_4$ (8 mg, 0.2 mmol) was added to a solution of (1a*S*,3a*S*,4*S*,5*R*,7*R*,8a*R*)-5-((*tert*-butyldimethylsilyl)-oxy)-7-isopropyl-1a,4-dimethyl-hexahydro-1aH-4,7-epoxyazuleno[1,8a-b]oxiren-8(2H)-one **II-96** (20 mg, 0.053 mmol) and $CeCl_3{\cdot}(H_2O)_7$ (20 mg, 0.053 mmol) in MeOH (0.5 mL) at room temperature. The reaction was exothermic and complete after 2 min. The mixture was hence diluted with Et_2O, washed with water and the aqueous phase was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and solvents were evaporated. Chromatographic purification (30:1 to 15:1 hexanes/EtOAc) of the crude material yielded epoxy alcohol **II-97** as a colorless oil (20 mg, 100%).

(3a*R*,4*S*,5*R*,7*R*,8*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-7-isopropyl-1,4-dimethyl-2,3,3a,4,5,6,7,8-octahydro-4,7-epoxyazulen-8-ol II-98



Following a reported procedure,[95] *n*BuLi (1.5 M in hexane, 2.44 mL, 3.66 mmol) was added dropwise to a solution of WCl_6 (726 mg, 1.83 mmol) in THF (5 mL) at -78 ºC. The mixture was slowly

95. Umbreit, M.A.; Sharpless, K.B., *Org. Synth*. **1981**, *60*, 29-32.

warmed to room temperature, stirred for additional 10 min and then cooled down to 0 ºC. A solution of epoxy alcohol **II-97** (350 mg, 0.915 mmol) in THF (2 mL) was added and the mixture was warmed to room temperature and then to 50 ºC. After stirring for 2 h at this temperature the solution was poured into aq. Rochelle salt/NaOH (1.5 M/2 M, 200 mL). After vigorous stirring for 10 min the aqueous phase was extracted with Et_2O, the combined organic layers were dried over Na_2SO_4 and solvents were evaporated. Chromatographic purification (30:1 hexanes/Et_2O) of the crude material yielded the allyl alcohol **II-98** as a white solid (274 mg, 82%).

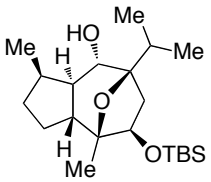
m.p.: 58 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.36 (bs, 1H), 3.89 (dd, J = 7.3, 2.0 Hz, 1H), 2.70-2.66 (m, 1H), 2.37-2.19 (m, 2H), 2.12 (dd, J = 13.6, 7.4 Hz, 1H), 1.95 (hept, J = 6.9 Hz, 1H), 1.88 (s, 3H), 1.85-1.80 (m, 1H), 1.54 (dd, J = 13.9, 1.6 Hz, 1H), 1.31-1.20 (m, 1H), 1.12 (s, 3H), 1.04 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 133.4 (C), 133.3 (C), 87.3 (C), 85.9 (C), 73.6 (CH), 73.1 (CH), 56.5 (CH), 41.3 (CH_2), 39.1 (CH_2), 33.4 (CH), 25.9 (3xCH_3), 23.8 (CH_2), 19.3 (CH_3), 18.2 (C), 18.1 (CH_3), 17.3 (CH_3), 14.7 (CH_3), -4.4 (CH_3), -4.9 (CH_3). The structure assignment of this compound was confirmed by 2D COSY, HSQC, HMBC and NOESY spectra. HRMS-ESI calcd for $C_{21}H_{38}O_3SiNa$ $(M+Na)^+$: 389.2482; found: 389.2469.

(1*R*,3a*R*,4*S*,5*R*,7*R*,8*S*,8a*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-7-isopropyl-1,4-dimethyldecahydro-4,7-epoxyazulen-8-ol II-100 and (1*S*,3a*R*,4*S*,5*R*,7*R*,8*S*,8a*S*)-5-((*tert*-butyldimethylsilyl)oxy)-7-isopropyl-1,4-dimethyldecahydro-4,7-epoxyazulen-8-ol II-99

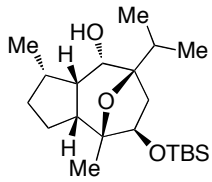
A solution of allyl alcohol **II-98** (30 mg, 0.082 mmol) and $[Ir(py)(PCy_3)(COD)][BAr_F]$[100] **II-101** (37 mg, 0.025 mmol) in CH_2Cl_2 (1 mL) was pressurized with H_2 (80 bar) and stirred for 4 days. The mixture was filtered through a pad of SiO_2 and the solvent was evaporated. Chromatographic purification (40:1 to 20:1

100. Wüstenberg, B.; Pfaltz, A. *Adv. Synth. Catal.* **2008,** *350*, 174-178.

hexanes/EtOAc) of the crude material yielded the hydrogenation products **II-100** as a white solid (15 mg, 50%) and **II-99** as a colorless oil (15 mg, 50%).

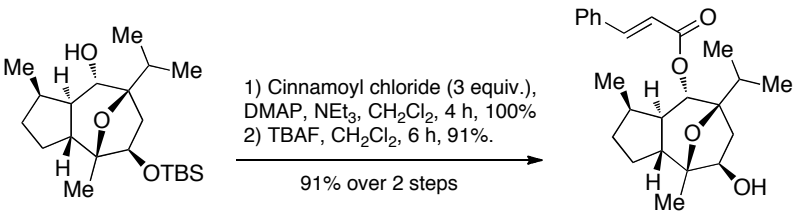


m.p.: 98 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.89 (dd, J = 7.4, 2.5 Hz, 1H), 3.61 (d, J = 10.2 Hz, 1H), 2.33-2.28 (m, 1H), 2.31 (dd, J = 13.7, 7.4 Hz, 1H), 2.03-1.93 (m, 2H), 1.71-1.52 (m, 4H), 1.24-1.19 (m, 2H), 1.16 (s, 3H), 1.05 (d, J = 6.9 Hz, 6H), 0.89 (s, 9H), 0.88 (d, J = 6.0 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 85.61 (C), 85.57 (C), 73.1 (CH), 71.1 (CH), 47.9 (2xCH), 42.4 (CH_2), 32.4 (CH), 31.5 (CH_2), 30.6 (CH), 26.1 (CH_2), 25.9 (3xCH_3), 19.8 (CH_3), 18.5 (CH_3), 18.3 (C), 17.6 (CH_3), 17.1 (CH_3), -4.5 (CH_3), -4.9 (CH_3). The structure assignment of this compound was confirmed by 2D COSY, HSQC, HMBC and NOESY spectra and X-ray diffraction. HRMS-ESI calcd for $C_{21}H_{40}O_3SiNa$ (M+Na)$^+$: 391.2639; found: 391.2651.



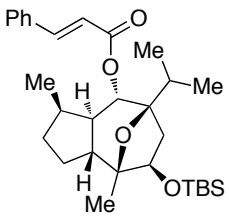
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.36 (dd, J = 6.9, 1.2 Hz, 1H), 4.04 (dd, J = 5.2, 3.6 Hz, 1H), 2.59 (dd, J = 12.0, 7.0 Hz, 1H), 2.49 (q, J = 9.0 Hz, 1H), 2.14-2.03 (m, 2H), 1.88 (hept, J = 6.8 Hz, 1H), 1.80-1.74 (m, 1H), 1.70-1.48 (m, 3H), 1.27 (dd, J = 12.0, 5.1 Hz, 1H), 1.22 (s, 3H), 1.18 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 3.9 Hz, 1H), 0.95 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 85.8 (C), 84.4 (C), 73.8 (CH), 70.6 (CH), 50.3 (CH), 44.5 (CH), 41.0 (CH_2), 36.4 (CH), 36.0 (CH), 34.9 (CH_2), 26.0 (3xCH_3), 25.5 (CH_2), 23.7 (CH_3), 18.2 (C), 17.4 (CH_3), 17.3 (CH_3), 15.8 (CH_3), -4.3 (CH_3), -4.8 (CH_3). The structure assignment of this compound was confirmed by 2D COSY, HSQC, HMBC and NOESY spectra. HRMS-ESI calcd for $C_{21}H_{40}O_3SiNa$ (M+Na)$^+$: 391.2639; found: 391.2656.

(-)-Englerin B II-2



II-100 (-)-englerin B **II-2**

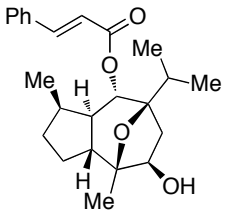
TBS-protected II-2



A solution of **II-100** (34 mg, 0.093 mmol), cinnamoyl chloride (46 mg, 0.28 mmol) and DMAP (34 mg, 0.28 mmol) in CH_2Cl_2 (0.4 mL) and NEt_3 (0.2 mL) was stirred at 80 ºC for 4 h. Afterwards the solvents were evaporated. Chromatographic purification (50:1 hexanes/EtOAc) of the crude material yielded the desired **TBS-protected II-2** as a pale yellow oil (53 mg, 100%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.66 (d, J = 16.0 Hz, 1H), 7.54-7.52 (m, 2H), 7.39-7.37 (m, 3H), 6.40 (d, J = 16.0 Hz, 1H), 5.09 (d, J = 10.2 Hz, 1H), 4.01 (dd, J = 7.4, 2.6 Hz, 1H), 2.50 (dd, J = 13.8, 7.4 Hz, 1H), 2.15-2.07 (m, 1H), 1.97-1.86 (m, 1H), 1.88 (hept, J = 7.0 Hz, 1H), 1.79-1.68 (m, 3H), 1.51-1.43 (m, 1H), 1.27-1.24 (m, 1H), 1.20 (s, 3H), 1.10-1.05 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 7.1 Hz, 3H), 0.94 (d, J = 7.1 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 165.8 (C), 145.0 (CH), 134.5 (C), 130.4 (CH), 129.0 (2xCH), 128.2 (2xCH), 118.4 (CH), 85.8 (C), 85.2 (C), 73.0 (CH), 71.9 (CH), 47.5 (CH), 46.9 (CH), 43.7 (CH_2), 33.2 (CH), 31.3 (CH), 31.2 (CH_2), 26.0 (3xCH_3), 25.1 (CH_2), 19.8 (CH_3), 18.5 (CH_3), 18.3 (C), 17.7 (CH_3), 17.2 (CH_3), -4.4 (CH_3), -4.8 (CH_3). The structure assignment of this compound was confirmed by 2D COSY, HSQC, HMBC and NOESY spectra. HRMS-ESI calcd for $C_{30}H_{46}O_4SiNa$ $(M+Na)^+$: 521.3058; found: 521.3044.

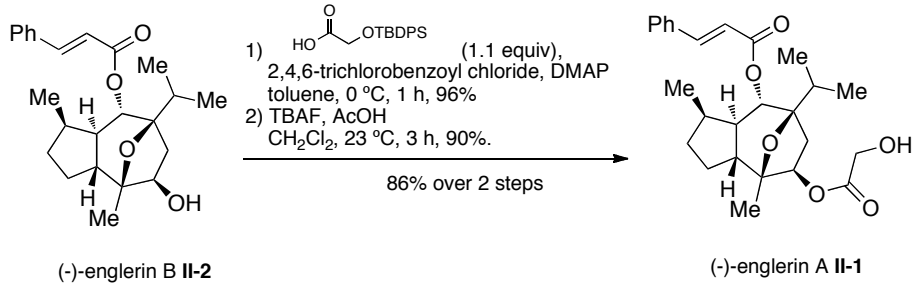
(-)-Englerin B II-2



A TBAF solution (1.0 M in THF, 0.15 mL, 0.15 mmol) was added to a solution of **TBS-protected II-2** (50 mg, 0.10 mmol) in THF (1.5 mL) at 0 ºC. After stirring the mixture at room temperature for 6 h the reaction was stopped by addition of water followed by extractive work up with EtOAc. The organic layers were dried over Na_2SO_4 and the solvents were evaporated. Chromatographic purification (5:1 hexane/EtOAc) of the crude material yielded (-)-**englerin B II-2** as a white solid (35 mg, 91%).

$[\alpha]_D^{25}$ = -29.8±1.7 (*c* = 0.17, MeOH). m.p.: 131 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.66 (d, *J* = 16.0 Hz, 1H), 7.54-7.51 (m, 2H), 7.39-7.38 (m, 3H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.11 (d, *J* = 10.3 Hz, 1H), 4.04 (dd, *J* = 7.4, 2.2 Hz, 1H), 2.64 (dd, *J* = 14.4, 7.6 Hz, 1H), 2.16-2.07 (m, 1H), 1.96-1.85 (m, 1H), 1.89 (hept, *J* = 6.9 Hz, 1H), 1.81-1.68 (m, 3H), 1.52-1.43 (m, 1H), 1.27 (s, 3H), 1.24-1.19 (m, 1H), 1.15-1.11 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 165.8 (C), 145.2 (CH), 134.5 (C), 130.5 (CH), 129.0 (2xCH), 128.2 (2xCH), 118.3 (CH), 85.4 (C), 85.2 (C), 73.2 (CH), 71.7 (CH), 47.5 (CH), 46.8 (CH), 43.1 (CH_2), 33.0 (CH), 31.3 (CH), 31.2 (CH_2), 25.0 (CH_2), 19.4 (CH_3), 18.3 (CH_3), 17.7 (CH_3), 17.1 (CH_3). ^{1}H- and ^{13}C-NMR spectra in CD_3OD and DMSO-D_6 are provided as well. The structure assignment of this compound was confirmed by 2D COSY, HSQC, HMBC and NOESY spectra. HRMS-ESI calcd for $C_{24}H_{32}O_4Na$ (M+Na)$^+$: 407.2193; found: 407.2196.

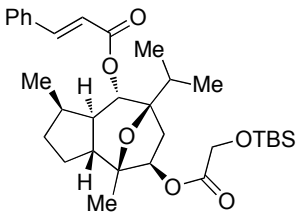
(-)-Englerin A II-1



(-)-englerin B **II-2**

(-)-englerin A **II-1**

TBDPS-protected II-1



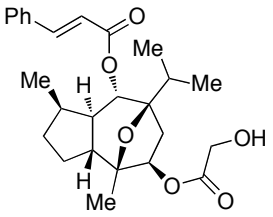
NEt_3 (4.5 μL, 33 μmol) and 2,4,6-trichlorobenzoyl chloride[102] (1.4 M in toluene, 10 μL, 14 μmol) were added to a stirred solution of **II-2** (5.1 mg, 13 μmol), TBDPS-protected glycolic acid[108] (4.5 mg, 14 μmol) and DMAP (3.2 mg, 26 μmol) in toluene (0.5 mL) at 0 ºC. The resulting white suspension was stirred at room temperature for 1 h before being quenched by addition of sat. aq. NH_4Cl solution. Et_2O was added and the layers were separated. The aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification (10:1 hexanes/EtOAc) afforded **TBDPS-protected II-1** as a colorless oil (9.3 mg, 96%).

^{1}H-NMR (400 MHz, CD_2Cl_2): δ (ppm) = 7.70-7.68 (m, 4H), 7.65 (d, J = 16.0 Hz, 1H), 7.57-7.54 (m, 2H), 7.47-7.37 (m, 9H), 6.42 (d, J = 16.0 Hz, 1H), 5.14 (dd, J = 8.1, 3.0 Hz, 1H), 5.07 (d, J = 10.1 Hz, 1H), 4.28 (s, 2H), 2.62 (dd, J = 14.6, 7.9 Hz, 1H), 2.16-2.07 (m, J = 7 Hz, 1H), 2.00-1.90 (m, 1H), 1.83 (m, J = 6.9 Hz, 1H), 1.76-1.69 (m, 3H), 1.61-1.55 (m, 1H), 1.27 (s, 3H), 1.30-1.21 (m, 2H), 1.08 (s, 9H), 0.96 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H). ^{13}C-NMR (125 MHz, CD_2Cl_2): δ (ppm) = 171.3 (C), 166.0 (C), 145.3 (CH), 136.1 (4xCH), 135.0 (C), 133.4 (2xC), 130.8 (CH), 130.5 (2xCH), 129.4 (2xCH), 128.6 (2xCH), 128.3 (4xCH), 118.8 (CH), 85.9 (C), 85.0 (C), 75.9 (CH), 71.7 (CH), 62.9 (CH_2), 48.1 (CH), 47.4 (CH), 40.4 (CH_2), 33.3 (CH), 31.8 (CH), 31.5 (CH_2), 27.0 (3xCH_3), 25.1 (CH_2), 19.7 (CH_3), 19.3 (CH_3), 18.5 (CH_3), 17.7 (CH_3), 17.2 (CH_3). HRMS-ESI calcd for $C_{42}H_{52}O_6SiNa$ $(M+Na)^+$: 703.3426; found: 703.3425.

102. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem, Soc. Jpn.* **1979**, *52*, 1989-1993.

108. Fanjul, S.; Hulme, A. N. *J. Org. Chem.* **2008,** *73*, 9788-9791.

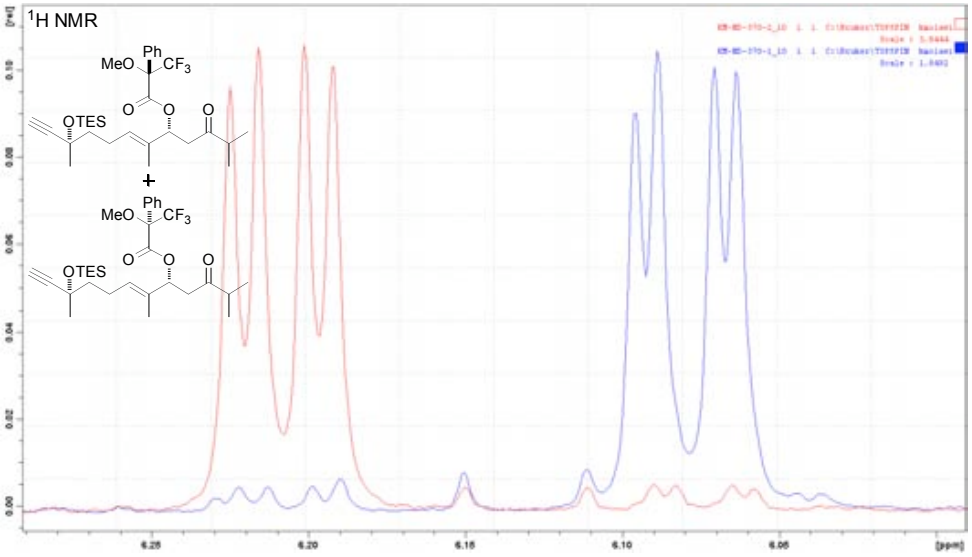
(-)-Englerin A II-1

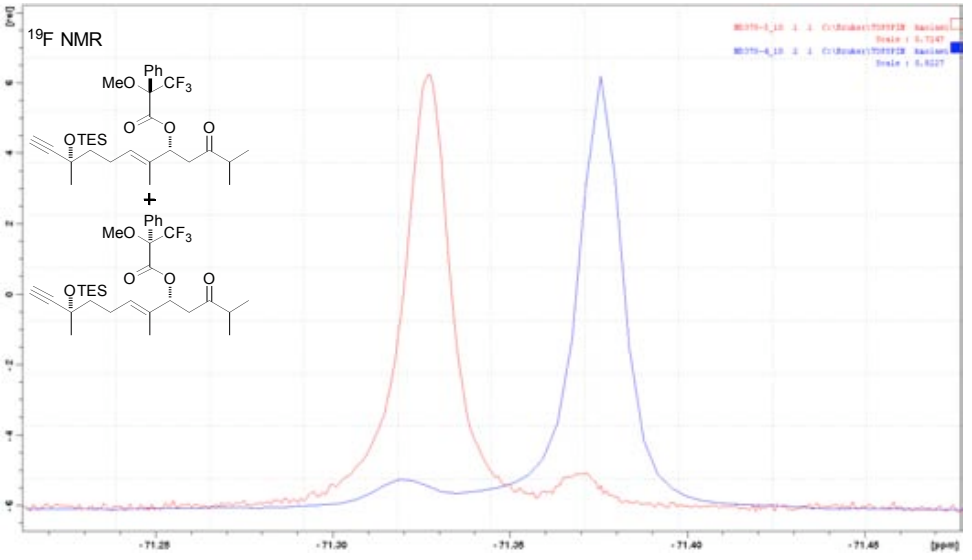


To a solution of **TBDPS-protected II-1** (16.6 mg, 24.3 μmol) in THF (1.5 mL) was added acetic acid (30 μL, 31 mg, 0.52 mmol) and TBAF (1 M in THF, 30 μL, 30 μmol) at 0 ºC. The mixture was stirred for 4 h at room temperature before being quenched by addition of sat. aq. NH_4Cl solution. EtOAc was added and the layers were separated. The aqueous layer was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification (4:1 to 2:1 hexanes/EtOAc) yielded **(-)-englerin A II-1** as a colorless compound (9.7 mg, 90%).

$[\alpha]_D^{25}$ = -58.7±2.5 (*c* = 0.52, MeOH). ^{1}H-NMR (500 MHz, CD_3OD): δ (ppm) = 7.69 (d, *J* = 16.0 Hz, 1H), 7.62-7.60 (m, 2H), 7.41-7.40 (m, 3H), 6.51 (d, *J* = 16.0 Hz, 1H), 5.26 (dd, *J* = 8.0, 3.0 Hz, 1H), 5.12 (d, *J* = 10.1 Hz, 1H), 4.15 (s, 2H), 2.70 (dd, *J* = 14.5, 7.9 Hz, 1H), 2.13 (m, *J* = 7.0 Hz, 1H), 2.03-1.96 (m, 1H), 1.91-1.82 (m, 2H), 1.79-1.72 (m, 2H), 1.70-1.64 (m, 1H), 1.38-1.26 (m, 2H), 1.19 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.1 Hz, 3H). ^{13}C-NMR (125 MHz, CD_3OD): δ (ppm) = 173.9 (C), 167.3 (C), 146.8 (CH), 135.6 (C), 131.6 (CH), 130.1 (2xCH), 129.3 (2xCH), 118.8 (CH), 86.7 (C), 86.0 (C), 76.6 (CH), 72.4 (CH), 61.05 (CH_2), 48.9 (CH), 48.0 (CH), 40.7 (CH_2), 34.1 (CH), 32.5 (CH), 32.0 (CH_2), 25.2 (CH_2), 19.2 (CH_3), 18.6 (CH_3), 17.7 (CH_3), 17.2 (CH_3). ESI-MS, m/z: 465.2 $(M+Na)^+$.

***S*- and *R*- Mosher ester analysis of aldol reaction product II-90:**

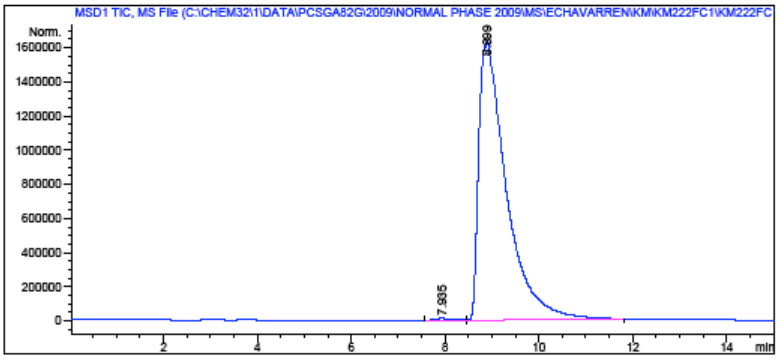




Chiral HPLC analysis of (1*S*,3a*R*,4*S*,5*R*,7*R*)-5-((*tert*-butyldimethylsilyl)oxy)-7-isopropyl-1,4-dimethyl-1,2,3,3a,4,5,6,7-octahydro-4,7-epoxyazulen-1-ol II-95:

Data File C:\CHEM32\...L PHASE 2009\MS\ECHAVARREN\KM\KM222FC1\KM222FC1_IC_HEX-DCM_10_SIM.D
Sample Name: KM222FC1

Acq. Operator	: ecm		
Acq. Instrument	: LC-MS	Location	: -
Injection Date	: 10/28/2009 10:42:06 AM	Inj	: 1
		Inj Volume	: No inj
Acq. Method	: C:\CHEM32\1\METHODS\AA.M		
Last changed	: 10/28/2009 10:41:20 AM by ecm (modified after loading)		
Analysis Method	: C:\CHEM32\1\METHODS\FIN-µSF.M		
Last changed	: 10/28/2009 11:15:15 AM by ecm (modified after loading)		
Sample Info	: Chiralpak IC 4.6x250mm, 5µm Hexane / DCM 90:10 1 mL/min 1.7mg/mL (Hex/DCM 4:1) T 25°C		



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

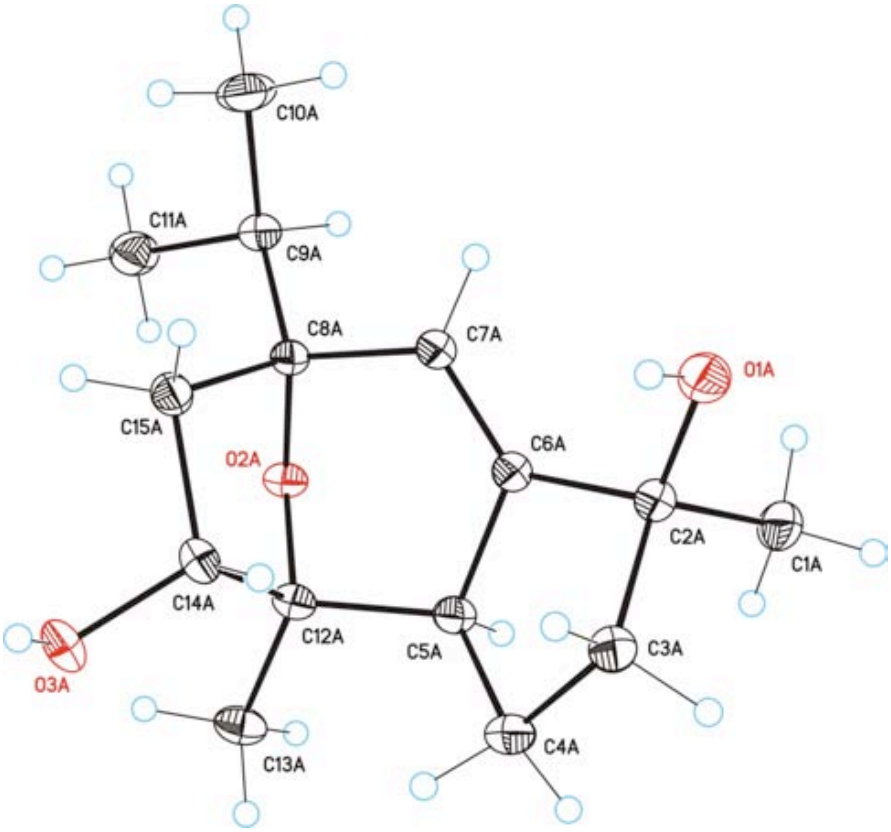
Signal 1: MSD1 TIC, MS File

Peak #	RetTime [min]	Type	Width [min]	Area	Height	Area %
1	7.935	BV	0.3764	2.75344e5	1.06817e4	0.4114
2	8.899	VB	0.5502	6.66503e7	1.63885e6	99.5886
Totals :				6.69256e7	1.64953e6	

*** End of Report ***

LC-MS 10/28/2009 11:18:16 AM ecm Page 1 of 1

Crystallographic data for (1*S*,3a*R*,4*S*,5*R*,7*R*)-7-isopropyl-1,4-dimethyl-1,2,3,3a,4,5,6,7-octahydro-4,7-epoxyazulene-1,5-diol II-94:



Crystal data and structure refinement for (1*S*,3a*R*,4*S*,5*R*,7*R*)-7-isopropyl-1,4-dimethyl-1,2,3,3a,4,5,6,7-octahydro-4,7-epoxyazulene-1,5-diol **II-94**.

Identification code	**II-94**
Empirical formula	C15 H24 O3
Formula weight	252.34
Temperature	100(2) K
Wavelength	0.71073 Å

Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 10.6035(3) Å a= 90.00°.
	b = 15.3304(4) Å b = 90.00°.
	c = 17.6128(5) Å g = 90.00°.
Volume	2863.06(14) $Å^3$
Z	8
Density (calculated)	1.171 mg/m^3
Absorption coefficient	0.080 mm^{-1}
F(000)	1104
Crystal size	0.60 x 0.30 x 0.25 mm^3
Theta range for data collection	1.76 to1.76°.
Index ranges	-16<=h<=17, -25<=k<=10,
	-28<=l<=28
Reflections collected	12960
Independent reflections	11774 [R(int) = 0.0307]
Completeness to theta =36.37 °	0.954%
Absorption correction	Empirical
Max. and min. transmission	0.9804 and 0.9538
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12960 / 0 / 337
Goodness-of-fit on F^2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0435, wR2 = 0.1179
R indices (all data)	R1 = 0.0494, wR2 = 0.1225
Largest diff. peak and hole	0.498 and -0.215 $e.Å^{-3}$

Crystallographic data for (1*R*,3a*R*,4*S*,5*R*,7*R*,8*S*,8a*R*)-5-((*tert*-butyldimethylsilyl) oxy)-7-isopropyl-1,4-dimethyldecahydro-4,7-epoxyazulen-8-ol II-100:

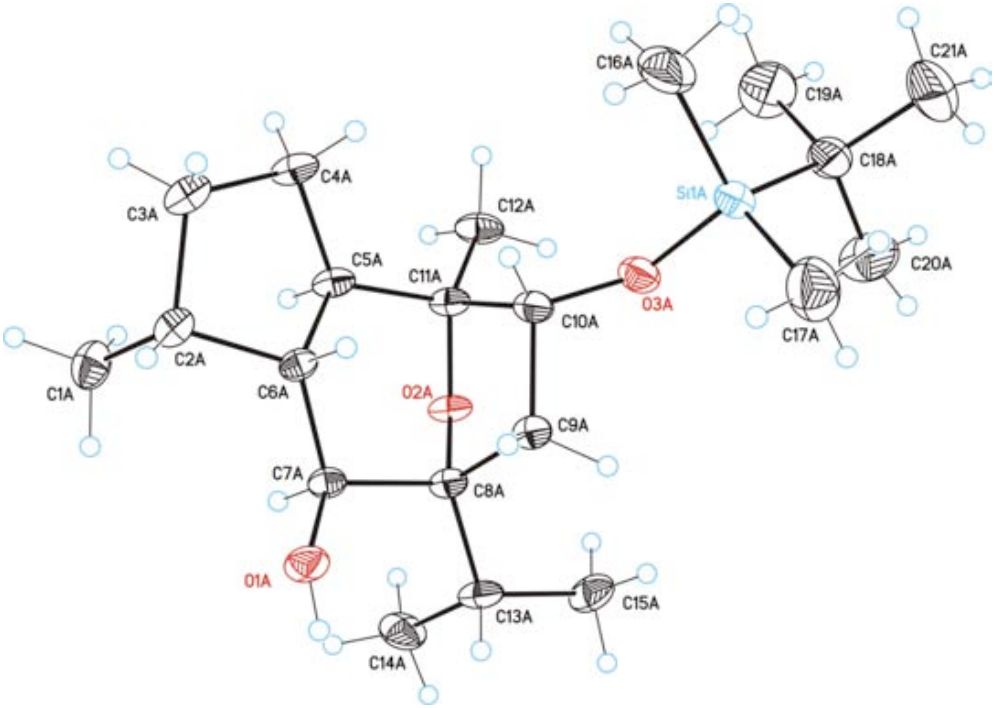


Table 1. Crystal data and structure refinement for (1*R*,3a*R*,4*S*,5*R*,7*R*,8*S*,8a*R*)-5-((*tert*-butyldimethylsilyl) oxy)-7-isopropyl-1,4-dimethyldecahydro-4,7-epoxyazulen-8-ol **II-100**.

Identification code	**II-100**
Empirical formula	C84 H160 O12 Si4
Formula weight	1474.48
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 15.66300(10) Å α= 90.00°.

	b = 19.7430(2) Å β = 90.00 °.
	c = 31.3050(3) Å γ = 90.00 °.
Volume	9680.59(15) $Å^3$
Z	4
Density (calculated)	1.012 Mg/m^3
Absorption coefficient	0.111 mm^{-1}
F(000)	3264
Crystal size	0.90 x 0.50 x 0.20 mm^3
Theta range for data collection	2.44 to 36.41 °.
Index ranges	-11<=h<=26, -32<=k<=30, -43 <=l<=52
Reflections collected	47070
Independent reflections	29204 [R(int) = 0.0692]
Completeness to theta =36.41 °	0.997%
Absorption correction	Empirical
Max. and min. transmission	0.9781 and 0.9464
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	47070 / 1 / 953
Goodness-of-fit on F^2	0.935
Final R indices [I>2sigma(I)]	R1 = 0.0580, wR2 = 0.1281
R indices (all data)	R1 = 0.0985, wR2 = 0.1444
Absolute Structure Flack parameter	x =-0.07(5)
Largest diff. peak and hole	0.622 and -0.261 $e.Å^{-3}$

III. Towards the Synthesis of Schisanwilsonene A

A. Introduction

1. Chemistry of [5.3.0] Bicyclic Compounds – An Overview

One area of natural product synthesis that has been heavily investigated during the last 80 years is the total synthesis of terpenes, also referred to as terpenoids or isoprenoids. These metabolites represent the largest class of natural products with over 55.000 members isolated to date,[109] and still serve as a source of inspiration for the development of strategies and tactics in organic chemistry.[110] Amongst the numerous existing subgroups of terpenes, the sesquiterpenes possess 15 carbons, derived from the assembly of three isoprene units. A common motif is the hydroazulene or bicyclo[5.3.0]decane skeleton (Figure 23).

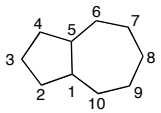


Figure 23. Bicyclo[5.3.0]decane skeleton.

Traditionally, synthetic approaches this bicyclic core involve the manipulation of six membered ring intermediates either to the corresponding cyclopentanoids by ring contraction or to the cycloheptanoids by ring expansion, and base-mediated cyclizations with aldol condensations.[111,112] More recent approaches including ring-closing

109. Gershenzon, J.; Dudareva, N. *Nat. Chem. Biol.* **2007,** *3*, 408-414.

110. Maimone, T. J.; Baran, P. S. *Nat. Chem. Biol.* **2007,** *3*, 396-407.

111. For a comprehensive treatise on the synthesis of sesquiterpenes, see: (a) Goldsmith, D.; Pirrung, M.; Morehead, A. T. "Total Synthesis of Natural Products: A Sesquidecade of Sesquiterpenes: Total Synthesis, 1980-1994. Part A: Acyclic and Monocyclic

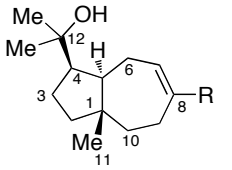
metathesis,[72,113,114] cycloaddition reactions,[115,116,117] metal-catalyzed reactions[118,119,120] and photochemical rearrangements have been reported.[121]

Sesquiterpenes", **1997**, *10,* John Wiley & Sons, Inc. (b) Goldsmith, D.; Pirrung, M.; Morehead, A. T.; Young, B. "Total Synthesis of Natural Products: A Sesquidecade of Sesquiterpenes: Total Synthesis, 1980-1994. Part B: Bicyclic and Tricyclic Sesquiterpenes", **2000**, *11,* John Wiley & Sons, Inc.

112. For a recent review on the synthetic approaches to bicyclo[5.3.0]decane sesquiterpenes, see: Foley, D. A.; Maguire, A. R. *Tetrahedron* **2010,** *66*, 1131-1175.
72. Willot, M.; Radtke, L.; Könning, D.; Fröhlich, R.; Gessner, V. H.; Strohmann, C.; Christmann, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 9105-9108.
113. For a review on macrocyclization by ring-closing metathesis in the total synthesis of natural products, see: Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086-6101.
114. For seminal examples of ring closing metathesis in sesquiterpenes synthesis, see: (a) Srikrishna, A.; Dethe, D. H. *Org. Lett.* **2003,** *6*, 165-168. (b) Oliver, S. F.; Högenauer, K.; Simic, O.; Antonello, A.; Smith, M. D.; Ley, S. V. *Angew. Chem. Int. Ed.* **2003**, *42*, 5996-6000. (c) Michalak, K.; Michalak, M.; Wicha, J. *Tetrahedron Lett.* **2008,** *49*, 6807-6809. (d) Dowling, M. S.; Vanderwal, C. D. *J. Org. Chem.* **2010,** *75*, 6908-6922.
115. Harmata, M.; Carter, K. W. *Tetrahedron Lett.* **1997,** *38*, 7985-7988.
116. For a mechanistic study of the rhodium(I)-catalyzed [5+2] cycloaddition, see: Liu, P.; Sirois, L. E.; Cheong, P. H.-Y.; Yu, Z.-X.; Hartung, I. V.; Rieck, H.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2010,** *132*, 10127-10135.
117. For a review on recent advances in asymmetric [4+3] cycloaddition reactions, see: Harmata, M. *Adv. Synth. Catal.* **2006,** *348*, 2297-2306.
118. For a seminal work on Mo-catalyzed [4+2+1] cycloaddition, see: Harvey, D. F.; Grenzer, E. M.; Gantzel, P. K. *J. Am. Chem. Soc.* **1994,** *116*, 6719-6732.
119. For a report on Ni-catalyzed [4+2+1] cycloaddition, see: Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2006,** *128*, 2609-2614.
120. Deng, L.; Giessert, A. J.; Gerlitz, O. O.; Dai, X.; Diver, S. T.; Davies, H. M. L. *J. Am. Chem. Soc.* **2005,** *127*, 1342-1343.
121. Sarpong, R.; Su, J. T.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003,** *125*, 13624-13625.

2. Schisanwilsonenes A-C

Schisanwilsonenes A-C (Figure 24) belong to the carotane group of sesquiterpenes, also called daucanes.



Schisanwilsonenes A-C

A: R = CH_2OH
B: R = CH_2OAc
C: R = CHO

Figure 24. Schisanwilsonenes A (**III-1**), B (**III-2**) and C (**III-3**).

These compounds were isolated in 2009 from a medicinal plant indigenous of southern China, *Schisandra wilsoniana* (Figure 25).[122]

122. Ma, W.-H.; Huang, H.; Zhou, P.; Chen, D.-F. *J. Nat. Prod.* **2009,** *72*, 676-678. Isolation yield of **III-1**: 4mg/kg of raw material.

Figure 25. *Schisandra wilsoniana.*

Its fruits are used in Chinese folk medecine as a substitute to treat hepatitis and early studies reported that the Et_2O extract showed a certain inhibiting activity against hepatitis-B virus (HBV).[123] Biological properties of the schisanwilsonenes were studied and schisanwilsonene A showed interesting antiviral properties (i.e. 77% and 29% inhibition effect of Anti-HBsAg and Anti-HBeAg respectively at 50 μg/mL). Comparative biological studies between **III-1**, **III-2** and **III-3** demonstrated the influence of the substituents at C8 towards the antiviral activity with best results obtained with **III-1.**

123. Bao, T. T.; Liu, T. G.; Song, Z. Y.; Sun, R. H., *Chin. Med. J.* **1980**, *93*, 41.

Structure elucidation was achieved by NMR studies and the relative configuration of Schisanwilsonene A (**III-1**) was assigned *via* X-ray struture analysis (Figure 26).[122]

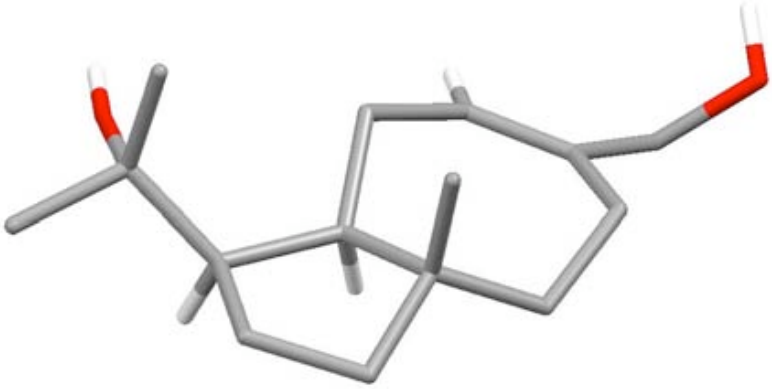


Figure 26. X-Ray structure of schisanwilsonene A **III-1**.

The bicyclo[5.3.0]decane skeleton of **III-1** has a total of three stereocenters and shows a relatively planar shape. Methyl group at C1 and isopropyl group at C4 are both *syn*-oriented.

122. Ma, W.-H.; Huang, H.; Zhou, P.; Chen, D.-F. *J. Nat. Prod.* **2009,** *72*, 676-678.

Similar structures were also found in other related terpenes (Figure 27).[124,125]

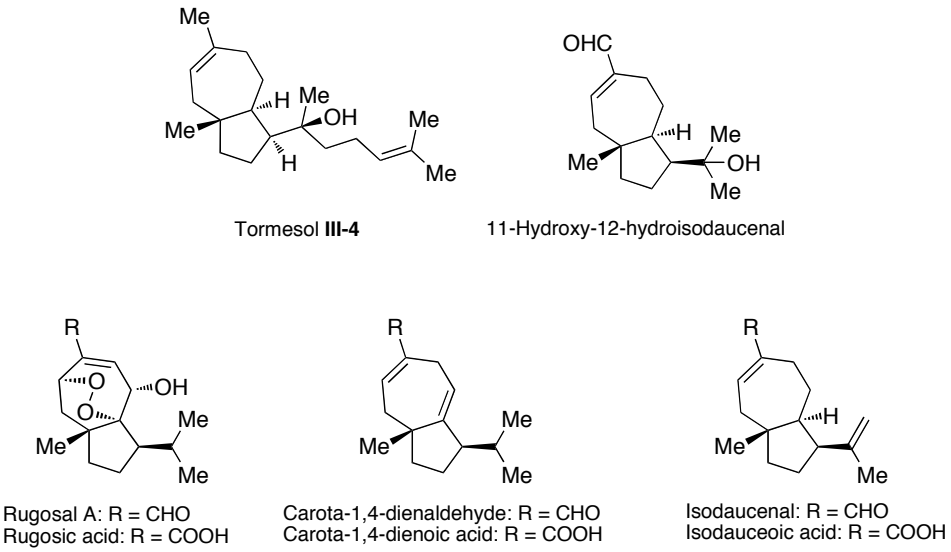


Figure 27. Structurally related carotane sesquiterpenes.

To date no synthesis of schisanwilsonenes A-C has been reported, although various approaches towards related terpenes have been published.[112] In the next section, theses syntheses will be briefly reviewed.

124. Urones, J. G.; Marcos, I. S.; Garrido, N. M.; de Pascual Teresa, J.; Feliciano Martìn, A. S. *Phytochemistry* **1989**, *28*, 183-187.

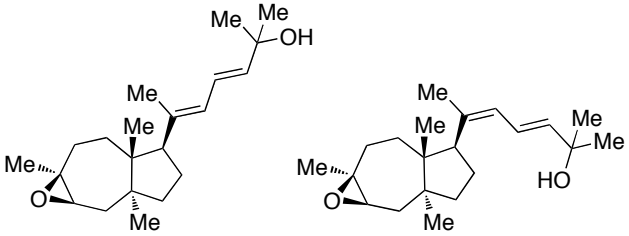
125. Beyer, J.; Becker, H.; Toyota, M.; Asakawa, Y. *Phytochemistry* **1987**, *26*, 1085-1089.

112. For a recent review on the synthetic approaches to bicyclo[5.3.0]decane sesquiterpenes, see: Foley, D. A.; Maguire, A. R. *Tetrahedron* **2010,** *66*, 1131-1175.

3. Previous Syntheses of Carotane Sequiterpenoids

The carotane skeleton is found in a variety of natural occurring sesquiterpenoids.[126] However, only few syntheses of carotane sesquiterpenoids have been reported to date.

A major contribution featured a ring-closing metathesis reaction applied to seven-membered carbocycles to access to tormesol **III-4** (Figure 27) and liverwort diterpenes **III-5** and **III-6** (Figure 28).[127,128]

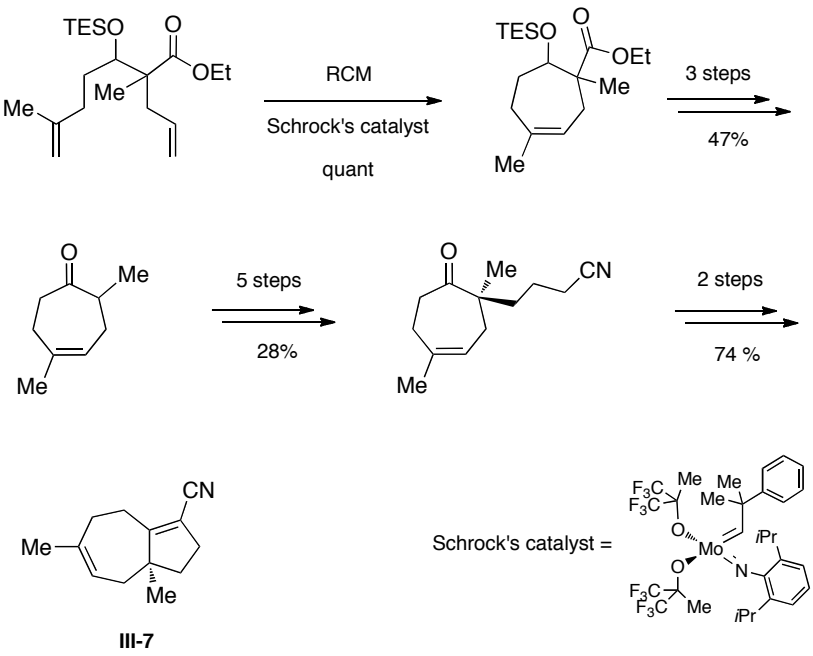


III-5 **III-6**

Figure 28. Liverwort diterpenes **III-5** and **III-6** with a bicyclo[5.3.0]decane skeleton.

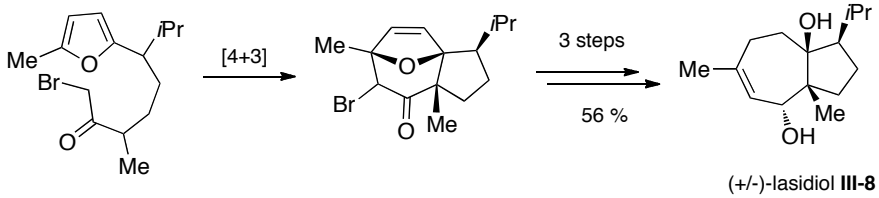
A common intermediate to the synthesis of these three products is the bicyclic intermediate **III-7** bearing a nitrile group obtained after an olefin metathesis using Schrock's catalyst followed by an intramolecular aldol reaction (Scheme 50).

126. For a study on the biological pathways occurring in the carotane sesquiterpenes synthesis, see: Zalkow, L. H.; Clower, M. G.; Gordon, M. M.; Gelbaum, L. T. *J. Nat. Prod.* **1980,** *43*, 382-394.
127. Nakashima, K.; Inoue, K.; Sono, M.; Tori, M. *J. Org. Chem.* **2002,** *67*, 6034-6040.
128. Nakashima, K.; Fujisali, N.; Inoue, K.; Minami, A.; Nagya, C.; Sono, M.; Tori, M., *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1955-1962.



Scheme 50. Synthesis of nitrile **III-7**.

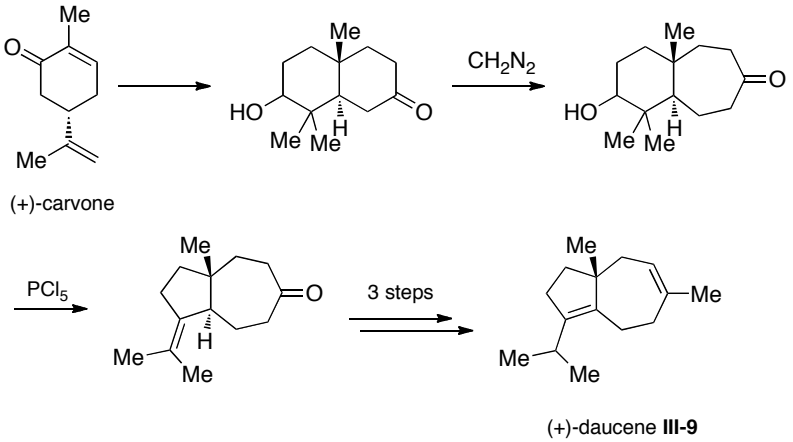
Another strategy towards the synthesis of carotane sesquiterpene (±)-lasidiol **III-8** relied on an intramolecular [4+3] cycloaddition followed by the cleavage of the oxo-bridge by reductive elimination with sodium naphthalenide (Scheme 51).[129]



Scheme 51. Synthesis of (±)-lasidiol **III-8**.

129. Kreiselmeier, G. n.; Föhlisch, B. *Tetrahedron Lett.* **2000,** *41*, 1375-1379.

A more classic approach involved a ring expansion reaction with diazomethane[130] as shown in the synthesis of (+)-daucene **III-9** from (+)-carvone (Scheme 52).[131]



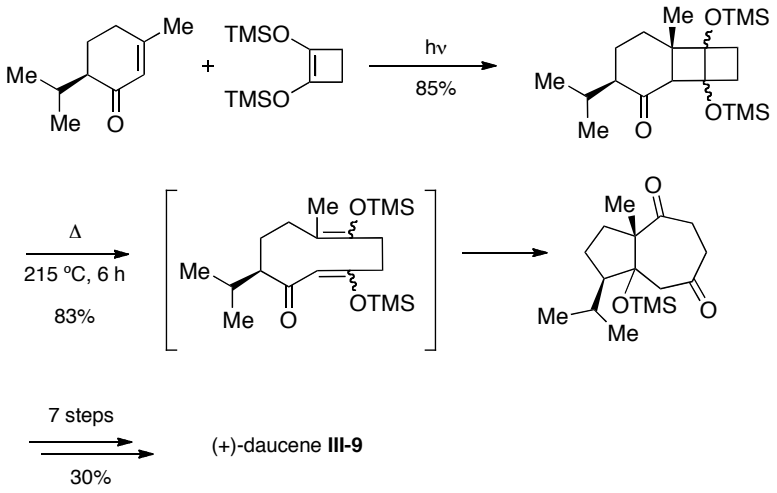
Scheme 52. Synthesis of (+)-daucene **III-9** using a ring expansion reaction.

An elegant strategy based on the thermolysis of tricyclo[4.4.0.0]decanes obtained from a [2+2] photocycloaddition, allowed the access to a series of carotane sesquiterpenoids and (+)-daucene **III-9** in particular (Scheme 53).[132]

130. Nelson, N. A.; Schut, R. N. *J. Am. Chem. Soc.* **1959**, *81*, 6486-6490.

131. Broissia, H. D.; Levisalles, J.; Rudler, H. *J. Chem. Soc., Chem. Commun.* **1972**, 855-855.

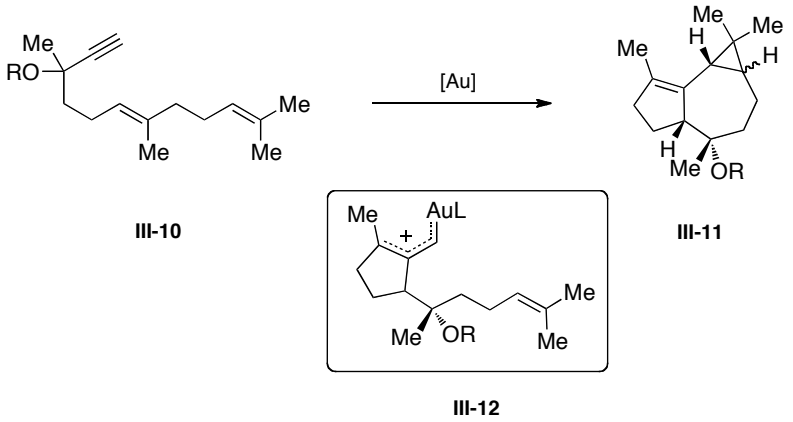
132. Audenaert, F.; De Keukeleire, D.; Vandewalle, M. *Tetrahedron* **1987**, *43*, 5593-5604.



Scheme 53. Synthesis of (+)-daucene **III-9** *via* a thermolysis reaction.

4. Intramolecular 1,5-Migrations *via* Allyl Gold Cations

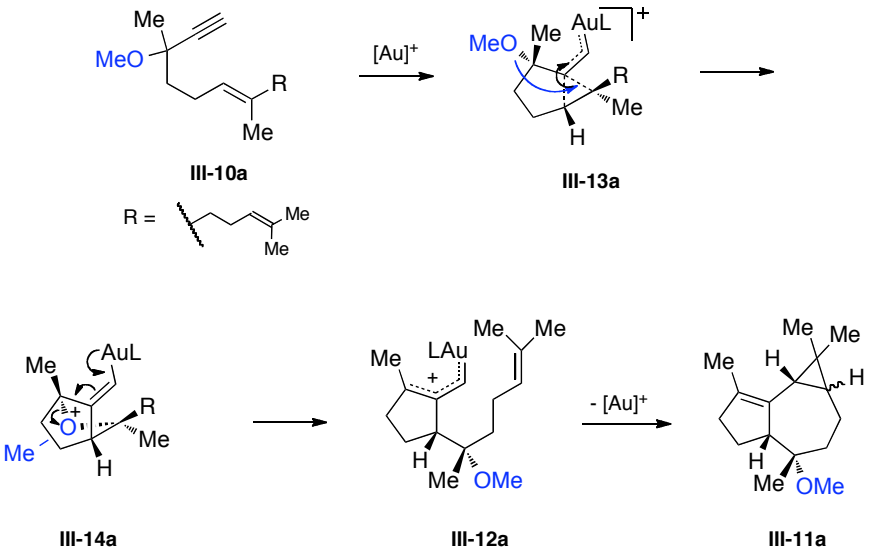
As part of our investigations on the gold(I)-catalyzed cycloisomerization of enynes, our group reported in 2009 the intramolecular 1,5-migration of the protected propargylic alcohol OR of dienyne **III-10** to form the allyl Au(I) cation intermediate **III-12** that undergoes a cyclopropanation reaction to afford tricyclic compound **III-11** (Scheme 54).[133]



Scheme 54. Formation of tricyclic adduct **III-11** from **III-10** by gold(I)-catalyzed intramolecular 1,5-migration.

Mechanistic studies demonstrated that the 1,5-migration proceeds *via* an intramolecular pathway (Scheme 55). Accordingly, upon activation of the alkyne **III-10a** with Au(I), an intermediate such as **III-13a** is formed. The OMe group migrates to form **III-14a**, that opens to give allyl Au(I) cation **III-12a**. Then an intramolecular cyclopropanation with the alkene on the side chain then gives tricyclic compound **III-11a**.

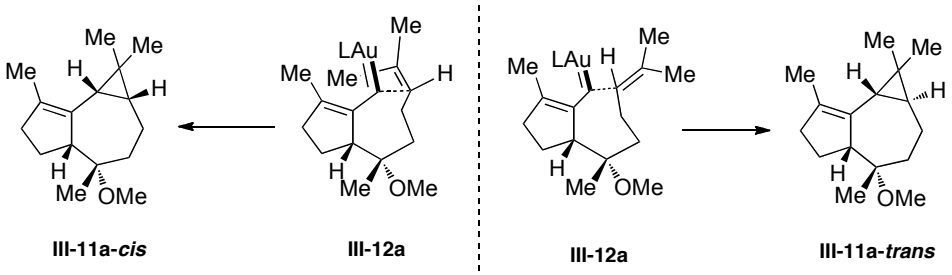
133. Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6152-6155.



Scheme 55. Mechanistic rationale of the gold(I)-catalyzed intramolecular 1,5-migration.

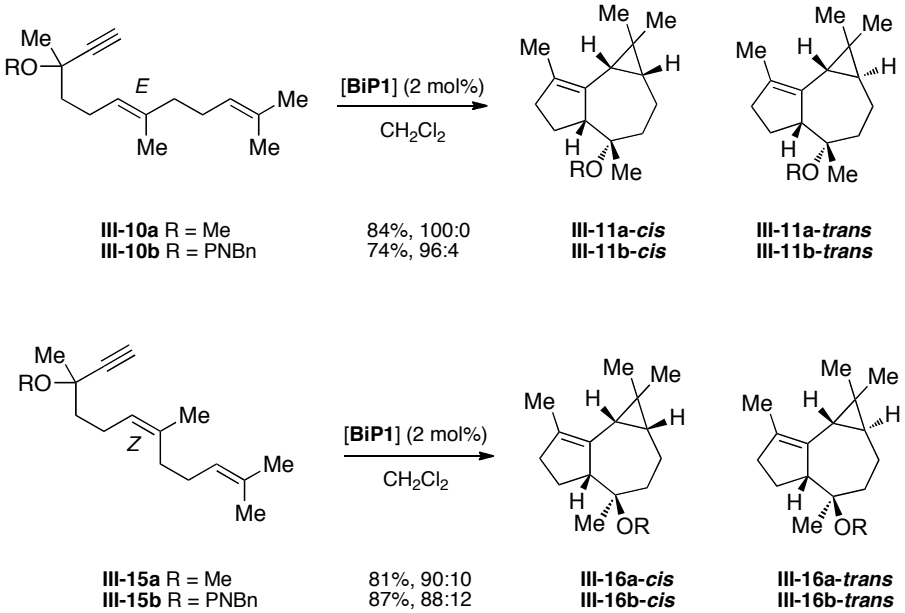
Noteworthy, the migration of the OMe group is much faster than the direct cyclopropanation by the pendant alkene of cyclopropyl Au(I) carbene **III-13a**.[134] Cycloadduct **III-11a** was isolated as a separable mixture of two diastereoisomers containing either a *cis*- or a *trans*-cyclopropane owing to the approach of the terminal alkene towards the allyl Au(I) cation in **III-12a** (Scheme 56). In all cases, the formation of **III-11a-*cis*** was highly favored (*cis*:*trans* > 8:1).

134. For examples of gold(I)-catalyzed cyclopropanation reactions with dienynes, see: (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402-2406. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006,** *12*, 1677-1693.



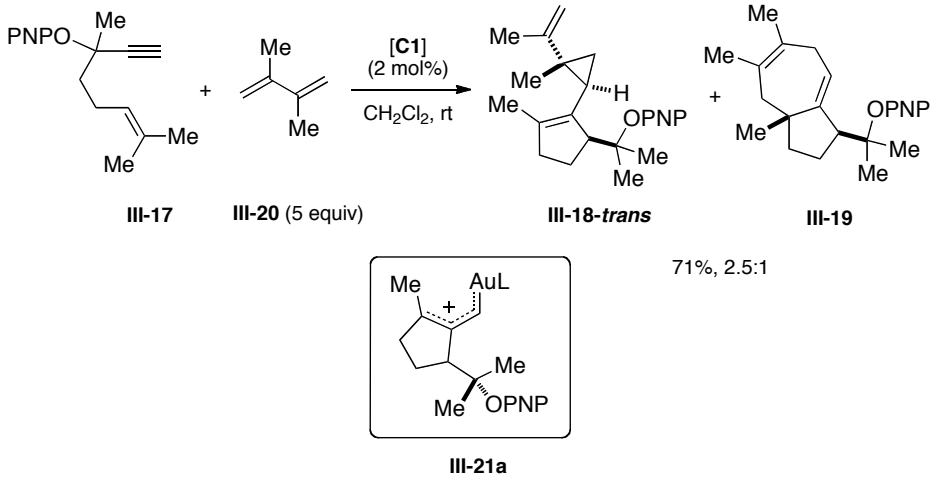
Scheme 56. Cyclopropanation of **III-12a** into **III-11a-*cis*** or **III-11a-*trans***.

As mentioned in the synthesis of englerins A and B (Part 2, Figure 19), the configuration of the internal double bond also controlled the newly formed quaternary stereocenter (Scheme 57). The outcome of the reaction is highly dependant on the nature of the migrating group. The best results were obtained with enynes bearing simple alkyl ethers although benzyl ethers were tolerated in the presence of Au(I) catalyst **BiP1**.



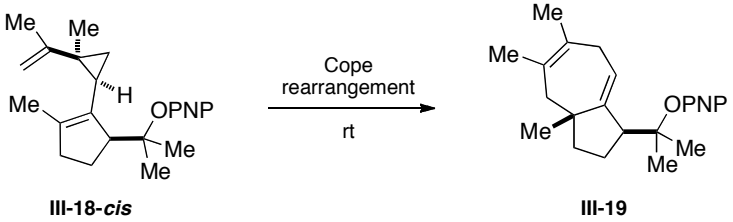
Scheme 57. Formation of tricyclic adducts **III-11** and **III-16**.

An interesting result was the trapping of allyl Au(I) cation **III-21a** through an intermolecular cyclopropanation with diene **III-20**, affording the corresponding divinylcyclopropane **III-18-*trans*** and hydroazulene **III-19** (Scheme 58).



Scheme 58. Formation of **III-18-*trans*** and **III-19** *via* cyclopropanation with diene **III-20**.

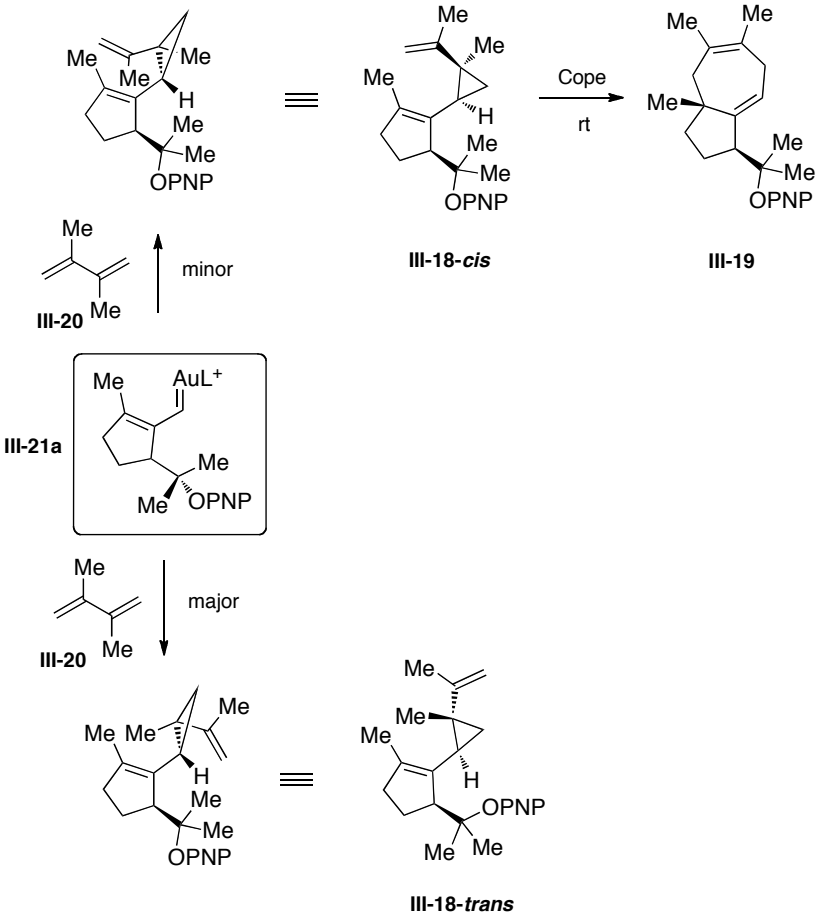
Compound **III-19** arised from an *in situ* Cope rearrangement of *cis*-cyclopropane **III-18-*cis*** subsequent to the intermolecular reaction with diene **III-20** (Scheme 59).[135,136]



Scheme 59. Cope rearrangement of *cis*-cyclopropane **III-18-*cis*** into bicyclic adduct **III-19**.

135. For a mechanistic study of the Cope cyclization with divinylcyclopropanes, see: Ullenius, C.; Ford, P. W.; Baldwin, J. E. *J. Am. Chem. Soc.* **1972,** *94*, 5910-5911.
136. For a related Cope cyclization of a divinylcyclopropane yielding a bicyclo[5.3.0]decane skeleton, see: Wender, P. A.; Filosa, M. P. *J. Org. Chem.* **1976,** *41*, 3490-3491.

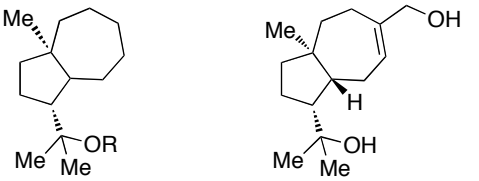
Insight into the mechanism of the reaction showed two possible approaches of diene **III-20** towards allyl Au(I) cation **III-21a** (Scheme 60).



Scheme 60. Mechanistic rationale of the intermolecular cyclopropanation reaction between diene **III-20** and allyl Au(I) cation **III-21a**.

Indeed, the cyclopropanation reaction that led to cyclopropane **III-18-*trans*** with a *trans*-configuration is favored due to a less sterically hindered transition state. On the contrary, unfavored approach of diene **III-20** upon **III-21a** afforded *cis*-cyclopropane **III-18-*cis*** that underwent a Cope rearrangement to yield **III-19.**

Thus, the gold(I)-catalyzed intramolecular 1,5-migration followed by the Cope rearrangement provides a straightforward access to bicyclo[5.3.0]decane skeletons with a methyl group *cis* to an isopropyl group (Figure 29).



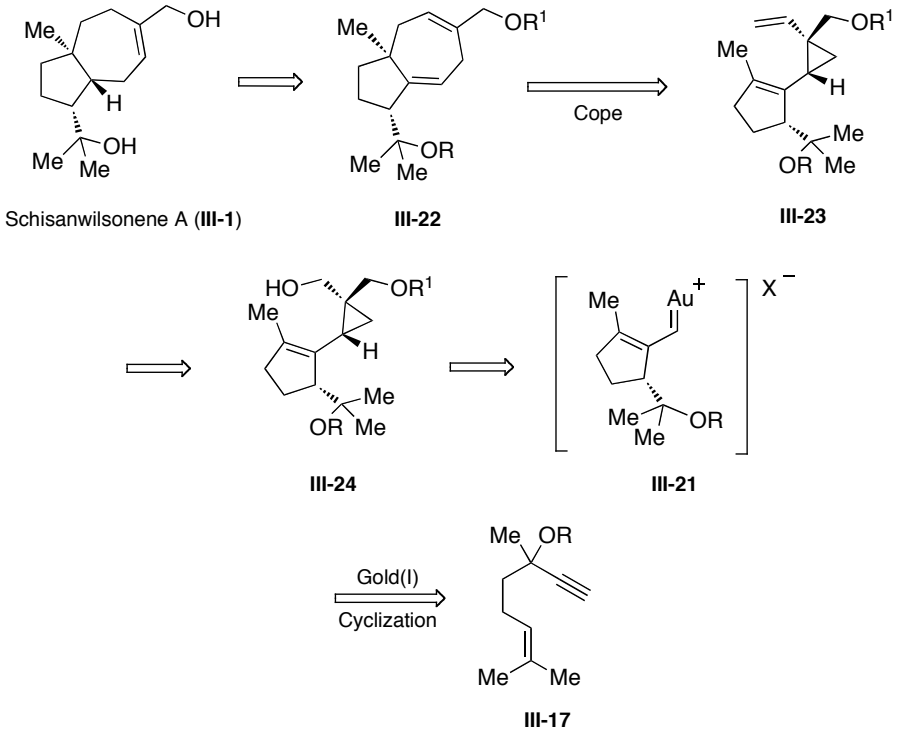
OR = migrating group Schisanwilsonene A (**III-1**)

Figure 29. Sesquiterpenoid skeleton available by a tandem gold(I)-catalyzed intramolecular 1,5-migration/Cope rearrangement and natural product schisanwilsonene A (**III-1**).

With the aim to use new gold(I)-catalyzed reactions towards the total synthesis of natural products, this methodology was applied to the synthesis of natural product schisanwilsonene A (**III-1**).

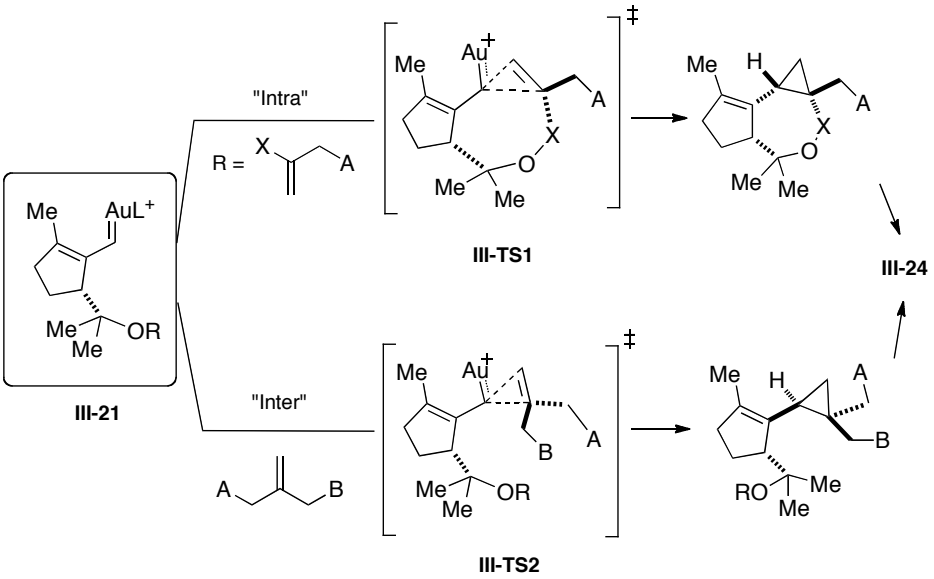
B. Results

Retrosynthetically, **III-1** would be obtained from **III-22**, which is the product of Cope rearrangement of cyclopropane **III-23** with the adequate *cis*-configuration (Scheme 61). **III-23** would be synthesized from **III-24** after transformations into the corresponding terminal alkene. Finally, **III-24** would be produced through cyclopropanation of the allyl Au(I) cationic intermediate **III-21** generated from enyne **III-17** by a gold(I)-catalyzed intramolecular 1,5-migration.



Scheme 61. Retrosynthetic analysis of the synthesis of schisanwilsonene A (**III-1**).

Two approaches were considered in order to obtain cyclopropane intermediate **III-24** with the correct *cis*-configuration from allyl Au(I) cation **III-21** (Scheme 62).



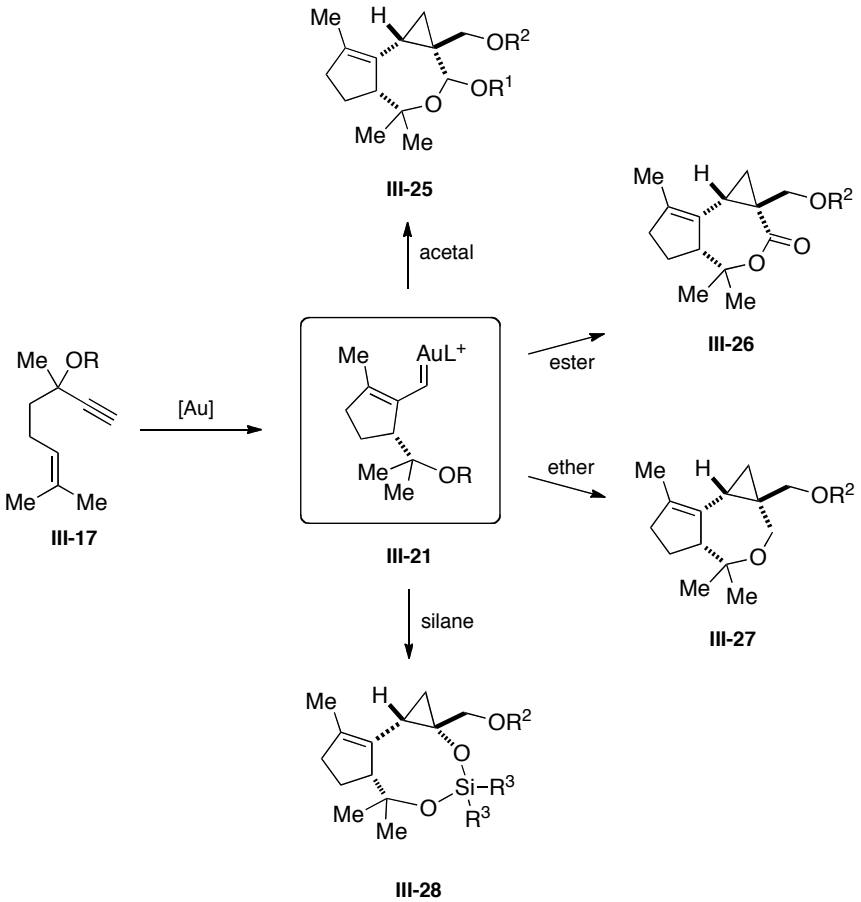
Scheme 62. Intramolecular and intermolecular strategies.

An *intermolecular approach* would deliver **III-24** in a straightforward manner but it would require a control of the *cis*/*trans* stereoselectivity. In addition, side products could be formed by a faster rearrangement of the allyl Au(I) cationic intermediate **III-21** if no reaction takes place with the trapping agent.

On the other hand, *an intramolecular strategy* based on a tethered alkene would confer a higher level of stereocontrol by temporally forming a cycle, which could be converted later into **III-24**. However, this approach makes the whole synthesis longer and involves a challenging intramolecular 1,5-migration.

1. Intramolecular Strategy: a Highly Streocontrolled Approach

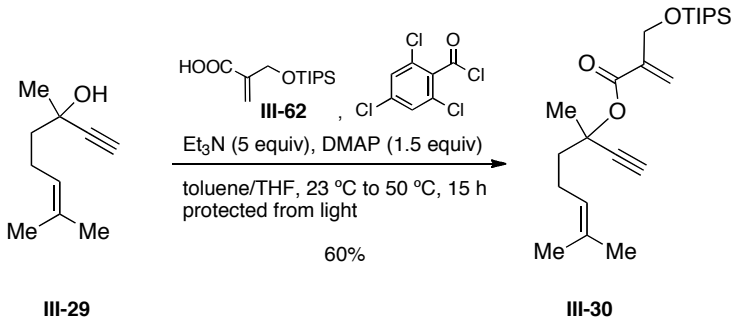
The key points of this approach are the ability of the propargylic oxy-group OR to migrate (Scheme 55, intermediate **III-13**), and the ease to cleave the tethered link in the tricyclic adduct to liberate the corresponding cyclopropane **III-24** (Scheme 61). Several linker groups were investigated under various conditions.



Scheme 63. Summary of the intramolecular cyclopropanation strategies using different linkers.

(1) Intramolecular Strategy: Acetal as a Linker

The ester **III-30** was obtained from **III-29** and **III-62** by an esterification reaction using Yamaguchi conditions[102] in 60% yield. Procedures using BopCl or the corresponding acyl chloride substrate were unsuccessful.



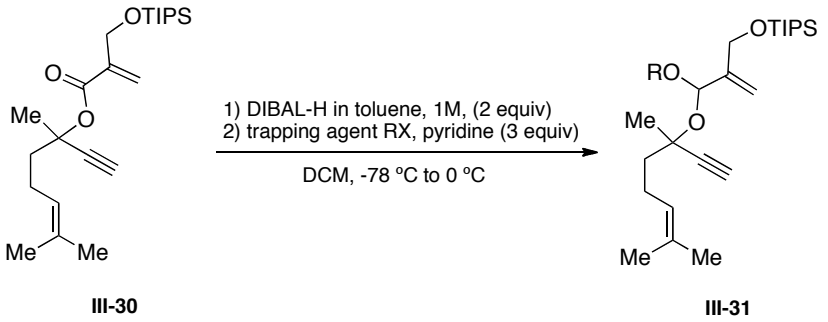
III-29 **III-30**

Scheme 64. Synthesis of ester **III-30**.

With ester **III-30** in hands, the reduction with DIBAL-H at low temperature (-78 ºC) followed by the trapping of the *in situ* formed hemiacetal was investigated (Scheme 65).[137]

102. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.

137. (a) Kiyooka, S.-i.; Shirouchi, M.; Kaneko, Y. *Tetrahedron Lett.* **1993,** *34*, 1491-1494. (b) Sames, D.; Liu, Y.; DeYoung, L.; Polt, R. *J. Org. Chem.* **1995,** *60*, 2153-2159. (c) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996,** *61*, 8317-8320. (d) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **1999,** *65*, 191-198.



III-30 **III-31**

Scheme 65. *In situ* formation of acetal **III-31**.

Unfortunately all attempts with various trapping agent failed (Table 24, entries 1-5). Considering the bulkiness around the propargylic alcohol, these results are not surprising and only few examples have been reported with α,β-unsaturated ester.[138]

Table 24. Screening of conditions for the synthesis of **III-31.**

Entry	*RX*	*Product*
1	Ac_2O	mixture
2	MeI	decomp
3[a]	Ac_2O	mixture
4[a]	MeI	decomp

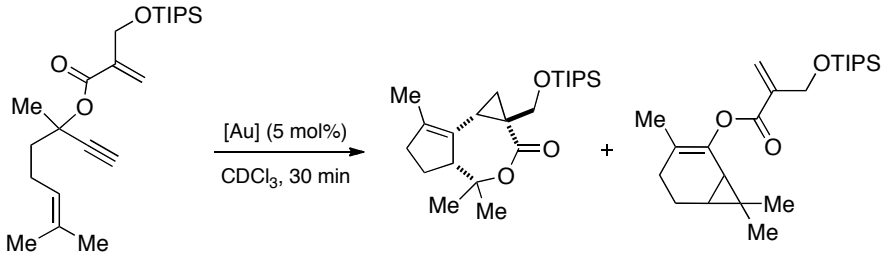
138. For two examples of reductive acetylation of α,β-unsaturated ester, see: (a) Haynes, R. K.; Fugmann, B.; Stetter, J.; Rieckmann, K.; Heilmann, H.-D.; Chan, H.-W.; Cheung, M.-K.; Lam, W.-L.; Wong, H.-N.; Croft, S. L.; Vivas, L.; Rattray, L.; Stewart, L.; Peters, W.; Robinson, B. L.; Edstein, M. D.; Kotecka, B.; Kyle, D. E.; Beckermann, B.; Gerisch, M.; Radtke, M.; Schmuck, G.; Steinke, W.; Wollborn, U.; Schmeer, K.; Römer, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 2082-2088. (b) Zurwerra, D.; Gertsch, J.; Altmann, K.-H. *Org. Lett.* **2010**, *12*, 2302-2305.

Entry	*RX*	*Product*
5[b]	TESOTf	mixture

[a] 1.1 equiv DIBAL-H used. [b] 1.5 equiv trapping agent used.

(2) Intramolecular Strategy: Ester as a Linker

All attempts to cyclize ester **III-30** in cycloadduct **III-32** with different Au(I) catalysts failed (Table 25, entries 1-5). A complex mixture was obtained with mainly product **III-33** formed by a 1,2-acyloxy migration.[139]



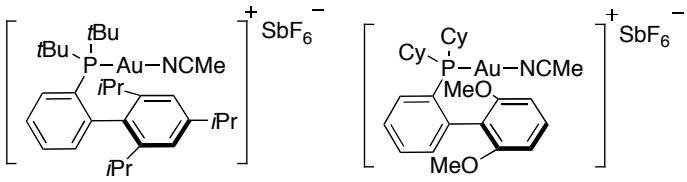
III-30 **III-32** **III-33**

Table 25. Screening of conditions for the gold(I)-catalyzed cyclization of **III-30**.

Entry	*[Au]*	*Product*
1	**C1**	**III-33** + mixture
2	**C2**	**III-33** + mixture

139. (a) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546-2547. (b) Fürstner, A.; Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006-3019.

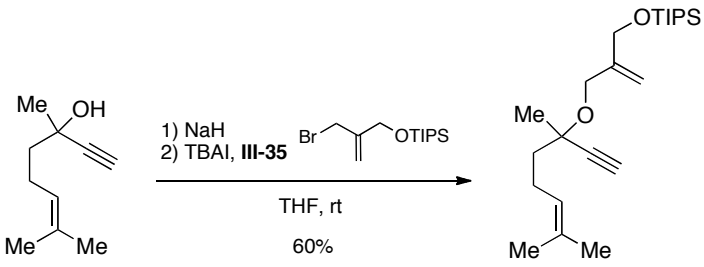
Entry	*[Au]*	*Product*
3	**BiP1**	**III-33** + mixture
4	**BiP2**	**III-33** + mixture
5	**BiP3**	**III-33** + mixture



BiP2 **BiP3**

(3) Intramolecular Strategy: Ether as a Linker

It has been shown that ethers (i.e. methyl ether or allyl ether) were suitable migrating groups for the gold(I)-catalyzed reaction.[133] Based on these observations, we envisaged using enyne **III-34** with a substituted allyl ether group (Scheme 66).



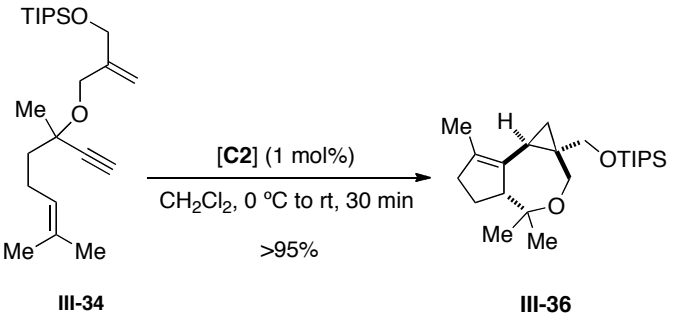
III-29 **III-34**

Scheme 66. Synthesis of substrate **III-34**.

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

Allyl bromide **III-35** was obtained in good yield from the corresponding allylic alcohol using a reported procedure.[140] Enyne **III-34** was obtained in 60% yield from **III-29**.

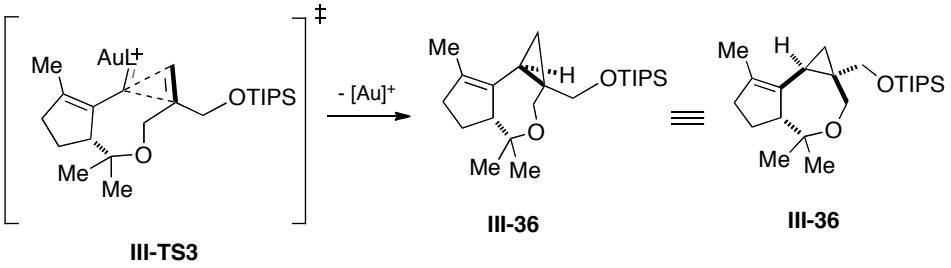
Remarkably, enyne **III-34** gave the corresponding cycloadduct **III-36** in excellent yield (> 95% yield) with **C2** as a catalyst (Scheme 67). This reaction was carried out up to a 500 mg scale.



III-34 **III-36**

Scheme 67. Synthesis of cycloadduct **III-36**.

The relative configuration of **III-36** was determined by NOE experiments. To rationalize the observed configuration in cyclopropane **III-36**, the reaction was assumed to proceed through **III-TS3** (Scheme 68).

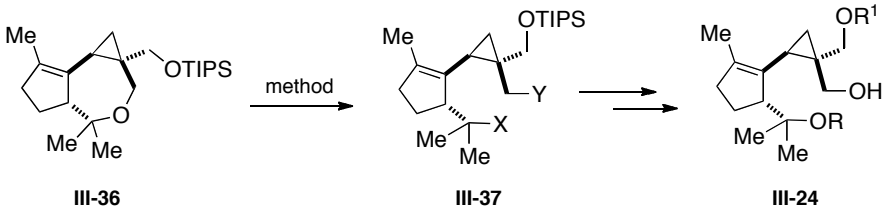


III-TS3 **III-36** **III-36**

Scheme 68. Rationale for the observed configuration of **III-36**.

140. Kiyota, H.; Takai, T.; Shimasaki, Y.; Saitoh, M.; Nakayama, O.; Takada, T.; Kuwahara, S. *Synthesis* **2007**, 2471-2480.

The next step of the synthesis required the opening of ether **III-36** in order to provide intermediate **III-37** that could be converted later into cyclopropane **III-24** (Scheme 69).[141]



Scheme 69. Opening of cyclic ether **III-36**.

Ideally, **III-37** would contain a tertiary alcohol at X and a halogenated sustituent at Y that could be transformed into the corresponding primary alcohol **III-24**.

The use of strong protic acids was excluded because it could promote elimination products. Therefore, several conditions and Lewis acids were tried to cleave ether **III-36** (Table 26). In all cases, decomposition of the starting material or no reaction was observed (Table 26, entries 1-4). Thus, H_3PO_4,[142] a known reagent for the cleavage of tertiary ethers under mild conditions, gave no reaction (Table 26, entry 1). $TiCl_4$ led to decomposition products and bromo-bis(dimethylamino)borane also gave no reaction (Table 26, entries 2 and 4).[143] Removal of the TIPS protecting group was observed when $CeCl_3 \cdot 7H_2O$/NaI was used (Table 26, entry 3).[144]

141. For a review on ether dealkylation, see: Weissman, S. A.; Zewge, D. *Tetrahedron* **2005**, *61*, 7833-7863.
142. Li, B.; Berliner, M.; Buzon, R.; Chiu, C. K. F.; Colgan, S. T.; Kaneko, T.; Keene, N.; Kissel, W.; Le, T.; Leeman, K. R.; Marquez, B.; Morris, R.; Newell, L.; Wunderwald, S.; Witt, M.; Weaver, J.; Zhang, Z.; Zhang, Z. *J. Org. Chem.* **2006**, *71*, 9045-9050.
143. Bell, T. W.; Ciaccio, J. A. *Tetrahedron Lett.* **1986**, *27*, 827-830.
144. Bartoli, G.; Marcantoni, E.; Sambri, L. *Synlett* **2003**, 2101-2116.

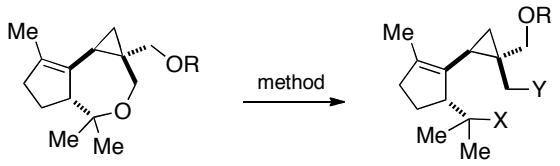


Table 26. Screening of conditions for the opening of ethers **III-36** and **III-38** to **III-40**.

Entry	*R*	*Substrate*	*Reagent*	*T (ºC)*	*Product*
1	TIPS	**III-36**	H_3PO_4 (85 % w/w)	rt	n.r.
2	TIPS	**III-36**	$TiCl_4$	0	decomp
3	TIPS	**III-36**	$CeCl_3 \cdot 7H_2O$/NaI	70	TIPS deprotection
4	TIPS	**III-36**	$((Me)_2N)_2BBr$	0 to rt	n.r.
5	H	**III-38**	BBr_3	0 to rt	complex mixture
6	H	**III-38**	SmI_2/AcCl	rt	acetylation
7	Bn	**III-39**	SmI_2/AcCl	rt	n.r.
8	Ac	**III-40**	BBr_3	-65 to rt	complex mixture

Other protecting groups, as well as the free OH, were also submitted to conditions for ether-opening (Table 26, entries 5-8). TIPS protecting group of **III-36** was removed with TBAF to give **III-38** in 84% yield. A complex mixture containing acetylation product was obtained with **III-38** in the presence of BBr_3 and SmI_2/AcCl respectively (Table 26, entries 5 and 6).[145,146] **III-39** containing a benzyl-protecting group gave no reaction with

145. Donner, C. D.; Gill, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 938-948.

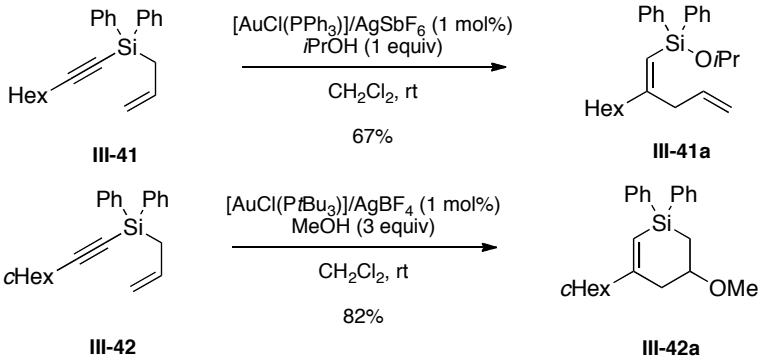
146. Kwon, D. W.; Kim, Y. H.; Lee, K. *J. Org. Chem.* **2002**, *67*, 9488-9491.

SmI_2/AcCl (Table 26, entry 7). **III-40** with an acetate as a protecting group also gave a complex mixture with BBr_3 (Table 26, entry 8).

(4) Intramolecular Strategy: Disiloxane as a Linker[147]

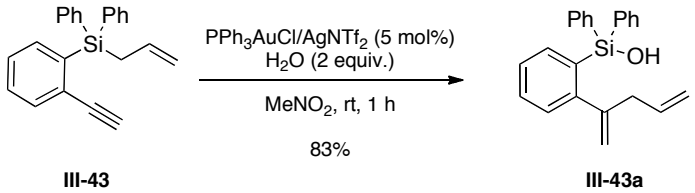
An alternative approach based on temporary silicon tethers was envisaged. The concept of tethering two reaction components to render a chemical process intramolecular is a well-established synthetic strategy and allows overcoming many of the problems associated with intermolecular reactions.[148] A significant advantage associated with intramolecularisation is the greater regio- and stereoselectivity that can be induced due to the inevitable increase in conformational restriction of the reaction transition state. Many applications with silicon tethers were found in cross coupling reactions and metathesis reactions.[149] However, few examples have been reported in gold chemistry. Alkynyl allyl silanes **III-41** and **III-42**, also described as 1,5-enynes, were converted to the corresponding alkoxy vinyl silanes **III-41a**[150] and the silacycle adduct **III-42a**[151] respectively, with a phosphine Au(I) catalyst and an alcohol as a nucleophile (Scheme 70).

147. This work was carried out in collaboration with Dr. Nolwenn Martin.
148. For a recent review on the use of temporary silicon tethers, see: Bracegirdle, S.; Anderson, E. A. *Chem. Soc. Rev.* **2010**, *39*, 4114-4129.
149. For a striking example of temporary silicon-tethered ring-closing-metathesis reactions, see: Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 1734-1737.
150. Park, S.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 10664-10665.
151. Horino, Y.; Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 11364-11365.



Scheme 70. Gold(I)-catalyzed intramolecular allylation of silyl alkynes.

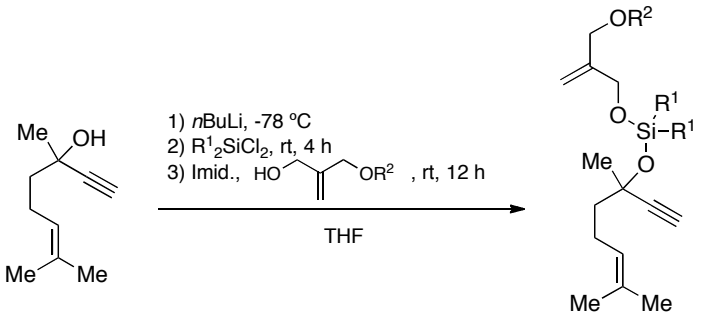
Extension to 1,7-enynes **III-43** was reported recently with the synthesis of **III-43a** containing a similar 1,4-diene framework (Scheme 71).[152]



Scheme 71. Gold(I)-catalyzed intramolecular allylation of 1,7-enyne with a silane linker.

Our strategy required the synthesis of enyne **III-44** containing the disiloxane linker with the trapping alkene. **III-44** was synthesized in moderate to good yield from **III-29** with different groups on the linker and a TIPS protecting group (Table 27, entries 1-3). Substrates with various silyl protecting groups were also synthesized based on the hypothesis that bulkiness may influence both the migration of the linker group during the gold(I)-catalyzed reaction and the cyclopropanation reaction (Table 27, entries 4-7).

152. Horino, Y.; Nakashima, Y.; Hashimoto, K.; Kuroda, S. *Synlett* **2010**, 2879-2882.



III-29 **III-44**

Table 27. Synthesis of **III-44** with various disiloxane linkers and protecting groups.

Entry	R^1	R^2	*Product*	*Yield(%)*
1	Me	TIPS	**III-44a**	40
2	*i*Pr	TIPS	**III-44b**	65
3	Ph	TIPS	**III-44c**	81
4	Me	TES	**III-44d**	70
5	Me	TBS	**III-44e**	66
6	Ph	TES	**III-44f**	80
7	Ph	TBS	**III-44g**	83

The gold(I)-catalyzed intramolecular 1,5-migration followed by the internal trapping of the allyl Au(I) cation was studied with these substrates (Table 28, entries1-7). A special work-up with a solution of HF·pyridine (2% w/w) was required in order to recover the corresponding diol **III-45** from the 9-membered ring intermediate. Alternative work-up with acids (HCl and *p*TSA) gave lower conversions.

Initial attempts were focused on the dimethyl disiloxane linker, but moderate yields were obtained with hardly reproductible results (Table 28, entry 1). As a consequence, more

robust disiloxane linkers were investigated. Diisopropyl disiloxane **III-44b** gave a complex mixture with no traces of **III-45** (Table 28, entry 2). Diphenyl disiloxane **III-44c** led to cycloadduct **III-45** in 47% yield (Table 28, entry 3).

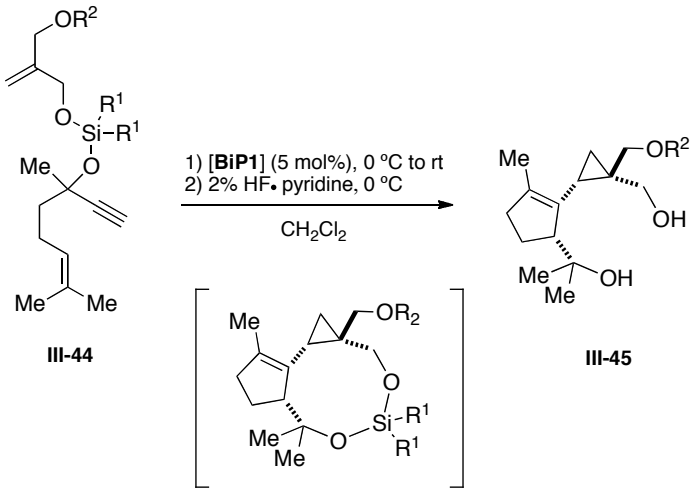


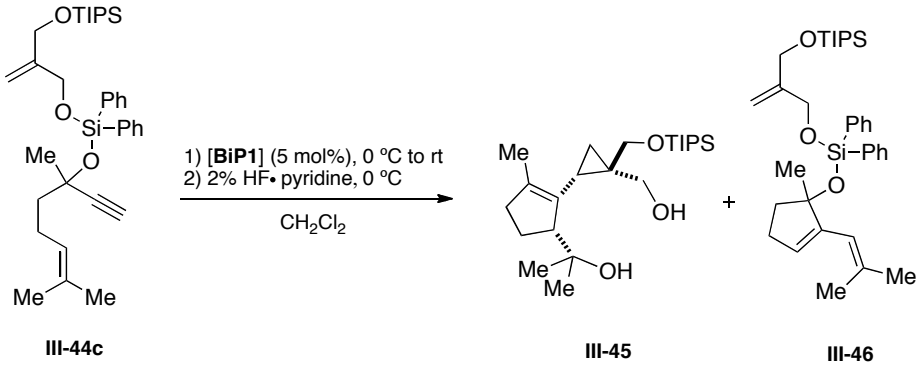
Table 28. Gold(I)-catalyzed cyclization of substrate **III-44** into **III-45**.

Entry	*Substrate*	*R^1*	*R^2*	*Yield(%)*	*Entry*	*Substrate*	*R^1*	*R^2*	*Yield(%)*
1	**III-44a**	Me	TIPS	40	5	**III-44e**	Me	TBS	complex mixture
2	**III-44b**	*i*Pr	TIPS	complex mixture	6	**III-44f**	Ph	TES	35
3	**III-44c**	Ph	TIPS	47	7[a]	**III-44f**	Ph	TES	34
4	**III-44d**	Me	TES	complex mixture	8	**III-44g**	Ph	TBS	38

Reactions were carried out with 5 mol% of catalyst from 0 ºC to rt until completion of the reaction followed by addition of a solution of HF•pyridine (2% w/w) at 0 ºC and stirring for 1 h. [a] Reaction run at 0 ºC.

Reducing the size of the silyl protecting group of the terminal primary hydroxyl group from TIPS to TBS or TES gave lower yields (Table 28, entries 3, 6-8). Deprotection of these silyl ethers might happen as a side reaction during the work-up leading to a water-soluble triol.

The moderate yields observed in this reaction are explained by the formation of by-product **III-46** *via* a single cleavage rearrangement and formed in equal proportion to product **III-45** (Scheme 72, see Scheme 37 for a mechanistic rationale of the single cleavage rearrangement).



III-44c **III-45** **III-46**

Scheme 72. Synthesis of **III-45** along with side product **III-46**.

In order to improve the selectivity of the reaction towards the formation of **III-45**, a series of optimizations concerning the catalyst, the solvent and the silver salt were made using **III-44c** as a model substrate.

Different catalysts including phosphine, phosphite and carbene gold(I) complexes were tested (Table 29, entry 1). Best results were obtained with catalyst **BiP1**.

Table 29. Catalyst screening for the synthesis of **III-45**.

Entry	*[Au]*	*Yield(%)*	*Entry*	*[Au]*	*Yield(%)*
1	**BiP1**	47	6[a]	**TriP**	25

Entry	*[Au]*	*Yield(%)*	*Entry*	*[Au]*	*Yield(%)*
2[a]	**BiP1**	47	7	**C1**	17
3[a]	**BiP2**	41	8[a]	**C1**	29
4	**BiP3**	47	9[a]	**C2**	26
5[a]	**BiP3**	40			

Reactions were carried out with **III-44c** and 5 mol% of catalyst from 0 ºC to rt until completion of the reaction followed by the addition of a solution of HF•pyridine (2% w/w) at 0 ºC and stirring for 1h at 0 ºC. [a] Reaction was run at 0 ºC.

In addition, no significant improvement was observed when the reaction was run at 0 ºC instead at room temperature (Table 29, entries 1 and 2).

A screening of different solvents was achieved to understand if a possible solvent effect could promote the gold(I)-catalyzed intramolecular 1,5-migration of the disiloxane linker. Chlorinated solvents, like CH_2Cl_2 and $CHCl_3$, gave the best results for this reaction. On the contrary, no significant improvement was made by using either non-polar solvents (toluene and benzene) or polar solvents (THF and dioxane) to favor the formation of **III-45**. No reaction occurred in MeCN or DMSO, even at 100 ºC for 15 min under microwave heating.

Finally, counterions were screened as known to influence both the yield and the selectivity of the reaction (Table 30, entries 1-3).

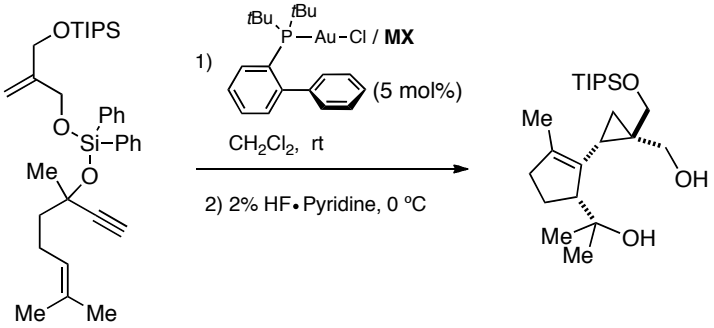
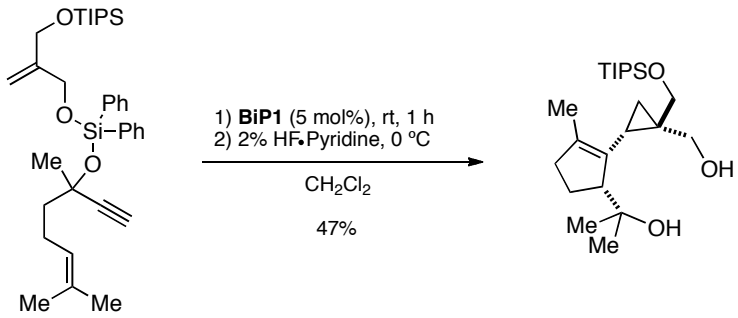


Table 30 Screening of silver salt for the synthesis of **III-45**

Entry	*MX*	*Yield(%)*
1	**$AgSbF_6$**	47
2	**$NaBAr_F$**	41
3	**$AgNTf_2$**	30

No better results were obtained compared to those initially reported with SbF_6^- as a counterion (Table 30, entry 1, **BiP1**).

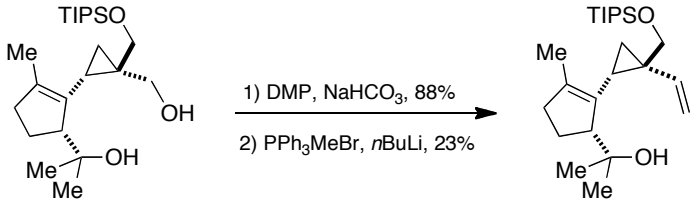
Although further optimizations may slightly improve the yield of this reaction, the synthesis was carried on using our best conditions with substrate **III-44c** and **BiP1** as a catalyst. **III-45** could be obtained in 47% yield (Scheme 73).



III-44c **III-45**

Scheme 73. Synthesis of **III-45** using optimised conditions.

Conversion of **III-45** into **III-46** was achieved in two steps and 20% overall yield through an oxidation with DMP followed by a Wittig olefination (Scheme 74).



III-45 **III-46**

Scheme 74. Synthesis of divinyl cyclopropane **III-46**.

Unfortunately, all attempts to cyclize divinyl cyclopropane **III-46** into the corresponding Cope product failed. Increasing the temperature gave no conversion (4 h at 170 ºC).[136] This result can be explained if **III-46** possesses the wrong configuration on the cyclopropane moiety. This hypothesis was confirmed by X-ray structure analysis of **III-45** that showed a misassigned configuration with actually a *trans*-configuration between the cyclopentene core and the primary free alcohol (Figure 30).

136. Wender, P. A.; Filosa, M. P. *J. Org. Chem.* **1976,** *41*, 3490-3491.

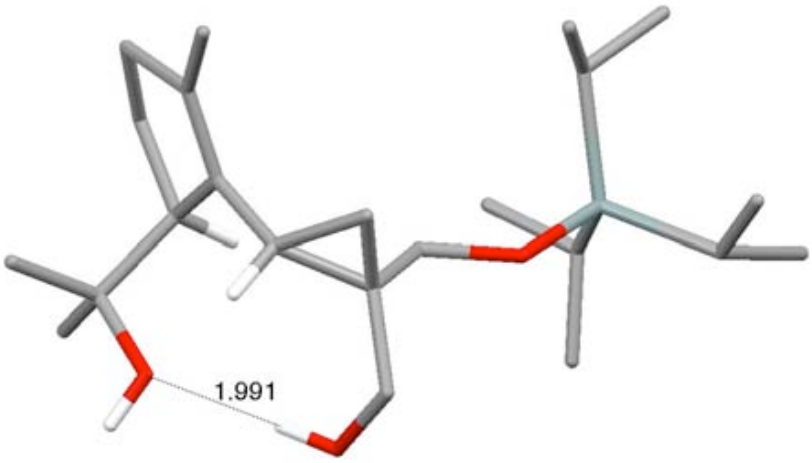
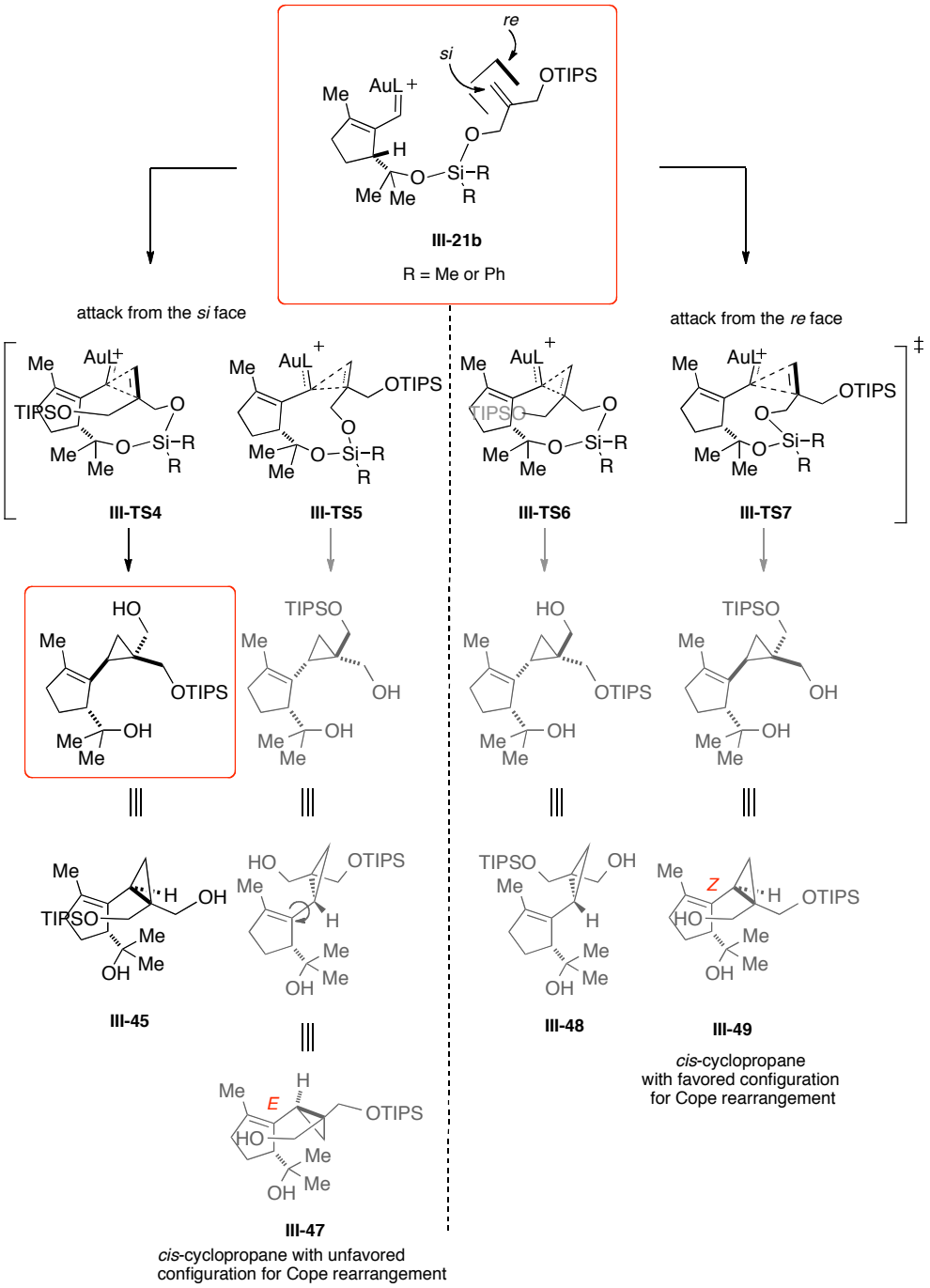


Figure 30. X-ray structure of the enantiomer of **III-45** with an intenal hydrogen bond depicted (1.99 Å).

A summary of the different pathways is proposed below to rationalize the observed stereochemistry (Scheme 75).



Scheme 75. Rationale for the observed stereoselectivity in the cyclopropanation reaction subsequent to the gold(I)-catalyzed 1,5-migration.

Allyl Au(I) cation intermediate **III-21b** can react by cyclopropanation with the internal alkene either from the *si* face (**III-TS4** and **III-TS5**) or the *re* face (**III-TS6** and **III-TS7**).

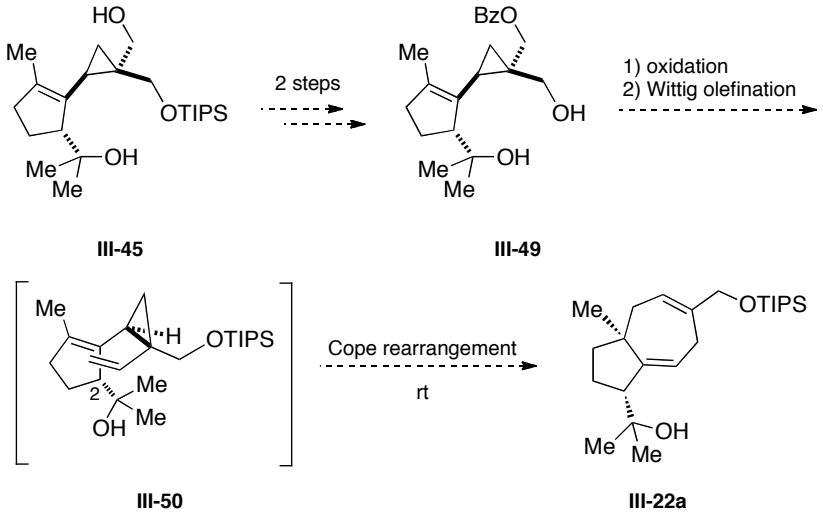
In the first case, **III-TS4** would afford product **III-45** which configuration has been correctly assigned by Xray structure analysis and **III-TS5** would give *cis*-cyclopropane **III-47** containing an unfavored configuration for the [3,3] rearrangement. Indeed, divinyl cyclopropanes with double bonds *trans* to the cyclopropane moiety are known to be unreactive substrate for Cope cyclization at room temperature.[135]

Attack from the *re* face would proceed through **III-TS6** and **III-TS7**. *Trans*-cyclopropane **III-48** would be obtained from **III-TS6** and *cis*-cyclopropane **III-49** would be obatined *via* **III-TS7**. Cyclopropane **III-49** would contain a divinylcyclopropane framework with two double bonds *cis* to the cyclopropane which could undergo a Cope rearrangement.

Remarkably, the gold(I)-catalyzed reaction of **III-44c** proceeded only through **III-TS4** to afford **III-45**.

Alternatively, conversion of **III-45** to **III-49** would afford the divinylcyclopropane **III-50** with the correct *cis*-configuration that could be converted *via* a Cope rearrangement into bicyclo[5.3.0]decane **III-22a** (Scheme 76).

135. Ullenius, C.; Ford, P. W.; Baldwin, J. E. *J. Am. Chem. Soc.* **1972,** *94*, 5910-5911.



Scheme 76. Currently investigated approach towards product **III-22a**.

III-49 could be obtained by protecting the primary alcohol of **III-45** followed by an orthogonal deprotection of the TIPS protecting group with TBAF. **III-49** would be transformed into divinylcyclopropane **III-50** in two steps by oxidation and a Wittig reaction. This approach is currently under investigation.

Amongst the four strategies investigated, the use of a disiloxane linker gave the best results, although key intermediate **III-45** was obtained in a moderate 47% yield.

This intramolecular approach would give access to an enantioselective synthesis of schisanwilsonene A **III-1**. Indeed, by using an enantiopure propargylic alcohol **III-29**, a chirality transfer would occur during the gold(I)-catalyzed intramolecular 1,5-migration and afford intermediate **III-45** as a single enantiomer (see Scheme 55, for a mechanistic rationale). The stereochemistry of the isopropyl alcohol group at C2 of **III-50** would control the Cope cyclization at a later stage of the synthesis to afford bicyclo[5.3.0]decane **III-22a** as a single stereoisomer (Scheme 76).

Conveniently, **III-29** can be obtained in high enantiopure form as mentionned in the chapter dealing with the synthesis of englerins A and B (see Scheme 38, **II-83**).

2. Intermolecular Strategy: a Straightforward Approach

In addition to the intramolecular approach (*vide supra*), a strategy relying on an intermolecular cyclopropanation reaction subsequent to the intramolecular 1,5-migration was studied (Scheme 62).[153] For this purpose, unsymmetrical and symmetrical alkenes were investigated with optimised conditions developed for this reaction.[133]

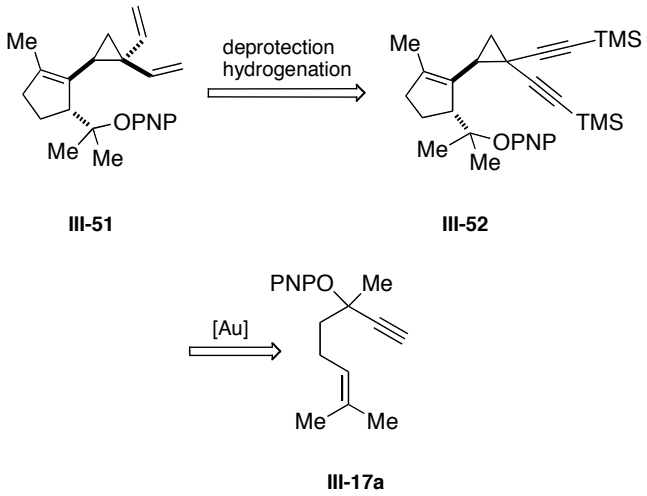
Enyne **III-17a** bearing a *para*-nitrophenyl ether on the propargylic position was chosen as a model substrate. Indeed, *para*-nitrophenyl ether showed good ability to migrate and proved to be a convenient substrate from an experimental point of view: during the course of the reaction, allyl Au(I) cation **III-21a** decomposed *in situ* if no cyclopropanation reaction occurred rending the purification and analysis of the crude mixture more convenient. However, no procedure has been reported to date on the preparation of propargylic aryl ethers in an enantiopure form.[154] For this reason the intermolecular approach, using a phenolic protecting group, would only give a racemic total synthesis of schisanwilsonene A.

153. This work was carried out in collaboration with Dr. Julien Ceccon.

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

154. (a) For a synthesis of racemic propargylic aryl ethers, see: Godfrey, J. D.; Mueller, R. H.; Sedergran, T. C.; Soundararajan, N.; Colandrea, V. J. *Tetrahedron Lett.* **1994,** *35*, 6405-6408. (b) For an example of chiral propargylic aryl ethers obtained *via* aziridine opening, see: Forbeck, E. M.; Evans, C. D.; Gilleran, J. A.; Li, P.; Joullié, M. M. *J. Am. Chem. Soc.* **2007,** *129*, 14463-14469.

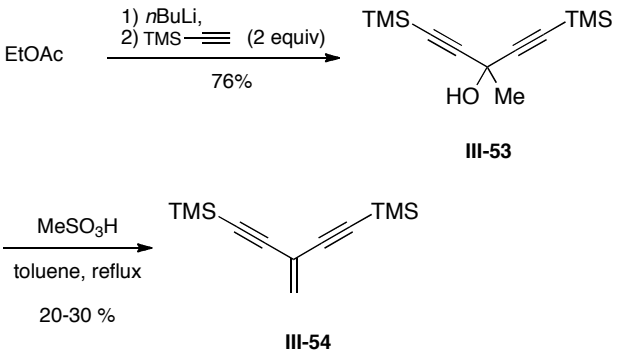
At first, an original approach was tried by mixing symmetrical diethynylethene **III-54** and enyne **III-17a** to give intermediate **III-52** with no *cis*- and *trans*-configuration issue (Scheme 77). Deprotection of both TMS group followed by hydrogenation with Raney nickel would lead to the desired *cis*-divinylcyclopropane **III-51** that could undergo a Cope rearrangement.



Scheme 77. Approach towards dialkene cyclopropane **III-51**.

Endiyne **III-54** was synthesized from EtOAc in a two-step procedure (Scheme 78). First step gave the corresponding propargylic alcohol in good yield (76% yield).[155] Dehydration of tertiary alcohol **III-53** afforded **III-54** in moderate yield (20% to 30%) due to the tendency of **III-54** to polymerize. Endiyne **III-54** could be stored in benzene at -10 ºC.

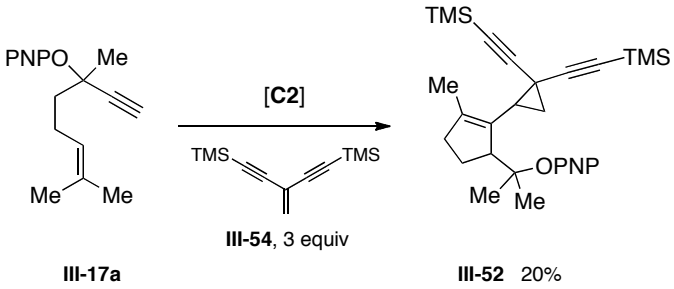
155. For the preparation of diethynylethenes, see: (a) Nielsen, M. B.; Diederich, F. *Synlett* **2002**, 544-552. (b) Alberts, A. H. *J. Am. Chem. Soc.* **1989,** *111*, 3093-3094.



Scheme 78. Synthesis of trapping agent **III-54**

Alternative methods using AcCl/pyridine in benzene or Burgess reagent[156] were unsuccessful.

Unfortunately, gold(I)-catalyzed reaction of enyne **III-17a** with trapping agent **III-54** gave **III-52** in only 20% yield (Scheme 79).

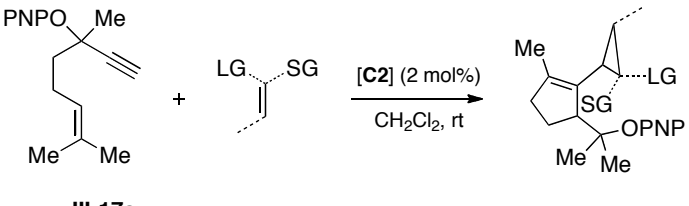


Scheme 79. Synthesis of dialkyne cyclopropane **III-52**.

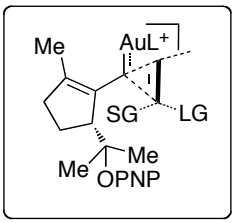
In order to obtain the *cis*-cyclopropane with high selectivity, unsymmetrical alkenes with large group (LG) on one side and smaller group on the other side (SG) were synthesized and tested as trapping agents towards the gold(I)-catalyzed intramolecular 1,5-migration

156. Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973,** *38*, 26-31.

reaction (Table 31, entries 1-4).[157] The trapping alkene was assumed to approach from the less hindered face of the allyl Au(I) gold cation as depicted in **III-TS8** (reaction scheme of Table 31).

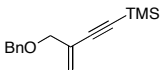
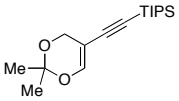
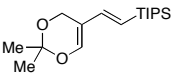


III-17a



III-TS8

Table 31. Screening of unsymmetrical alkenes as trapping agents.

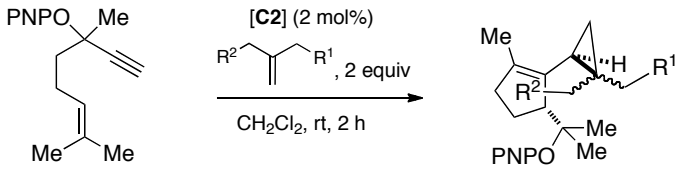
Entry	*Alkene*	*Product*
1		decomp
2		complex mixture
3		complex mixture
4		complex mixture

Reactions were carried out using 2 equiv of alkene. The crude mixture was analyzed by ^{1}H-NMR.

157. Part of this work was carried out by Mihai Raducan during his PhD. Thesis (2010).

In all cases, complex mixtures with decomposition products were obtained mainly due to steric reasons especially with trisubstituted alkenes (Table 31, entries 2 and 3).

A real improvement was obtained by using alkenes containing silyl ether protecting groups (Table 32, entries 1-7).



III-17a **III-55**

Table 32. Screening of trapping agents containing silyl protecting groups.

entry	R^1	R^2	*Results*	*d.r.*
1	TES	Ac	mainly **III-55a**	1.8:1
2	TBS	Ac	mainly **III-55b**	2:1
3	TDS	Ac	mixture containing **III-55c**	3.2:1
4	TIPS	Ac	complex mixture containing **III-55d**	4:1
5	TBS	TBS	mainly **III-55e**	-
6	TES	TES	mainly **III-55f**	-
7	Ac	Ac	decomp	-

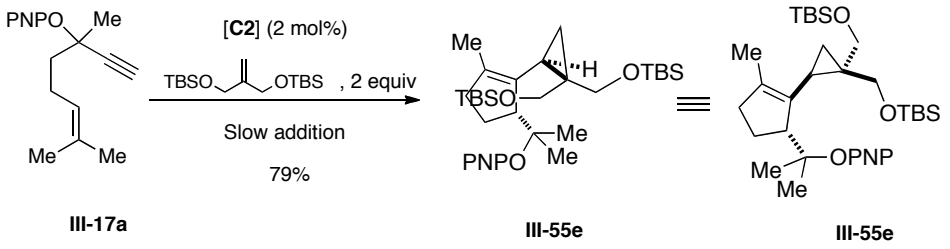
Reactions were carried out with catalyst **C2** (2 mol%) and slow addition of **III-17a** to the mixture over 30 min. The reaction was stopped after full conversion and the *d.r.* was determined by ^{1}H-NMR.

The size of the silyl protecting groups was found to be determinant (Table 32, entries 1-4). High selectivities were observed with bulky groups but cyclopropane **III-55** was generally obtained in low yield due to the steric environment of the protecting groups. The best compromise was obtained with a TBS protecting group and an acetate group to afford **III-55b** (Table 32, entry 2) as a 2:1 mixture of diastereoisomers.

However, the use of unsymmetrical alkene as a trapping agent had a major limitation due to the difficulty to isolate the desired diastereoisomer from the crude mixture. To overcome this issue, a series of symmetrical bis-protected alkenes were synthesized instead and tested as trapping agents in the reaction (Table 32, entries 5-7). The main advantage of this approach is to avoid any selectivity issue in the reaction, rendering the purification easier.

Initial attempts with bis-TES protected alkene afforded a hardly separable mixture of product cyclopropane **III-55f** and trapping alkene although with good yield (Table 32, entry 6). Gratifyingly with bis-TBS protected alkene, we were pleased to observe the formation of the desired product **III-55e** in good yield (Table 32, entry 5). In addition, the expected product came as a partially separable mixture with the trapping alkene. Conversely, bis-acetate alkene only gave decomposition product (Table 32, entry 7).

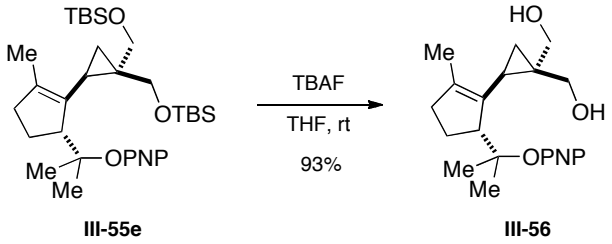
These conditions were used for the synthesis of **III-55e** in 79% yield, calculated on the basis of the ^{1}H-NMR of the purified mixture (Scheme 80).



Scheme 80. Synthesis of **III-55e** using bis-TBS protected alkene.

This reaction was carried out on a 500 mg scale and the relative configuration of cyclopropane **III-55e** was determined by NOE experiment.

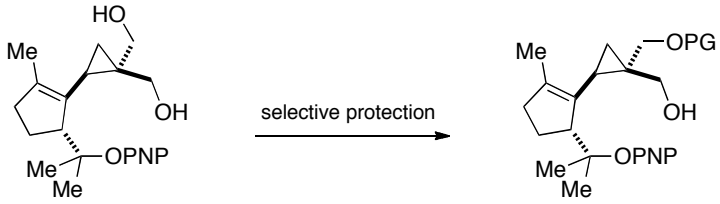
Deprotection of both TBS protecting groups of **III-55e** with TBAF afforded diol **III-56** in 93% yield (Scheme 81).



III-55e **III-56**

Scheme 81. Synthesis of diol **III-56**.

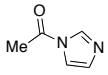
The selective protection of one of the primary alcohol of diol **III-56** was studied under different conditions (Table 33, entries 1-9).



III-56 **III-57**

Table 33. Screening of conditions for the selective protection of **III-56** into **III-57**.

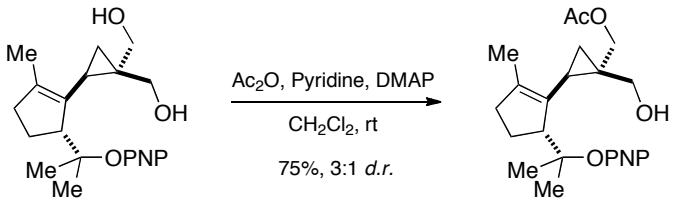
Entry	*Reagents*	*T(ºC)*	*d.r. (**III-57**)*
1	Ac_2O (1.05 equiv), Pyridine (2 equiv), DMAP (0.05 equiv)	0	3:1
2	Ac_2O (1.05 equiv), Pyridine (2 equiv), DMAP (0.05 equiv)	-20	3:1
3	Ac_2O (1.05 equiv), DBU (2 equiv), DMAP (0.05 equiv)	0	3.2:1
4	Ac_2O (1.05 equiv), 2,6-lutidine (2 equiv), DMAP (0.05 equiv)	0	2.7:1

Entry	*Reagents*	*T(ºC)*	*d.r. (**III-57**)*
5	Piv_2O (1.05 equiv), Pyridine (2 equiv), DMAP (0.05 equiv)	RT	3.2:1[a]
6	 (1.1 equiv), DBU (0.25 equiv)	RT	3:1[a]
7	AcCl (1.2 equiv), 2,4,6-collidine (2 equiv)	- 78	5:1[b]
8	AcCl (1.2 equiv), DIPEA (2 equiv)	- 78	6:1[b]
9	AcCl (1.2 equiv), 1,2,2,6,6-Pentamethylpiperidine (2 equiv)	- 78	4:1[b]

d.r. were determined by ^{1}H-NMR analysis of the crude mixture. In all cases, bis-protected diol was observed but in less than 10% yield. [a] Incomplete reaction. [b] Reaction was run over night at -78 ºC with ca. 80% conv.

Selective monoprotection of diol **III-56** into **III-57** could be obtained with good selectivity with standard conditions (Table 33, entry 1). Along with mono-protected alcohol **III-57**, bis-protected diol was obtained in less than 10% yield. Several bases were also tested without significant improvements at 0 ºC (Table 33, entries 3 and 4). Replacing acetic anhydride with the bulkier pivalic anhydride or 1-acetylimidazole was not successful either (Table 33, entries 5 and 6). With further optimizations, selectivity could be improved from 4:1 to 6:1 when a mixture of acetyl chloride and various hindered bases was used at – 78 ºC (Table 33, entries 6 - 8).

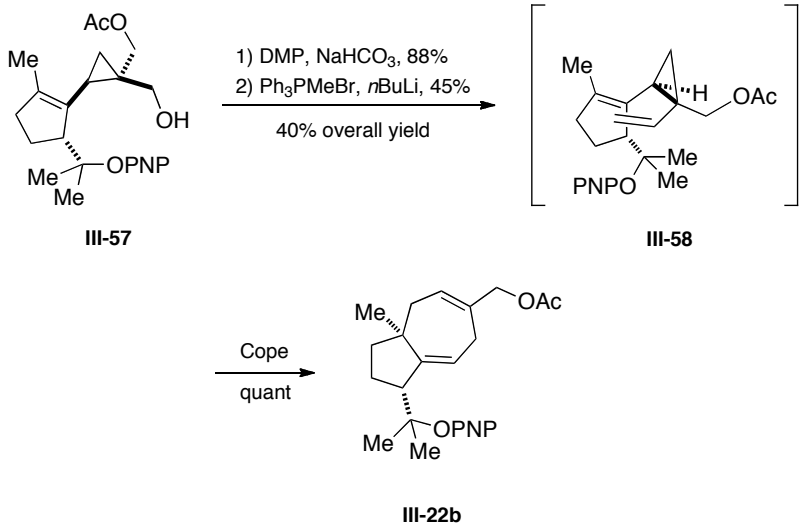
With the non-optimized conditions (Table 33, entry 1), **III-57** was isolated in a yield of 86% on a 2 grams scale with an identical ratio (i.e. 3:1 *d.r.*) and a reduced amount of the bis-protected product (Scheme 82). The selective protection of the hydroxyl group *trans* to the cyclopentene moiety was confirmed by NOE experiment.



III-56 **III-57**

Scheme 82. Synthesis of mono-protected alcohol **III-57**.

A two steps procedure from alcohol **III-57**, featuring a DMP oxidation followed by a Wittig olefination, yielded the corresponding diene **III-58**. The latter slowly evolved into the bicyclo[5.3.0]decane **III-22b** with the skipped heptadiene framework in 40% overall yield from alcohol **III-57** (Scheme 83).

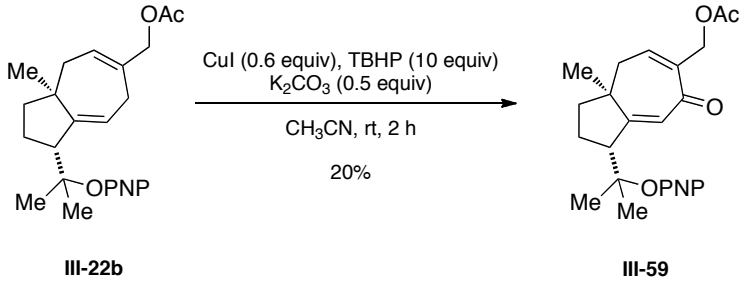


III-57 **III-58** **III-22b**

Scheme 83. Synthesis of bicyclo[5.3.0]decane **III-22b**.

Skipped diene are known to be sensitive to air and **III-22b** was partially oxidized if not stored under an inert atmosphere. The transformation of **III-22b** into the corresponding

dienone **III-59** is currently under investigation. Preliminary results indicated that the allylic oxidation with TBHP and CuI as a catalyst give rise to dienone **III-59**, albein in low yield (Scheme 84).[158]



III-22b **III-59**

Scheme 84. Synthesis of dienone **III-59**.

158. Arsenou, E. S.; Koutsourea, A. I.; Fousteris, M. A.; Nikolaropoulos, S. S. *Steroids* **2003,** *68*, 407-414.

C. Experimental Part

Approach Towards the Synthesis of Schisanwilsonene A

General Methods

All reactions were carried out under Ar unless otherwise specified, using magnetic stirring and in solvents dried with a Solvent Purification System (SPS) or using standard procedures. The rest of the reagents were used directly as provided from the commercial sources. Analytical thin layer chromatography was carried out using TLC aluminium sheets with 0.2 mm of silica gel (Merk GF_{234}). Flash chromatography purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm).

NMR spectra were recorded at 23 ºC on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus. NMR chemical shifts (δ) are expressed in ppm. ^{1}H-NMR chemical shifts are referenced to TMS (in the case of $CDCl_3$) or to the solvent residual signal (in the case of other NMR solvents).[57] ^{13}C-NMR chemical shifts are referenced to the solvent signal. ESI mass spectra were recorded on a Waters LCT Premier spectrometer.

Catalysts **TriP**, **BiP2**, **BiP3**, **C1** and **C2** were synthesized according to reported procedure.[58]

Compound **III-17a** was synthesized according to reported procedure.[133]

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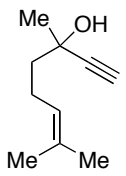
57. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997,** *62*, 7512-7515.
58. (a) Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008,** *73*, 7721-7730. (b) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007,** *63*, 6306-6316.
133. Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6152-6155.

3,7-Dimethyloct-6-en-1-yn-3-ol III-29

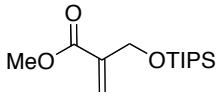


To a solution of 6-methyl-5-hepten-2-one (10 g, 79 mmol) in THF (120 mL) was added dropwise a solution of ethynylmagnesium bromide (1 M in THF) over 1 h at -10 ºC. The mixture was stirred for 12 h at room temprature. When no more starting material left, the mixture was quenched with an HCl aqueous solution (10% w/w) and the aqueous phase was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Chromatographic purification (10:1 to 5:1 cyclohexane/EtOAc) followed by Kugelrohr bulb-to-bulb distillation (3 mbar, 120 ºC) yielded **III-29** as a colorless oil (8.8 g, 73%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) =5.17 (ddd, J = 8.1, 2.7, 1.3 Hz, 1H), 2.46 (s, 1H), 2.35-2.25 (m, 1H), 2.23-2.13 (m, 1H), 2.11 (bs, 1H), 1.72-1.68 (m, 2H), 1.70 (s, 3H), 1.35 (s, 3H), 1.50 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) =133.3 (C), 124.3 (CH), 88.24 (C), 72.1 (CH), 68.9 (C), 43.8 (CH_2), 30.5 (CH_3), 26.4 (CH_2), 24.2 (CH_3), 18.4 (CH_3).

Preparation of compound **III-29** in an enantiopure form is described in the experimental part of chapter II (see **II-83**).

Methyl 2-(((triisopropylsilyl)oxy)methyl)acrylate III-60



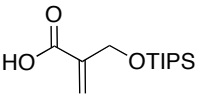
In a typical procedure, TIPSCl (10.38 g, 53.84 mmol) was added over 10 min to a solution of methyl 2-(hydroxymethyl)acrylate[159] (5.21 g, 44.8 mmol) and imidazole (4.58 g, 67.3 mmol) in CH_2Cl_2 (44 mL) at 0 ºC. After stirring the mixture for 30 min at 0 ºC, the mixture was stirred for 4 h at room temperature. When no more starting material left, the mixture was quenched with a saturated solution of NH_4Cl, extracted with CH_2Cl_2 then brine and dried over Na_2SO_4. The solvents were removed under *vacuo* and the crude was purified by

159. Pautigny, C.; Jeulin, S.; Ayad, T.; Zhang, Z.; Genêt, J.-P.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2008,** *350*, 2525-2532.

column chromatography (30:1 hexanes/EtOAc) to give the corresponding TIPS protected alcohol **III-60** as a clear oil (11.45 g, 93.6%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.28 (q, J = 2.0 Hz, 1H), 6.00 (q, J = 2.2 Hz, 1H), 4.46 (t, J = 2.2 Hz, 2H), 3.76 (s, 3H), 1.20-.1.05 (m, 21H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 166.5 (CO), 139.8 (C), 123.9 (CH_2), 61.8 (CH_2), 51.8 (CH_3), 18.1 (6xCH_3), 12.1 (3xCH).

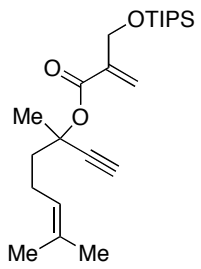
2-(((Triisopropylsilyl)oxy)methyl)acrylic acid III-61



To a solution of methyl-2-(((triisopropylsilyl)oxy)methyl)acrylate **III-60** (3.57 g, 13.1 mmol) in THF (20 mL) and water (20 mL) was added LiOH (628 mg, 26.2 mmol) in one portion and the mixture was stirred for 20 h at room temperature. When no more starting material left, the mixture was quenched with an HCl aqueous solution (10% w/w) and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4. Evaporation of the solvents yielded pure acid **III-61** as a white solid (3.37 g, 99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.41 (d, J = 1.8 Hz, 1H), 6.09 (bs, 1H), 4.47 (t, J = 1.9 Hz, 2H), 1.20-1.04 (m, 21H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) =171.4 (CO), 139.6 (C), 126.9 (CH_2), 62.2 (CH_2), 18.6 (3xCH_3), 12.6 (3xCH)

3,7-Dimethyloct-6-en-1-yn-3-yl 2-(((triisopropylsilyl)oxy)methyl)acrylate III-30

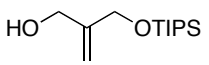


To a solution of TIPS protected acid **III-61** (1.5 g, 5.8 mmol) in THF (190 mL), 2,4,6-trichlorobenzoyl chloride (0.98 mL, 6.3 mmol) and NEt_3 (3.67 mL, 26.3 mmol) were added at room temperature. The mixture was stirred 3 h at room temperature then DMAP (967 mg, 7.91 mmol) was added followed by a solution of propargylic alcohol **II-29** (802.5 mg, 5.272 mmol) in toluene (60 mL). The mixture was stirred at 50 ºC for 13 h. When no more starting material left, the mixture was cooled to room temperature and quenched with a saturated solution of NH_4Cl, extracted twice with Et_2O. The combined organic layers were washed

with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification (20:1 hexanes/EtOAc) yielded ester **III-30** as a light yellow oil (1.2 g, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.24 (q, J = 2.0 Hz, 1H), 5.99 (q, J = 2.1 Hz, 1H), 5.13 (t, J = 7.2 Hz, 1H), 4.45 (t, J = 2.1 Hz, 2H), 2.57 (s, 1H), 2.24-2.16 (m, 2H), 2.03-1.95 (m, 1H), 1.91-1.82 (m, 1H), 1.73 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H), 1.21-1.04 (m, 21H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) =164.9 (CO), 141.0 (C), 133.1 (C), 124.2 (CH), 123.8 (CH), 84.2 (C), 75.6 (C), 74.2 (C), 62.2 (CH_2), 42.2 (CH_2), 27.1 (CH_2), 26.3 (CH_3), 23.6 (CH_3), 18.6 (6xCH_3), 18.3 (CH_3), 12.6 (3xCH). HRMS (EI) cald for [$C_{23}H_{40}O_3SiNa$]: 415.2644, found: 415.2653.

2-(((Triisopropylsilyl)oxy)methyl)prop-2-en-1-ol III-62



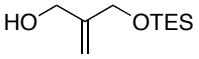
In a typical procedure, DIBAL-H (1M in hexane, 58 mL, 58 mmol) was added dropwise to a solution of **III-60** (6.29 g, 23.0 mmol) in Et_2O at -78 ºC. The whole was stirred at -20 ºC for 2 h followed by further stirring for 2 h at 0 ºC. When no more starting material left, the mixture was quenched with a saturated solution of Rochelle salt and stirred over night. The aqueous phase was extracted with EtOAc, the combined organic layers were washed with brine, dried over Na_2SO_4. Evaporation of the solvents yielded the pure alcohol **III-62** as a light yellow oil (5.68 g, 100%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.12 (s, 1H), 5.08 (s, 1H), 4.34 (s, 2H), 4.20 (d, J = 5.6 Hz, 2H), 1.20-1.05 (m, 21H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 148.1 (C), 111.7 (CH), 66.3 (CH_2), 65.6 (CH_2), 51.8 (CH_3), 18.6 (6xCH_3), 12.6 (3xCH). HRMS (EI) cald for [$C_{10}H_{22}O_2SiNa$]: 225.1287, found: 225.1291.

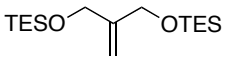
2-(((Triethylsilyl)oxy)methyl)prop-2-en-1-ol III-63 and 1,3-bis(((Triethylsilyl)oxy)methyl)prop-2-ene III-64

Imidazole (1.09 g, 16.0 mmol) and TESCl (1.81 g, 12.1 mmol) were added to a solution of 2-methylenepropane-1,3-diol (1.00 mL, 12.3 mmol) in DMF (24.5 mL) at 0 ºC. The resulting mixture was slowly warmed to room temperature and stirred overnight, then quenched with brine. The aqueous phase was extracted twice with Et_2O and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and

concentrated under *vaccuo*. Chromatographic purification (4:1 to 3:1 hexanes/Et_2O) of the crude material afforded the disilylated product **III-64** (888 mg, 23%), followed by the monosilylated alcohol **III-63** (1.04 g, 42 %) as colorless oils.

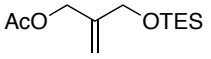


^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.10 (m, 2H), 4.25 (s, 2H), 4.18 (m, 2H), 0.97 (t, J = 7.9 Hz, 9H), 0.63 (q, J = 8.2 Hz, 6H). ^{13}C-NMR (160 MHz, $CDCl_3$): δ 148.0 (C), 112.0 (CH_2), 100.6 (CH_2), 65.5 (CH_2), 7.4 (3xCH_2), 5.0 (3xCH_3).



^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.10 (m, 2H), 4.17 (m, 4H), 0.96 (t, J = 7.9 Hz, 18H), 0.61 (q, J = 7.9 Hz, 12H).

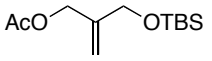
2-(((Triethylsilyl)oxy)methyl)allyl acetate III-65



Ac_2O (250 mg, 2.44 mmol) was added over 10 min to a solution of **III-63** (330 mg, 1.63 mmol), pyridine (645 mg, 8.15 mmol), DMAP (19.9 mg, 0.163 mmol) in CH_2Cl_2 (8 mL) at 0 ºC. After stirring the mixture at room temperature for 1 h, the reaction was quenched with an HCl aqueous solution (10% w/w) and the aqueous phase was extracted twice with Et_2O. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated under *vacuo*. The crude was purified by column chromatography (10:1 hexanes/EtOAc) to give **III-65** as a light yellow oil (356 mg, 89%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.25 (m, 1H), 5.14 (m, 1H), 4.58 (s, 2H), 4.16 (s, 2H), 2.08 (s, 3H), 0.91 (s, 9H), 0.62 (q, J = 8.0 Hz, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ (ppm) = 170.7 (CO), 143.2 (C), 113.0 (CH_2), 64.6 (CH_2), 63.4 (CH_2), 20.9 (CH_3), 6.7 (CH_3), 4.4 (CH_2).

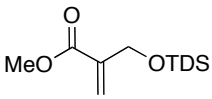
2-(((Tert-butyldimethylsilyl)oxy)methyl)allyl acetate III-66



Using a similar procedure, **III-66** was synthesized from TBS-protected alcohol.[160] Column chromatography (10:1 hexanes/EtOAc) afforded **III-66** as a light yellow oil (517 mg, 86%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.24 (m, 1H), 5.13 (m, 1H), 4.59 (s, 2H), 4.17 (s, 2H), 2.08 (s, 3H), 0.97 (t, J = 8.0 Hz, 9H), 0.07 (s, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ (ppm) = 170.7 (CO), 143.2 (C), 113.0 (CH_2), 64.7 (CH_2), 63.8 (CH_2), 25.8 (CH_3), 20.9 (CH_3), 18.3 (C), -5.5 (CH_3).

Methyl 2-(((Dimethylthexylsilyl)oxy)methyl)acrylate III-67

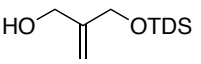


TDSCl (554 mg, 3.10 mmol) was added over 10 min to a solution of methyl 2-(hydroxymethyl)acrylate (300 mg, 2.58 mmol) and imidazole (264 mg, 3.87 mmol) in CH_2Cl_2 (10 mL) at room temperature. The mixture was stirred over night at room temperature. When no more starting material left, the mixture was quenched with an aqueous solution of HCl (0.5 M), extracted with Et_2O then brine and dried over Na_2SO_4. The solvent was removed under *vacuo* and the crude was purified by column chromatography (30:1 to 20:1 hexanes/EtOAc) to give the corresponding TDS protected ester **III-67** (611 mg, 97% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.25 (q, J = 1.8 Hz, 1H), 5.91 (q, J = 1.9 Hz, 1H), 4.35 (t, J = 2.0 Hz, 2H), 3.75 (s, 3H), 1.70-1.60 (m, 1H) 0.90 (d, J = 6.9 Hz, 6H), 0.88 (s, 6H), 0.12 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 167.1 (CO), 140.3 (C), 124.5 (CH_2), 62.1 (CH_2), 52.3 (CH_3), 34.8 (CH), 25.9 (C), 21.0 (2xCH_3), 19.2 (2xCH_3), -2.8 (2xCH_3). HRMS (EI) cald for [$C_{13}H_{26}O_3SiNa$]: 281.1549, found: 281.1543.

160. Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988,** *110*, 8129-8133.

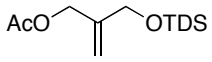
2-(((Dimethylthexylsilyl)oxy)methyl)prop-2-en-1-ol III-68



DIBAL-H (1.0 M in THF, 6.5 mL, 6.5 mmol) was added dropwise to a solution of **III-67** (611 mg, 2.50 mmol) in Et_2O (10 mL) at -78 ºC. The whole was stirred at -20 ºC for 2 h followed by further stirring for 2 h at 0 ºC. When no more starting material left, the mixture was quenched with a saturated solution of Rochelle salt and was stirred over night. The aqueous phase was extracted with Et_2O, the combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed under *vacuo* and the crude was purified by column chromatography (7:1 to 4:1 cyclohexane/EtOAc) to give the corresponding TDS protected alcohol **III-68** as a light yellow oil (447 mg, 83%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.10-5.09 (m, 1H), 5.07-5.06 (m, 1H), 4.22 (s, 2H), 4.17 (s, 2H), 1.63 (m, 1H), 0.90 (s, 3H), 0.88 (s, 3H), 0.86 (s, 6H), 0.12 (s, 6H).

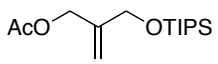
2-(((Dimethylthexylsilyl)oxy)methyl)allyl acetate III-69



Ac_2O (133 mg, 1.30 mmol) was added over 10 min to a solution of **III-68** (200 mg, 0.686 mmol), pyridine (343 mg, 4.34 mmol), DMAP (10.6 mg, 0.0868 mmol) in CH_2Cl_2 (8 mL) at 0 ºC. After stirring the mixture at room temperature for 1 h, the reaction was quenched with a saturated solution of NH_4Cl, extracted with CH_2Cl_2 then brine and dried over Na_2SO_4. The solvent was removed under *vacuo* and the crude was purified by column chromatography (20:1 to 10:1 cyclohexane/EtOAc) to give **III-69** as a light yellow oil (231 mg, 90%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.23-5.22 (m, 1H), 5.12-5.11 (m, 1H), 4.58 (s, 2H), 4.14 (s, 2H), 2.08 (s, 3H), 1.69-1.58 (m, 1H), 0.90 (s, 3H), 0.88 (s, 3H), 0.86 (s, 6H), 0.11 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.4 (CO), 144.0 (C), 113.6 (CH_2), 65.4 (CH_2), 64.3 (CH_2), 34.8 (CH_3), 25.9 (C), 21.6 (CH), 21.0 (CH_3), 19.2 (CH_3), -2.8 (CH_3).

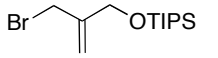
2-(((Triethylsilyl)oxy)methyl)allyl acetate III-70



Following a similar procedure to **III-65**, **III-70** was synthesized from **III-62**. Column chromatography (10:1 hexanes/EtOAc) afforded **III-70** as a light yellow oil (326 mg, 94%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.28 (m, 1H), 5.14 (m, 1H), 4.60 (s, 2H), 4.25 (s, 2H), 2.08 (s, 3H), 1.17 – 1.08 (m, 3H), 1.07 (s, 12H), 1.06 (s, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ (ppm) = 170.7 (CO), 143.3 (C), 112.6 (CH_2), 64.7 (CH_2), 64.0 (CH_2), 20.9 (CH_3), 18.0 (CH_3), 12.0 (CH).

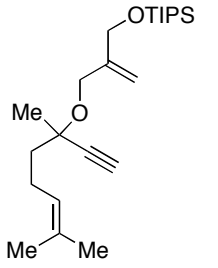
((2-(Bromomethyl)allyl)oxy)triisopropylsilane III-35



To a solution of TIPS protected alcohol **III-62** (8.92 g, 36.5 mmol) in CH_2Cl_2 (120 mL) at 0 ºC, was added CBr_4 (13.3 g, 40.2 mmol) followed by PPh_3 (11.4 g, 43.8 mmol). The whole was stirred at 0 ºC for 15 min then the mixture was quenched with a saturated solution of $NaHCO_3$ followed by further stirring for 20 min at 0 ºC. CH_2Cl_2 was removed under *vacuo* and the aqueous media was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification (pure hexane to 50:1 hexanes/EtOAc) yielded the allyl bromide **III-35** as a light yellow oil (9.48 g, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.29 (dd, J = 3.0, 1.5 Hz, 1H), 5.26-5.25 (m, 1H), 4.35 (s, 2H), 4.02 (s, 2H), 1.14-1.05 (m, 21H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 145.5 (C), 115.2 (CH), 64.4 (CH_2), 33.5 (CH_2), 18.7 (6xCH_3), 12.7 (3xCH).

((2-(((3,7-Dimethyloct-6-en-1-yn-3-yl)oxy)methyl)allyl)oxy)triisopropylsilane III-34

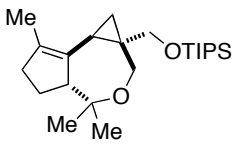


To a suspension of NaH (60% w/w, 247 mg, 6.18 mmol) in a minimum amount of THF was added dropwise a solution of alcohol **III-29** (784 mg, 5.15 mmol) in THF (10 mL) at 0 ºC and the mixture was stirred at room temperature for 45 min. A solution of TIPS protected allyl bromide **III-35** (1.74 g, 5.66 mmol) in THF (5 mL), and TBAI (381 mg, 1.03 mmol) were added at room temperature and the whole was stirred at room temperature for 12 h protected from light.

The mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted twice with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification (90:1 to 70:1 hexanes/EtOAc) yielded ether **III-34** as a light yellow oil (1.17 g, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.21 (bs, 1H), 5.14-5.10 (m, 2H), 4.31-4.23 (m, 2H), 4.11 (q, J = 11.7 Hz, 2H), 2.43 (s, 1H), 2.23-2.09 (m, 2H), 1.77-1.65 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.43 (s, 3H), 1.18-1.03 (m, 21H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 146.8 (C), 132.5 (C), 124.5 (CH), 111.0 (CH_2), 85.8 (C), 73.8 (C), 73.8 (CH), 65.7 (CH_2), 64.9 (CH_2), 42.4 (CH_2), 26.8 (CH_2), 26.3 (CH_3), 23.7 (CH_3), 18.7 (6xCH_3), 18.3 (CH_3), 12.7 (3xCH). HRMS (EI) cald for [$C_{23}H_{43}O_2Si$]: 379.3032, found: 379.3034.

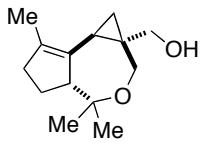
Triisopropyl((4,4,7-trimethyl-1,1a,2,4,4a,5,6,7b-octahydrocyclopenta[*c*]cyclopropa[*e*]oxepin-1a-yl)methoxy)silane III-36



Au(I) catalyst **C2** (12.3 mg, 0.0132 mmol) was added at 0 ºC to a solution of ether **III-34** (500 mg, 1.32 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 30 min and the reaction was quenched by the addition of NEt_3 (0.1 mL) followed by a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification (20:1 hexanes/EtOAc) of the crude material gave the cyclic product **III-36** as a light yellow oil (491 mg, 98%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.08 (d, J = 13.2 Hz, 1H), 3.79 (d, J = 10.0 Hz, 1H), 3.55 (d, J = 10.0 Hz, 1H), 3.37 (d, J = 13.2 Hz, 1H), 2.77 (d, J = 9.4 Hz, 1H), 2.33-2.25 (m, 1H), 2.10-2.03 (m, 1H), 1.98-1.87 (m, 1H), 1.75 (s, 3H), 1.45 (dd, J = 13.2, 8.0 Hz, 1H), 1.33-1.28 (m, 1H), 1.18 (s, 3H), 1.09-1.02 (m, 21H), 0.95 (s, 3H), 0.84 (dd, J = 9.0, 3.9 Hz, 1H), 0.70 (dd, J = 5.4, 4.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 138.2 (C), 135.3 (C), 80.1 (C), 67.8 (CH_2), 64.5 (CH_2), 58.5 (CH), 37.9 (CH_2), 28.4 (CH_3), 28.3 (C), 27.9 (CH_2), 21.0 (CH_3), 18.7 (3xCH_3), 17.8 (CH), 16.0 (CH_2), 15.0 (6xCH_3), 12.7 (3xCH). HRMS (EI) cald for [$C_{23}H_{43}O_2Si$]: 379.3032, found: 379.3048.

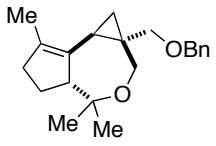
(4,4,7-Trimethyl-1,1a,2,4,4a,5,6,7b-octahydrocyclopenta[*c*]cyclopropa[*e*]oxepin-1a-yl)methanol III-38



A TBAF solution (1.0 M in THF, 1.3 mL, 1.3 mmol) was added to a solution of tricycle ether **III-36** (444 mg, 1.17 mmol) in THF (6 mL) at 0 ºC. After stirring the mixture at room temperature for 2 h the reaction was stopped by addition of a saturated aqueous solution of NH_4Cl followed by extractive work up with Et_2O. The organic layers were dried over Na_2SO_4 and the solvents were evaporated. Chromatographic purification (4:1 to 2:1 hexanes/EtOAc) of the crude material yielded alcohol **III-38** as a colorless oil (219 mg, 84%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.12 (dd, J = 13.5, 0.7 Hz, 1H), 3.76 (d, J = 10.9 Hz, 1H), 3.39 (d, J = 10.5 Hz, 1H), 3.23 (d, J = 13.4 Hz, 1H), 2.76 (d, J = 8.9 Hz, 1H), 2.35-2.25 (m, 1H+OH), 2.10-2.02 (m, 1H), 1.94 (dq, J = 13.4, 9.6 Hz, 1H), 1.75 (s, 3H), 1.45 (dd, J = 13.3, 7.9 Hz, 1H), 1.39-1.34 (m, 1H), 1.20 (s, 3H), 0.97 (s, 3H), 0.87 (dd, J = 8.7, 4.4 Hz, 1H), 0.77 (dd, J = 5.4, 4.6 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 139.3 (C), 134.4 (C), 81.0 (C), 70.5 (CH_2), 67.6 (CH_2), 59.6 (CH), 38.0 (CH_2), 29.8 (CH_2), 28.2 (CH_3), 28.1 (CH_3), 20.0 (C), 19.6 (CH_2), 18.4 (CH), 15.0 (CH_3). HRMS (EI) cald for [$C_{14}H_{22}O_2Na$]: 245.1517, found: 245.1526.

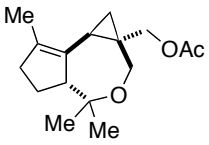
1a-((Benzyloxy)methyl)-4,4,7-trimethyl-1,1a,2,4,4a,5,6,7b-octahydrocyclopenta[*c*]cyclopropa[*e*]oxepine III-39



To a suspension of NaH (60% w/w, 14 mg, 0.36 mmol) in DMF (1 mL) was added dropwise a solution of alcohol **III-38** (50 mg, 0.33 mmol) in THF (1 mL) at 0 ºC. The mixture was stirred at room temperature for 30 min then benzylbromide (61 mg, 0.36 mmol) was added and the whole was stirred at room temperature for 12 h. The mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted twice with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification (20:1 to 10:1 hexanes/EtOAc) of the crude material yielded benzyl protected alcohol **III-39** as a colorless oil (50 mg, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.36-7.24 (m, 5H), 4.56 (d, J = 12.1 Hz, 1H), 4.49 (d, J = 12.1 Hz, 1H), 4.19 (d, J = 13.3 Hz, 1H), 3.65 (d, J = 10.1 Hz, 1H), 3.34 (d, J = 13.3 Hz, 1H), 3.18 (d, J = 10.1 Hz, 1H), 2.79 (d, J = 9.3 Hz, 1H), 2.35-2.25 (m, 1H), 2.10-2.03 (m, 1H), 1.93 (dq, J = 13.3, 9.6 Hz, 1H), 1.75 (s, 3H), 1.45 (dd, J = 13.3, 8.0 Hz, 1H), 1.28-1.24 (m, 1H), 1.20 (s, 3H), 0.95 (s, 3H), 0.84-0.80 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 139.3 (C), 138.7 (C), 134.7 (C), 129.0 (CH), 128.2 (CH), 128.1 (CH), 80.2 (C), 75.9 (CH_2), 73.4 (CH_2), 64.5 (CH_2), 58.6 (CH), 37.9 (CH_2), 28.5 (CH_3), 27.9 (CH_3), 26.5 (CH_2), 20.9 (CH_3), 18.9 (CH), 15.0 (CH_3). HRMS (EI) cald for [$C_{21}H_{28}O_2Na$]: 335.1987, found: 335.1995.

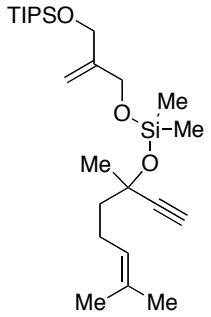
(4,4,7-Trimethyl-1,1a,2,4,4a,5,6,7b-octahydrocyclopenta[*c*]cyclopropa[*e*]oxepin-1a-yl)methyl acetate III-40



Acetyl chloride (6 µl, 0.09 mmol) was added to a solution of alcohol **III-38** (10 mg, 0.045 mmol), DMAP (1.0 mg, 4.5 µmol) and NEt_3 (15 µl, 0.090 mmol) in CH_2Cl_2 at 0 ºC. the whole was stirred at room temperature for 2 h before being quenched with a saturated aqueous solution of NH_4Cl and extracted twice with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification (20:1 to 10:1 pentane/Et_2O) of the crude material yielded **III-40** as a colorless oil (8.3 mg, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.23 (d, J = 11.5 Hz, 1H), 4.07 (d, J = 13.3 Hz, 1H), 3.80 (d, J = 11.5 Hz, 1H), 3.26 (d, J = 13.3 Hz, 1H), 2.75 (d, J = 9.5 Hz, 1H), 2.35-2.25 (m, 1H), 2.10-2.03 (m, 1H), 2.05 (s, 3H), 1.97-1.88 (m, 1H), 1.74 (s, 3H), 1.47-1.43 (m, 1 H), 1.37-1.29 (m, 1H), 1.18 (s, 3H), 0.95 (s, 3H), 0.89 (dd, J = 8.9, 4.3 Hz, 1H), 0.83 (t, J = 5.0 Hz, 1H).

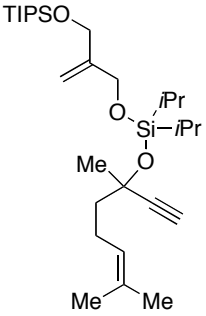
11-Ethynyl-3,3-diisopropyl-2,9,9,11,15-pentamethyl-6-methylene-4,8,10-trioxa-3,9-disilahexadec-14-ene III-44a



In a typical procedure, *n*BuLi (2.5 M in hexane, 1.25 mL, 3.13 mmol) was added dropwise to a solution of **III-29** (500 mg, 3.28 mmol) in THF (8 mL) at -78 ºC. The mixture was stirred 10 min at -78 ºC then dimethyldichlorosilane (2.02 g, 15.6 mmol) was added dropwise. The whole was slowly warmed to room temperature and stirred over night. The solvents and the excess of Me_2SiCl_2 were removed under *vaccuo* and the residue was kept under high *vacuo* (0.1 mmHg for 1 h) to give a clear oil with a white suspension. The crude was redissolved in THF (1 mL) followed by the addition of **III-62** in THF (20 mL) and imidazole (533 mg, 7.82 mmol) at room temperature. The mixture was stirred over night at room temperature before being quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted twice with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification (80:1 to 70:1 hexanes/EtOAc) of the crude material gave product **III-44a** as a light yellow oil (584 mg, 40%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.15-5.10 (m, 3H), 4.26 (bs, 4H), 2.44 (s, 1H), 2.19-2.15 (m, 2H), 1.74-1.64 (m, 5H), 1.62 (s, 3H), 1.51 (s, 3H), 1.16-1.02 (m, 21H), 0.22 (s, 3H), 0.19 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 148.1 (C), 132.4 (C), 124.3 (CH), 111.7 (CH_2), 88.3 (C), 72.1 (CH), 70.0 (C), 66.2 (CH_2), 65.6 (CH_2), 43.8 (CH_2), 30.5 (CH_3), 26.4 (CH_3), 24.2 (CH_2), 18.7 (6xCH_3), 18.4 (CH_3), 12.7 (3xCH), -0.1 (CH_3), -0.2 (CH_3).

11-Ethynyl-3,3,9,9-tetraisopropyl-2,11,15-trimethyl-6-methylene-4,8,10-trioxa-3,9-disilahexadec-14-ene III-44b

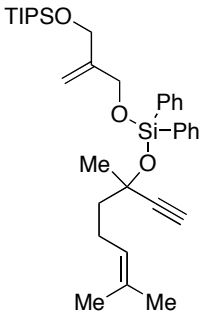


In a typical procedure, *n*BuLi (1.6 M in hexane, 0.40 mL, 0.64 mmol) was added dropwise to a solution of **III-29** (100 mg, 0.657 mmol) in THF (2 mL) at -78 ºC. The mixture was stirred 10 min at -78 ºC then a solution of diisopropyldichlorosilane (123 mg, 0.657 mmol) in THF (1 mL) was added dropwise. The whole was slowly warmed to room temperature and stirred for 1 h. After total

conversion of the starting material, a solution of **III-62** (169 mg, 0.691 mmol) in THF (1 mL) was added dropwise followed by the addition of imidazole (127 mg, 1.87 mmol). The mixture was stirred over night at room temperature before being quenched with a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification (70:1 hexanes/EtOAc) of the crude material gave product **III-44b** as a light yellow oil (220 mg, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.15-5.11 (m, 3H), 4.42-4.33 (m, 2H), 4.28 (s, 2H), 2.39 (s, 1H), 2.26-2.11 (m, 2H), 1.76-1.63 (m, 5H), 1.61 (s, 3H), 1.52 (s, 3H), 1.16-1.02 (m, 35H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 148.4 (C), 132.3 (C), 124.6 (CH), 109.0 (CH_2), 88.7 (C), 71.9 (CH), 69.9 (C), 64.9 (CH_2), 64.6 (CH_2), 45.8 (CH_2), 31.2 (CH_2), 26.3 (CH_3), 24.1 (CH_3), 18.7 (3xCH_3), 18.4 (CH_3), 18.3 (2xCH_3), 18.2 (2xCH_3), 13.7 (CH), 13.7 (CH), 12.7 (3xCH).

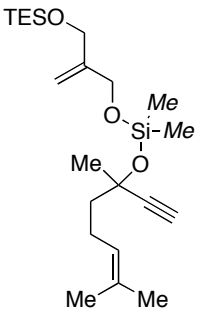
11-Ethynyl-3,3-diisopropyl-2,11,15-trimethyl-6-methylene-9,9-diphenyl-4,8,10-trioxa-3,9-disilahexadec-14-ene III-44c



The following compound was obtained using the same procedure than **III-44b** with TIPS protected alcohol **III-62** and diphenyldichlorosilane. Chromatographic purification (70:1 to 50:1 hexanes/EtOAc) of the crude material yielded product **III-44c** as a light yellow oil (2.94 g, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.69-7.66 (m, 4H), 7.41-7.37 (m, 2H), 7.35-7.30 (m, 4H), 5.17 (s, 2H), 5.11 (t, J = 7.1 Hz, 1H), 4.34 (q, J = 13.4Hz, 2H), 4.25 (s, 2H), 2.30 (s, 1H), 2.30-2.17 (m, 2H), 1.83-1.69 (m, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 1.50 (s, 3H), 1.12-1.02 (m, 21H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 147.8 (C), 135.8 (CH), 135.7 (CH), 135.6 (C), 132.5 (C), 131.0 (C), 130.7 (CH), 128.5 (C), 128.3 (CH), 128.2 (CH), 124.5 (CH), 109.7 (CH), 87.8 (C), 72.5 (CH), 71.4 (C), 64.7 (CH_2), 64.7 (CH_2), 45.5 (CH_2), 31.1 (CH_2), 26.3 (CH_3), 24.1 (CH_3), 18.7 (3xCH_3) 18.3 (CH_3), 12.7 (3xCH). HRMS (EI) cald for [$C_{35}H_{52}O_3NaSi_2$]: 599.3353, found: 599.3361.

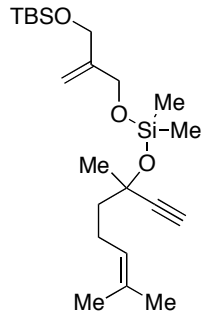
3,3-Diethyl-11-ethynyl-9,9,11,15-tetramethyl-6-methylene-4,8,10-trioxa-3,9-disilahexadec-14-ene III-44d



The following compound was obtained using the same procedure than **III-44a** with TES protected alcohol **III-63**. Chromatographic purification (50:1 hexanes/EtOAc) of the crude material yielded product **III-44d** as a light yellow oil (488 mg, 70%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.15-5.10 (m, 3H), 4.26 (bs, 4H), 2.44 (s, 1H), 2.19-2.15 (m, 2H), 1.74-1.64 (m, 5H), 1.62 (s, 3H), 1.51 (s, 3H), 1.16-1.02 (m, 21H), 0.97 (t, J = 7.9 Hz, 9H), 0.62 (q, J = 8.0 Hz, 6H), 0.22 (s, 3H), 0.20 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 148.1 (C), 132.4 (C), 124.5 (CH), 110.1 (CH_2), 88.3 (C), 72.6 (CH), 70.0 (C), 64.2 (CH_2), 63.9 (CH_2), 45.5 (CH_2), 31.4 (CH_2), 26.3 (CH_3), 24.1 (CH_3), 18.3 (CH_3), 7.5 (3xCH_2), 5.1 (3xCH_3), -0.1 (CH_3), -0.2 (CH_3). HRMS (EI) cald for [$C_{22}H_{42}O_3Si_2Na$]: 433.2570, found: 433.2567.

11-Ethynyl-2,2,3,3,9,9,11,15-octamethyl-6-methylene-4,8,10-trioxa-3,9-disilahexadec-14-ene III-44e



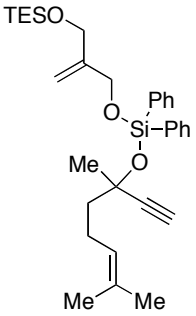
The following compound was obtained using the same procedure than **III-44a** and the TBS protected alcohol.[160] Chromatographic purification (50:1 hexanes/EtOAc) of the crude material yielded product **III-44e** as a light yellow oil (459 mg, 66%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.14-5.11 (m, 1H), 5.10 (bs, 2H), 4.25 (s, 2H), 4.17 (s, 2H), 2.44 (s, 1H), 2.23-2.12 (m, 2H), 1.73-1.64 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 0.91 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H), 0.07 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 148.1 (C), 132.4 (C), 124.5 (CH), 110.1 (CH_2), 88.3 (C), 72.6 (CH), 70.0 (C), 64.6 (CH_2), 63.9

160. Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988,** *110*, 8129-8133.

(CH_2), 45.5 (CH_2), 31.4 (CH_2), 26.6 (3xCH_3), 26.3 (CH_3), 24.1 (CH_3), 19.1 (C), 18.3 (CH_3), -0.1 (CH_3), -0.2 (CH_3), -4.7 (CH_3).

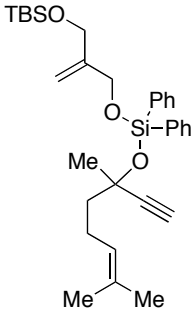
3,3-Diethyl-11-ethynyl-11,15-dimethyl-6-methylene-9,9-diphenyl-4,8,10-trioxa-3,9-disilahexadec-14-ene III-44f



The following compound was obtained using the same procedure than **III-44b** with TES protected alcohol **III-63**. Chromatographic purification (70:1 to 50:1 hexanes/EtOAc) of the crude material yielded product **III-44f** as a clear oil (1.01 g, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.71-7.61 (m, 4H), 7.44-7.32 (m, 6H), 5.21-5.09 (m, 3H), 4.39-4.30 (m, 2H), 4.19 (s, 2H), 2.33 (s, 1H), 2.30-2.18 (m, 2H), 1.85-1.70 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.52 (s, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.60 (q, J = 7.7 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 147.7 (C), 135.8 (CH), 135.7 (CH), 135.6 (C), 132.5 (C), 131.0 (C), 130.7 (CH), 128.5 (C), 128.3 (CH), 128.2 (CH), 124.5 (CH), 110.1 (CH_2), 87.8 (C), 72.6 (CH), 71.5 (C), 64.6 (CH_2), 64.2 (CH_2), 45.5 (CH_2), 31.1 (CH_2), 26.3 (CH_3), 24.1 (CH_3), 18.3 (CH_3), 7.4 (3xCH_2), 5.1 (3xCH_3). HRMS (EI) cald for [$C_{32}H_{46}O_3NaSi_2$]: 557.2883, found: 557.2892.

11-Ethynyl-2,2,3,3,11,15-hexamethyl-6-methylene-9,9-diphenyl-4,8,10-trioxa-3,9-disilahexadec-14-ene III-44g



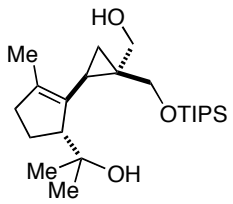
The following compound was obtained using the same procedure than **III-44b** with TBS protected alcohol.[160] Chromatographic purification (70:1 to 50:1 hexanes/EtOAc) of the crude material yielded product **III-44g** as a light yellow oil (1.05 g, 83%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.71-7.67 (m, 4H), 7.46-7.32 (m, 6H), 5.20-5.17 (bs, 1H), 5.16-5.10 (m, 2H), 4.40-4.30 (m,

160. Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988,** *110*, 8129-8133.

2H), 4.19 (s, 2H), 2.33 (s, 1H), 2.32-2.19 (m, 2H), 1.86-1.69 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.52 (s, 3H), 0.9 (s, 9H), 0.05 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 147.7 (C), 135.8 (CH), 135.7 (CH), 135.6 (C), 132.5 (C), 131.0 (C), 130.7 (CH), 128.5 (C), 128.3 (CH), 128.2 (CH), 124.5 (CH), 110.1 (CH_2), 87.8 (C), 72.6 (CH), 71.5 (C), 64.6 (CH_2), 64.6 (CH_2), 45.5 (CH_2), 31.1 (CH_2), 26.6 (3xCH_3), 26.3 (CH_3), 24.1 (CH_3), 19.04 (C), 18.3 (CH_3), -4.7 (2xCH_3). HRMS (EI) cald for [$C_{32}H_{46}O_3NaSi_2$]: 557.2883, found: 557.2874.

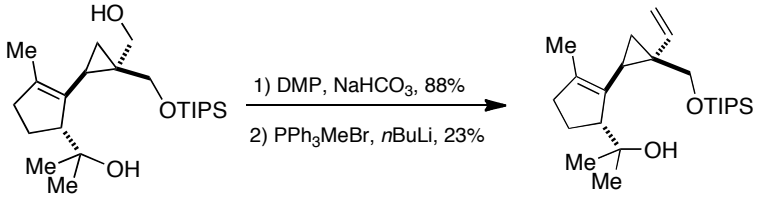
2-(2-(2-(Hydroxymethyl)-2-(((triisopropylsilyl)oxy)methyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-ol III-45



In a typical procedure, Au(I) catalyst **BiP1** (6.7 mg, 0.0090 mmol) was added to a dried schlenk, dried under vacuum und put under argon. The catalyst was dissolved in CH_2Cl_2 (1 mL) at room temperature and a solution **III-44c** (98 mg, 0.17 mmol) in CH_2Cl_2 (0.8 mL) was added dropwise under stirring conditions. The reaction mixture was stirred at room temperature for 45 min and cooled to 0 ºC. A solution of 2% HF/pyridine (0.2 mL, 0.2 mmol) was added dropwise at 0 ºC and the mixture was stirred at 0 ºC for 1 h. After adding a saturated aqueous solution of $NaHCO_3$ (1 mL), the two phases were separated and the aqueous one was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under *vacuo*. Chromatographic purification (9:1 to 6:1 cyclohexane/EtOAc) of the crude material afforded **III-45** as a yellowish solid (32 mg, 47%).

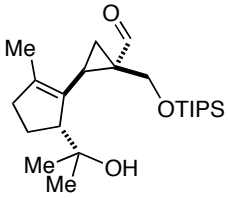
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.95 (d, J = 10.9 Hz, 1H), 3.70 (d, J = 10.2 Hz, 1H), 3.62 (d, J = 10.2 Hz, 1H), 3.23 (d, J = 11.0 Hz, 1H), 2.73-2.70 (m, 1H), 2.26-2.23 (m, 1H), 2.18-2.13 (m, 1H), 1.90-1.82 (m, 1H), 1.73 (s, 3H), 1.68-1.64 (m, 1H), 1.51-1.44 (m, 1H), 1.42, 1.39, 1.22 (s, 3H), 1.15-1.07 (m, 21H+3H), 0.91 (dd, J = 8.3, 4.8 Hz, 1H), 0.57 (dd, J = 6.5, 4.9 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 140.3 (C), 133.6 (C), 75.9 (C), 69.7 (CH_2), 66.2 (CH_2), 60.6 (CH), 38.2 (CH_2), 31.4 (CH_3), 30.4 (C), 26.6 (CH_2), 24.1 (CH), 24.0 (CH_3), 18.7 (CH_3), 17.1 (CH_2), 15.7 (CH_3), 12.7 (CH). HRMS (EI) cald for [$C_{23}H_{44}O_3NaSi$]: 419.2957, found: 419.2961.

2-(3-Methyl-2-(2-(((triisopropylsilyl)oxy)methyl)-2-vinylcyclopropyl)cyclopent-2-en-1-yl)propan-2-ol III-46



III-45 **III-46**

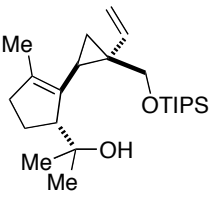
2-(5-(2-Hydroxypropan-2-yl)-2-methylcyclopent-1-en-1-yl)-1-(((triisopropylsilyl)oxy)methyl)cyclopropanecarbaldehyde III-45A



$NaHCO_3$ (29.4 mg, 0.350 mml) and Dess-Martin periodinane (44.6 mg, 0.105 mmol) were added to a solution of **III-45** (27.8 mg, 0.0700 mmol) in CH_2Cl_2 (1.4 mL, 0.05 M) at room temperature. The resulting mixture was stirred for 1 h, then quenched with a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3. The aqueous were extracted with EtOAc twice and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product (19.1 mg, 69%) was used in the following step.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.43 (s, 1H), 3.94 (d, J = 10.8 Hz, 1H), 3.83 (d, J = 10.8 Hz, 1H), 2.74 (s, 1H), 2.34-2.16 (m, 2H), 1.91-1.81 (m, 1H), 1.77 (s, 3H), 1.64 (d, J = 8.7, 4.4 Hz, 1H), 1.60-1.51 (m, 1H), 1.43 (s, 1H), 1.26 (bs, 3H), 1.17 (s, 3H), 1.16-1.09 (m, 3H), 1.09 (s, 12H), 1.07 (s, 6H), 0.98-0.82 (m, 2H).

2-(3-Methyl-2-(2-(((triisopropylsilyl)oxy)methyl)-2-vinylcyclopropyl)cyclopent-2-en-1-yl)propan-2-ol III-46

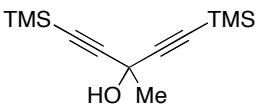


*n*BuLi (0.056 mL, 1.6 M, 0.090 mmol) was added dropwise to a suspension of PPh_3CH_3Br (36.7 mg, 0.103 mmol) in anhydrous THF (0.6 mL) at -20 ºC. The resulting yellowish solution was stirred for 10 min at -20 ºC, whereupon a solution of **III-45A**

(16.2 mg, 0.0410 mmol) was added dropwise. After 15 min at -20 ºC, the reaction mixture was allowed to warm to room temperature, then quenched with saturated aqueous NH_4Cl, extracted with Et_2O, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification over silica gel (20:1 to 10:1 Hexanes/EtOAc) afforded diene **III-46** (3.6 mg, 22%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.10 (dd, J = 17.3, 10.7 Hz, 1H), 5.05 (dd, J = 17.3, 1.4 Hz, 1H), 4.96 (dd, J = 10.7, 1.4 Hz, 1H), 3.84 (d, J = 10.5 Hz, 1H), 3.42 (d, J = 10.5 Hz, 1H), 2.90 (s, 1H), 2.46 (br. s, 1H), 2.27-2.12 (m, 2H), 1.86 (dtd, J = 13.3, 9.2, 5.9 Hz, 1H), 1.74 (s, 3H), 1.71-1.64 (m, 1H), 1.56-1.45 (m, 1H), 1.25 (s, 3H), 1.18 (s, 3H), 1.17-1.09 (m, 3H), 1.09 (s, 12H), 1.07 (s, 6H), 0.94-0.83 (m, 1H), 0.63 (dd, J = 6.8, 4.5 Hz, 1H).

3-Methyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol III-53

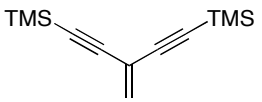


Following reported procedures,[155] a solution of *n*BuLi (2.5 M in hexanes, 29.4 mL, 73.5 mmol) was added to a solution of trimethylsilylacetylene (10 mL, 77 mmol) in THF (200 mL) at -78 ºC and the whole was stirred 1 h at -78 ºC. EtOAc (3.4 mL, 35 mmol) was added dropwise and the mixture was slowly warmed to room temperature then stirred for 12 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl and the aqueous phase was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification (30:1 to 20:1 hexanes/EtOAc) of the crude material gave product **III-53** as a white solid (6.32 g, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.46 (s, -OH), 1.74 (s, 3H), 0.18 (s, 18 H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ (ppm) = 105.8 (C), 87.1 (C), 60.4 (C), 31.8 (CH_3), 0.3 (CH_3).

155. (a) Nielsen, M. B.; Diederich, F. *Synlett* **2002**, 544-552. (b) Alberts, A. H. *J. Am. Chem. Soc.* **1989,** *111*, 3093-3094.

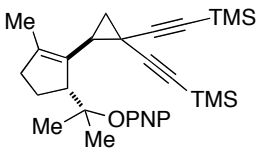
(3-Methylenepenta-1,4-diyne-1,5-diyl)bis(trimethylsilane) III-54



To a solution of alcohol **III-53** (581 mg, 2.43 mmol) in toluene (25 mL) was added $MeSO_3H$ (10 mg, 0.10 mmol) and the mixture was refluxed for 2 h. After cooling the system, the crude was filtered over a pad of silica and the solvent was removed to give a crude yellow oil. Chromatographic purification (pure pentane) of the crude material afforded product **III-54** as a clear oil (220 mg, 40%). **III-54** was storred as a solution in benzene at low temperature (i.e. -10 ºC).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.81 (s, 2H), 0.20 (s, 18H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) = 133.4 (CH_2), 113.7 (C), 102.4 (C), 94.6 (C), 0.4 (6xCH_3)

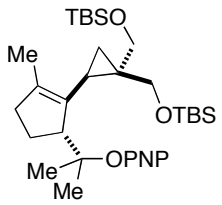
((2-(2-Methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)cyclopropane-1,1-diyl)bis(ethyne-2,1-diyl))bis(trimethylsilane) III-52



To a solution of **III-17a** (100 mg, 0.365 mmol) and **III-54** (96.8 mg, 0.439 mmol) in CH_2Cl_2 (2 mL), Au(I) catalyst **C2** (17 mg, 0.018 mmol) was added at 0 ºC and the whole was stirred at room temperature for 1 h. The reaction was quenched by addition of NEt_3 (0.1 mL) and the aqueous phase was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatographic purification (60:1 to 30:1 hexanes/EtOAc) of the crude material afforded **III-52** as a yellow oil (36 mg, 20%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.14 (d, J = 9.2 Hz, 2H), 7.17 (d, J = 9.2 Hz, 2H), 3.66 (d, J = 9.3 Hz, 1H), 2.39-2.30 (m, 1H), 2.23-2.15 (m, 2H), 1.74 (s, 3H), 1.70 (dd, J = 8.5, 4.2 Hz, 1H), 1.48 (s, 3H), 1.41 (s, 3H), 1.41-1.37 (m, 2H), 0.88 (t, J = 7.1 Hz, 1H), 0.13 (s, 9H), 0.05 (s, 9H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ (ppm) = 163.0 (C), 142.5 (C), 132.4 (C), 125.9 (C), 125.8 (CH_2), 121.8 (CH_2), 108.0 (C), 106.0 (C), 87.3 (C), 83.4 (C), 81.7 (C), 58.4 (CH), 38.40 (CH_2), 32.74 (CH_2), 30.1 (C), 26.05 (CH_2), 25.7 (CH_3), 24.41 (CH_3), 15.9 (CH_3), 11.0 (CH), 0.7 (CH_3), 0.6 (CH_3). HRMS (EI) cald for [$C_{28}H_{40}NO_3Si_2$]: 494.2547, found: 494.2544.

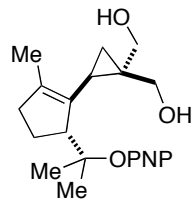
(((2-(2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)cyclopropane-1,1-diyl)bis(methylene))bis(oxy))bis(tert-butyldimethylsilane) III-55e



A solution of **III-17a** (500 mg, 1.83 mmol) in anhydrous CH_2Cl_2 (6.1 mL) was added dropwise over 30 min to a solution of gold catalyst **C2** (34.0 mg, 0.0365 mmol) and bis-TBS protected alkene[160] (1.16 g, 3.66 mmol) in anhydrous CH_2Cl_2 (12.2 mL) at room temperature. A few drops of NEt_3 were added and the solution was filtered through a short pad of SiO_2 (washed with 4:1 hexanes/EtOAc) then concentrated. Purification over silica gel (hexanes to 50:1 hexanes/EtOAc) afforded a 1:1.14 mixture (ratio determined by ^{1}H-NMR) of cyclopropane **III-55e** and bis-TBS protected alkene as a colourless oil (total 1.37 g, 79% calculated yield, 62 wt% purity).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.15-8.11 (m, 2H), 7.06-7.02 (m, 2H), 3.66 (dd, J = 16.2, 10.1 Hz, 2H), 3.26 (dd, J = 26.1, 10.1 Hz, 2H), 3.24 (br. s, 1H), 2.40-2.28 (m, 1H), 2.20-2.11 (m, 1H), 1.91-1.81 (m, 2H), 1.75 (s, 3H), 1.47-1.43 (m, 1H), 1.43 (s, 3H), 1.35 (s, 3H), 0.91 (s, 9H), 0.91-0.84 (m, 1H), 0.84 (s, 9H), 0.41 (dd, J = 5.9, 4.8 Hz, 1H), 0.05 (s, 3H), 0.04 (s, 3H), -0.03 (s, 3H), -0.04 (s, 3H).

(2-(2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)cyclopropane-1,1-diyl)dimethanol III-56

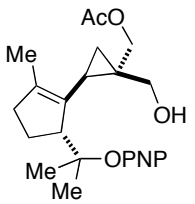


TBAF (4.88 mL, 1.0M, 4.88 mmol) was added dropwise to a solution of **III-55e** (928 mg, 0.975 mmol) in anhydrous THF (9.8 mL, 0.10 M) at room temperature. The resulting mixture was stirred for 1 h, then quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification over silica gel (1:1 to 1:2 hexanes/EtOAc) afforded **III-56** (315 mg, 89%) as a white solid.

160. Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988,** *110*, 8129-8133.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.17 (d, J = 9.1 Hz, 2H), 7.09 (d, J = 9.1 Hz, 2H), 3.70 (d, J = 11.1 Hz, 1H), 3.55 (d, J = 11.2 Hz, 2H), 3.38 (d, J = 11.1 Hz, 1H), 3.13 (d, J = 9.4 Hz, 1H), 2.37-2.27 (m, 1H), 2.24-2.18 (m, 1H), 2.00-1.93 (m, 1H), 1.79 (s, 3H), 1.69-1.63 (m, 1H), 1.59-1.55 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 0.99 (dd, J = 8.4, 4.9 Hz, 1H), 0.67 (dd, J = 5.8, 5.4 Hz, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ (ppm) = 161.3 (C), 144.0 (C), 142.4 (C), 132.8 (C), 125.9 (CH), 124.2 (CH), 89.2 (C), 70.4 (CH_2), 65.8 (CH_2), 59.8 (CH), 38.2 (CH_2), 29.1 (CH_2), 26.3 (C), 26.2 (CH_3), 23.8 (CH), 22.7 (CH_2), 17.0 (CH_3), 15.9 (CH_3).

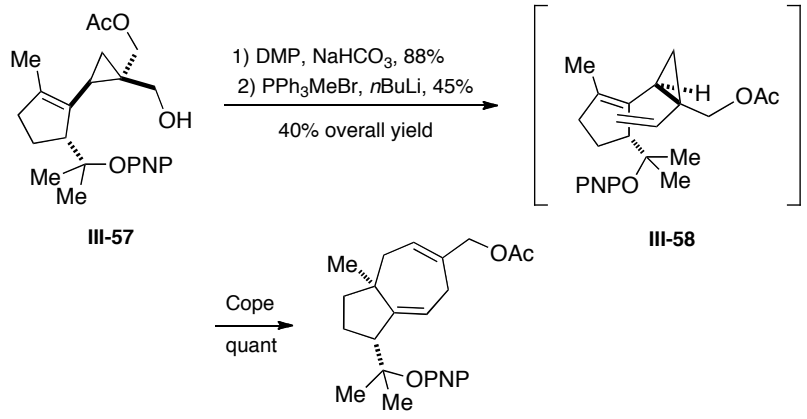
(1-(hydroxymethyl)-2-(2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)cyclopropyl)methyl acetate III-57



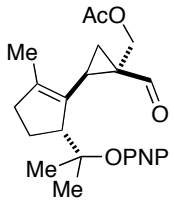
Ac_2O (5.60 mL, 1.0 M solution in CH_2Cl_2, 5.60 mmol) was added dropwise over 1 h to a solution of DMAP (32.0 mg, 0.266 mmol), anhydrous pyridine (0.860 mL, 10.6 mmol) and **III-56** (1.92 g, 5.31 mmol) at 0 ºC. The resulting mixture was subsequently stirred for 1 h at 0 ºC, then quenched with aqueous HCl (0.5 M). The aqueous were extracted with EtOAc and the combined organic layers were washed with aqueous HCl (0.5M), water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification over silica (10:1 to 3:1 hexanes/EtOAc) afforded monoacetate **III-57** (1.39 g, 65%) as a colourless oil. The undesired monoacetate and bis-acetate were combined (total 766 mg) in order to be submitted to a recycling procedure.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.18-8.14 (m, 2H), 7.11-7.07 (m, 2H), 4.23 (d, J = 11.6 Hz, 1H), 3.60 (br. d, J = 11.2 Hz, 1H), 3.57 (d, J = 11.6 Hz, 1H), 3.28 (d, J = 11.2 Hz, 2H), 2.66 (bs, 1H), 2.38-2.26 (m, 1H), 2.26-2.16 (m, 1H), 2.02 (s, 3H), 1.93 (dtd, J = 13.7, 9.6, 6.3 Hz, 1H), 1.77 (s, 3H), 1.77-1.69 (m, 1H), 1.62-1.55 (m, 1H), 1.36 (s, 3H), 1.33 (s, 3H), 1.05 (dd, J = 8.4, 5.0 Hz, 1H), 0.86 (tdd, J = 6.4, 5.3, 2.4 Hz, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ (ppm) = 172.3 (CO), 161.2 (C), 143.5 (C), 143.3 (C), 132.1 (C), 125.9 (CH), 122.8 (CH), 88.1 (C), 69.5 (CH_2), 63.6 (CH_2), 58.6 (CH), 38.1 (CH_2), 26.7 (CH_2), 26.0 (C), 25.6 (CH_3), 24.1 (CH), 23.6 (CH_3), 21.6 (CH_2), 17.0 (CH_3), 15.9 (CH_3). The relative configuration was determined by NOE spectra.

Synthesis of III-22b



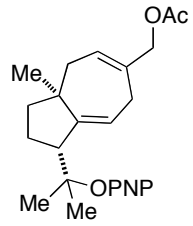
(1-Formyl-2-(2-methyl-5-(2-(4-nitrophenoxy)propan-2-yl)cyclopent-1-en-1-yl)cyclopropyl)methyl acetate III-57A



III-57A was obtained using the same procedure than **III-45A**, from alcool **III-57** (221 mg, 0.548 mmol). The crude material was used in the following step (220 mg, quant).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.84 (d, J = 0.6 Hz, 1H), 8.19-8.15 (m, 2H), 7.02-6.98 (m, 2H), 4.39 (d, J = 11.9 Hz, 1H), 3.74 (d, J = 11.9 Hz, 1H), 2.77 (d, J = 8.8 Hz, 1H), 2.41-2.30 (m, 1H), 2.28-2.20 (m, 2H), 1.96 (s, 3H), 1.96-1.89 (m, 1H), 1.89 (s, 3H), 1.73-1.64 (m, 3H), 1.30 (s, 3H), 1.28 (s, 3H).

III-22b

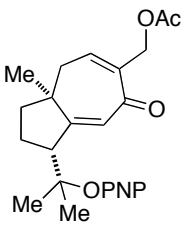


*n*BuLi (0.307 mL, 2.5 M, 0.767 mmol) was added dropwise to a suspension of PPh_3CH_3Br (294 mg, 0.822 mmol) in anhydrous THF (8.0 mL) at -20 ºC. The resulting yellowish solution was stirred for 10 min at -20 ºC, whereupon a solution of **III-57A** (220 mg, 0.548 mmol) was added dropwise. After 10 min at -20 ºC, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction

was quenched with saturated aqueous NH_4Cl, extracted with Et_2O, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification over silica gel (20:1 to 10:1 hexanes/EtOAc) afforded diene **III-60** (80.0 mg, 37%) as a colourless oil. The compound was stored in a glove box to avoid oxidation in the presence of air (storage in a vial under inert atmosphere proved to be insufficient).

1H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.16 (d, J = 9.2 Hz, 2H), 7.07 (d, J = 9.2 Hz, 2H), 5.83 (ddd, J = 6.4, 4.0, 2.3 Hz, 1H), 5.80-5.78 (m, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.42 (d, J = 12.0 Hz, 1H), 3.18-3.13 (m, 1H), 3.00-2.86 (m, 2H), 2.35 (d, J = 14.4 Hz, 1H), 2.13 (dd, J = 15.6, 8.3 Hz, 1H), 2.07 (s, 3H), 1.82-1.73 (m, 1H), 1.63-1.45 (m, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.11 (s, 3H). ^{13}C-NMR (126 MHz, $CDCl_3$): 171.7 (CO), 162.3 (C), 150.5 (C), 143.1 (C), 133.4 (C), 128.3 (CH), 125.9 (CH), 122.7 (CH), 120.3 (CH), 86.4 (C), 71.4 (CH_2), 55.1 (CH), 46.68 (C), 41.88 (CH_2), 41.29 (CH_2), 31.84 (CH_2), 27.41 (CH_2), 26.86 (CH_3), 24.50 (CH_3), 23.61 (CH_3), 21.75 (CH_3). The structure assignment of this compound was confirmed by 2D COSY, HSQC and pendant spectra.

III-59



TBHP (65 μL, 025 mmol) was added in three portions over 1h30 to a solution of **III-22b** (10 mg, 0.025 mmol), K_2CO_3 (1.72 mg, 0.0125 mmol) and CuI (2.8 mg, 0.015 mmol) in degassed acetonitrile (0.8 mL) at RT. After stirring the mixture at room temperature for 1 h, the reaction was quenched with an aqueous solution of $Na_2S_2O_3$ (10% w/w), extracted with CH_2Cl_2 then brine and dried over Na_2SO_4. The solvent was removed under *vacuo* and the crude was purified by column chromatography (3:1 to 1:1 pentane/Et_2O) to give **III-59** as a light yellow oil (2 mg, 20% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.17 (d, J = 9.3 Hz, 2H), 7.10 (d, J = 9.3 Hz, 2H), 6.67 (d, J = 2.1 Hz, 1H), 6.64 (dd, J = 9.0, 3.2 Hz, 1H), 4.88 (d, J = 12.7 Hz, 1H), 4.78 (d, J = 12.8 Hz, 1H), 3.38-3.33 (m, 1H), 2.70 (d, J = 17.9 Hz, 1H), 2.48 (dd, J = 16.8, 9.0 Hz, 1H), 2.08 (s, 3H), 2.02-1.96 (m, 1H), 1.73-1.63 (m, 3H), 1.42 (s, 3H), 1.38 (s, 3H), 1.17 (s, 3H).

Crystallographic data for 2-(2-(2-(hydroxymethyl)-2-(((triisopropylsilyl)oxy)methyl)cyclopropyl)-3-methylcyclopent-2-en-1-yl)propan-2-ol III-45:

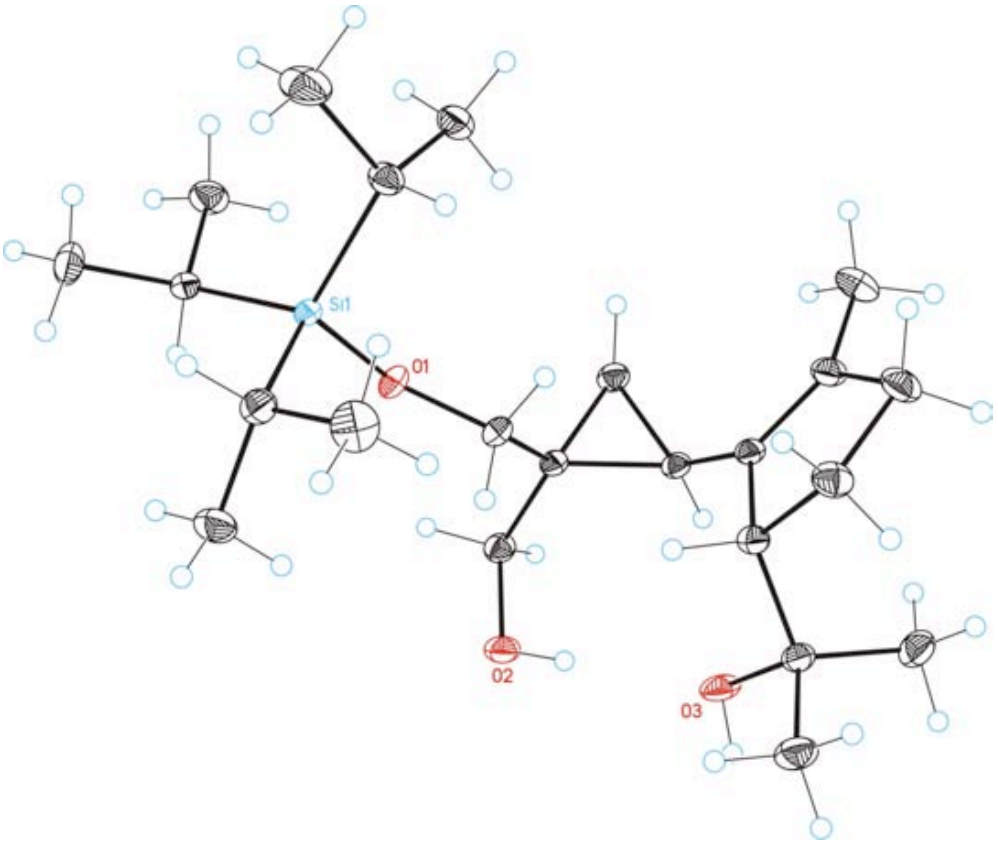


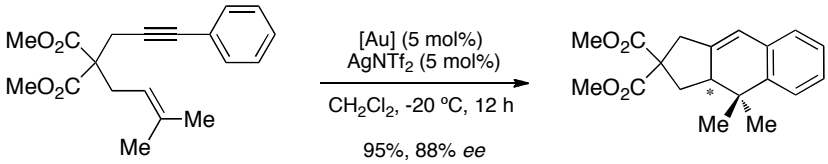
Table 1. Crystal data and structure refinement for **III-45**.

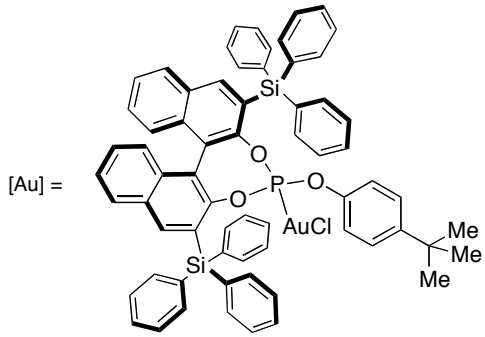
Identification code	**III-45**
Empirical formula	C23 H44 O3 Si
Formula weight	396.67
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.2446(4) Å α= 75.141(2)°.

	b = 9.9300(4) Å β = 84.050(2)°.
	c = 13.7156(6) Å γ = 84.427(2)°.
Volume	1207.15(9) $Å^3$
Z	2
Density (calculated)	1.091 mg/m3
Absorption coefficient	0.116 mm-1
F(000)	440
Crystal size	0.4 x 0.3 x 0.3 mm3
Theta range for data collection	2.22 to 33.50°.
Index ranges	-14<=h<=14, -14<=k<=15,
	-21 <=l<=21
Reflections collected	22803
Independent reflections	9350 [R(int) = 0.0340]
Completeness to theta =33.50 °	0.988%
Absorption correction	Empirical
Max. and min. transmission	0.9329 and 0.8016
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	9350 / 0 / 255
Goodness-of-fit on F2	1.059
Final R indices [I>2sigma(I)]	R1 = 0.0461, wR2 = 0.1176
R indices (all data)	R1 = 0.0692, wR2 = 0.1381
Largest diff. peak and hole	0.549 and -0.467 e.Å-3

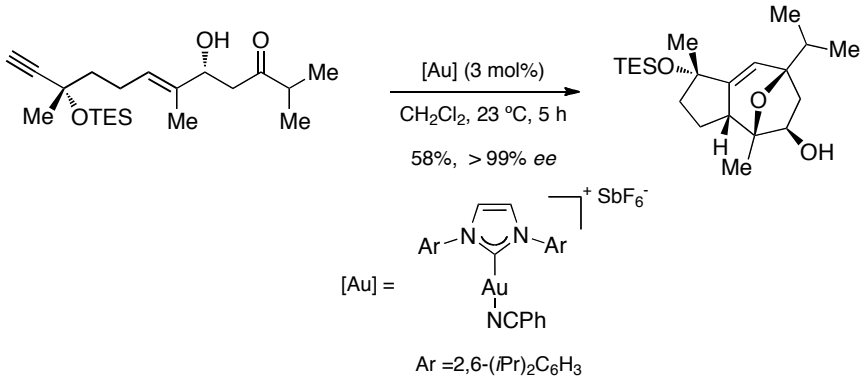
Conclusions

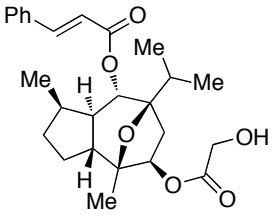
- The gold(I)-catalyzed intramolecular [4+2] cycloaddition of arylenynes could be achieved with up to 88% *ee* with an excellent yield by using a bulky chiral gold(I) phosphite complex.





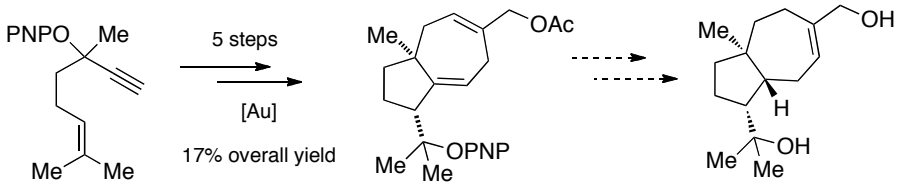
- The total synthesis of the natural enantiomers of englerins A and B was achieved in 18 steps and 16 steps and in 7% and 8% overall yield, respectively, through a stereoselective aldol reaction and a selective gold(I)-catalyzed cyclization.



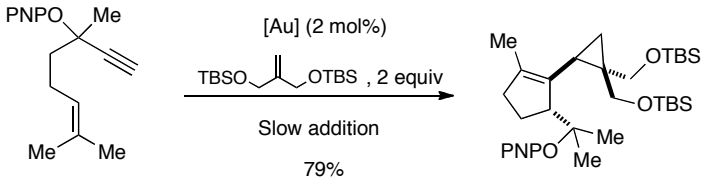


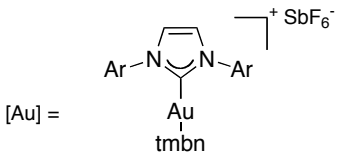
(-)-Englerin A

- A study towards the synthesis of schisanwilsonene A provided a route to the construction of the bicyclo[5.3.0]decane skeleton subsequent to a gold(I)-catalyzed intramolecular 1,5-migration reaction and a Cope rearrangement.



Schisanwilsonene A





Ar =2,4,6-$(Me)_3C_6H_2$

Dipòsit Legal: T.1321-2013
Notes

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Dipòsit Legal: T.1321-2013
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