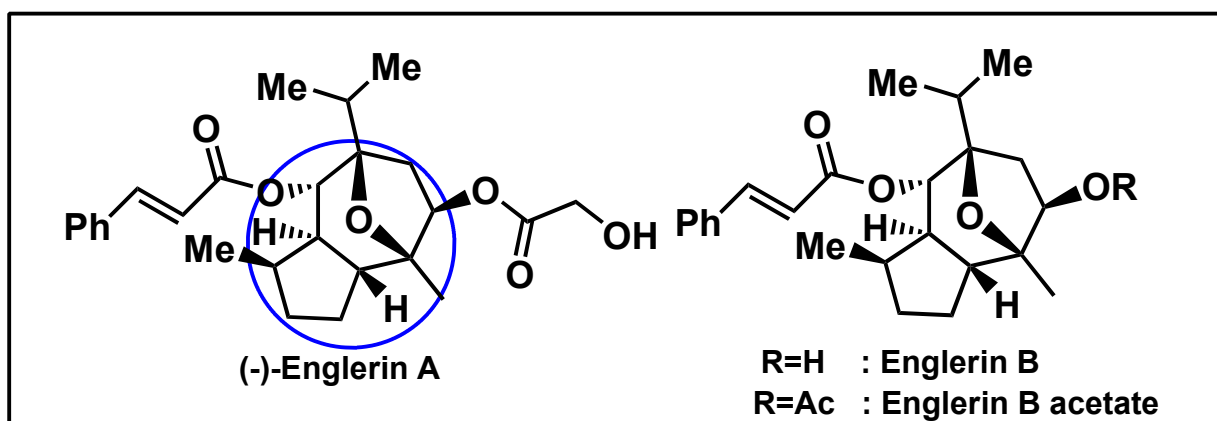


# Enantioselective Synthesis of (-)-Englerins A and B

2010. 09. 22 (Wed) Hirotomo Komai (M1)



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## 0. Introduction

### Isolation

J. A. Beutler et al. *Org. Lett.* **2009**, *11*, 57-60.  
From the stem bark of the east African (Tanzania and Zimbabwe) plant "*Phyllanthus engleri*".

### First Total Synthesis((+)-Englerin A)

M. Christmann et al. *Angew. Chem., Int. Ed.* **2009**, *48*, 9105-9108.

(Olefin metathesis using the Grubbs II catalyst)

However..... (+)-Englerin A was not natural product.

### Total Synthesis ((-)-Englerin A)

1. A.M.Echavarren *Angew. Chem. Int. Ed.* **2010**, *49*, 3517-3519.

([2+2+2] alkyne/alkene/carbonyl cycloaddition using Au(I) catalyst.)

2. D. Ma *Angew. Chem. Int. Ed.* **2010**, *49*, 3513-3516.

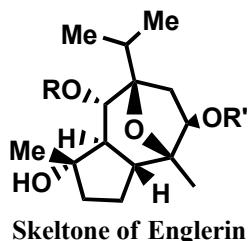
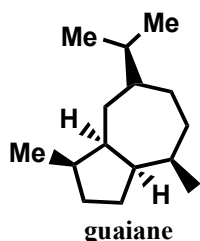
(The same key reaction of Echavarren)

3. K.C. Nicolaou *J. Am. Chem. Soc.* **2010**, *132*, 8219-8222.  
([5+2] cycloaddition reaction)

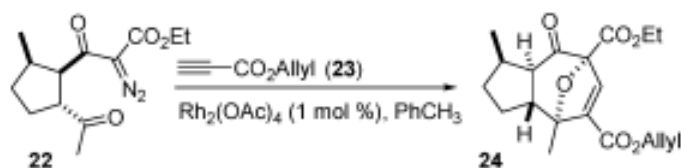
4. Emmanuel A. Theodorakis et al. *Org. Lett.* **2010**, *12*, 3708-3711.

### Challenging

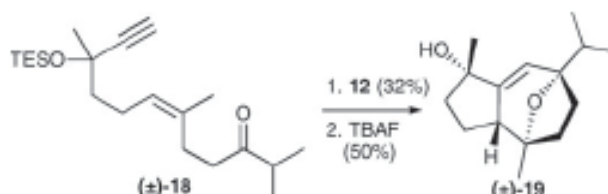
1. Construction of guaiane-type sesquiterpene that contains uncommon oxygenated motif.
2. Tricyclic motif carrying two esters, one to a cinnamic acid and the other to a glycolic acid residue.



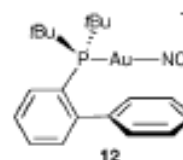
## Examples of making guaiane sesquiterpene skeltone



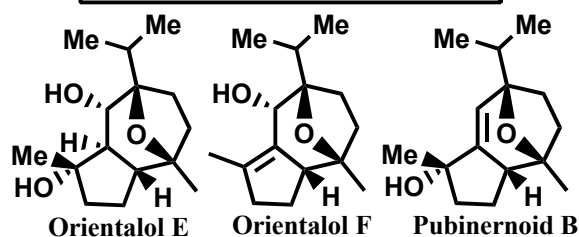
Martin E. Maier et al. *Org. Lett.* **2010**, *12*, 3418-3421.



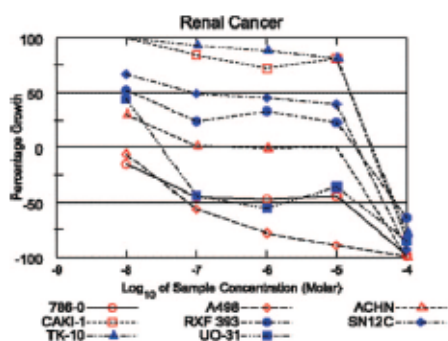
A. M. Echavarren et al. *Chem. Commun.*, **2009**, 7327



### Other guaiane-type sesquiterpenes



**Englerins A** ;It demonstrated excellent selectivity for the renal cancer cell line panel, with 5 of 8 renal lines having GI<sub>50</sub> values under 20 nM (Table 2, Figure 3),



**Figure 3.** Dose–response curves for cytotoxic activity of englerin A (1) against the renal cancer cell lines in the NCI 60-cell panel.

**Table 2.** Renal Cancer Cell Growth Inhibition Data (Mean GI<sub>50</sub> in μM) for Englerin A (1), Compared to Average Values for Taxol

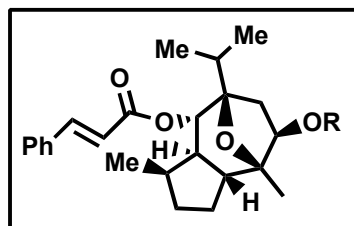
renal cell line	1	Taxol
786-0	<0.01	0.034
A498	<0.01	0.10
ACHN	<0.01	0.65
CAKI-1	15.5	0.35
RXF-393	0.011	0.041
SN12C	0.087	0.018
TK-10	15.5	0.11
UO-31	<0.01	0.45

### Englerins B;

Renal Cancer	A	B
	Growth Percent	
786-0	27.08	85.89
A498	38.95	71.54
ACHN	16.36	81.98
CAKI-1	-52.30	65.40
RXF 393	85.04	45.23
SN12C	44.12	100.37
TK-10	136.12	148.74
UO-31	-81.64	66.21

This result means Englerins B is lower activity than Englerin A.

Why?  
What's difference?

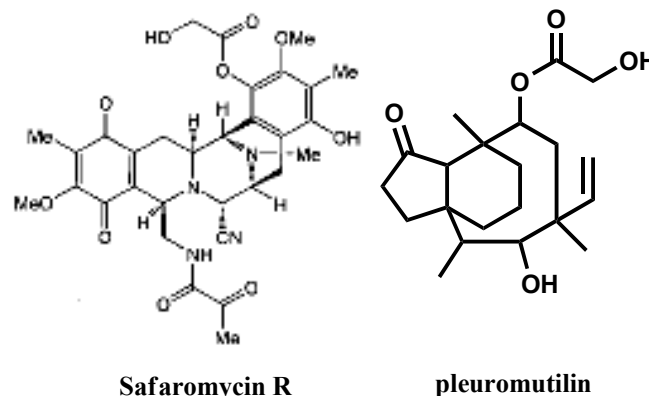


Englerins A:  
R = glycolic acid  
Englerin B :  
R = H

- Glycolic acid may play a important role in the activity.
- or
- Substitution at the C-9 position by the glycolate ester may be important for the observed potency.

### Search of reason

#### 1. Hydroxy acid containing natural products

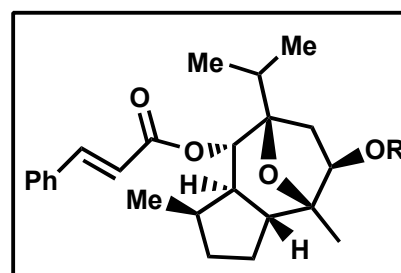


The NCI 60-cell data **Pleuromutilin** indicated no significant cytotoxicity. **Safaromycin R**, although quite potent, did not show renal selectivity.

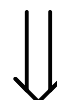


Glycolate substitution alone cannot account for the renal selectivity of Englerins A.

#### 2. Other ester motif compounds.



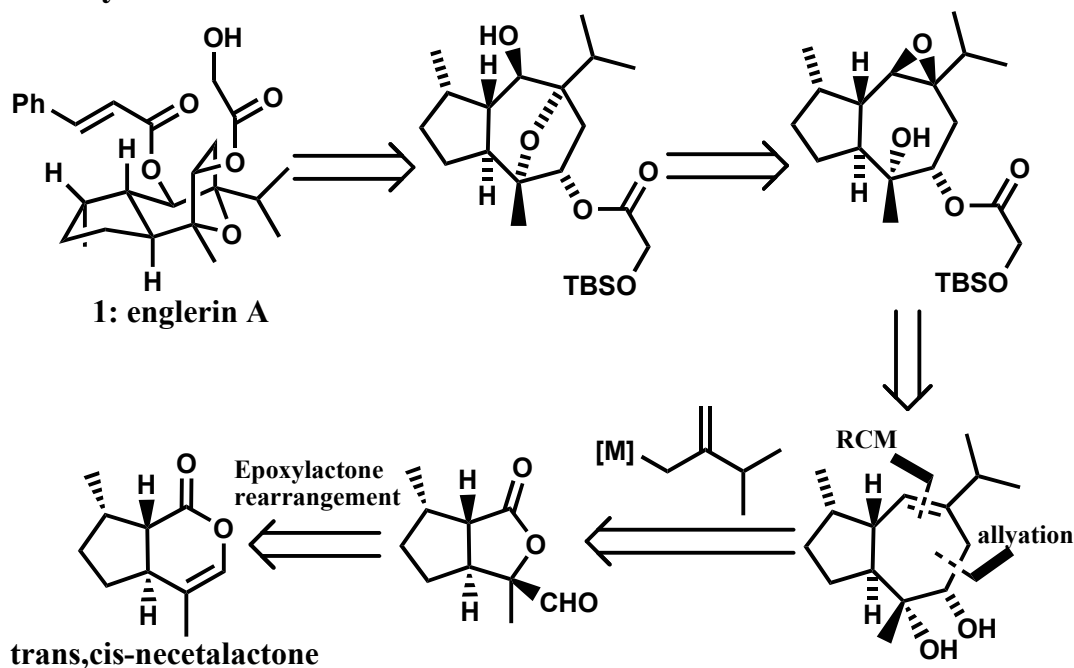
Englerin B acetate showed an approximately 400-fold selectivity against the renal cell line (A498).



It's vital to synthesize a series of englerin analogues with different ester substitution at both C-6 and C-9 for biological evaluation.

# 1. Christmann's Total Synthesis

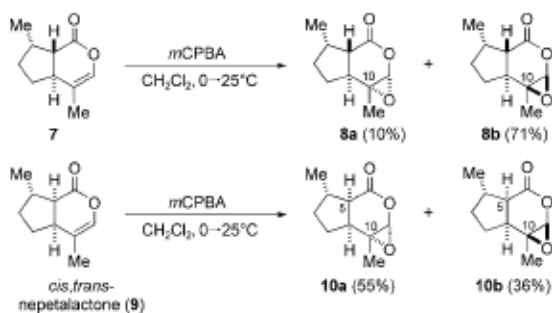
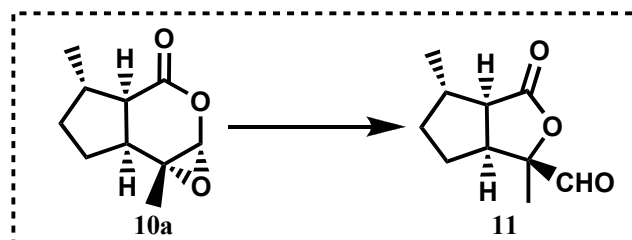
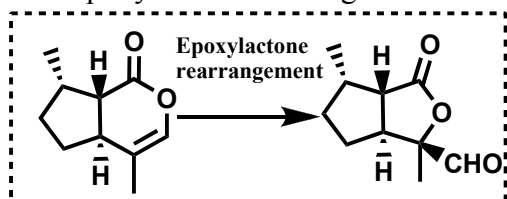
## 1.1 Retrosynthesis



Mathias Christmann et al. *Angew. Chem. Int. Ed.* **2009**, *48*, 9105-9108.

## 1.2 Key Reaction

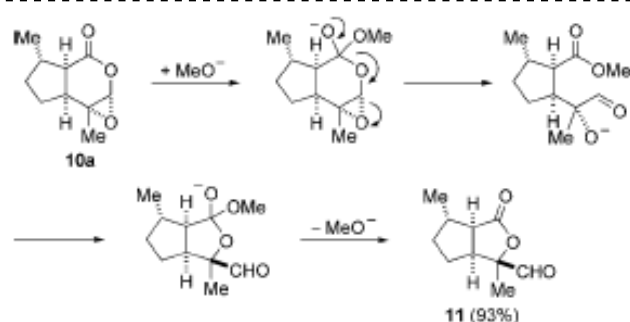
### 1.2.1 Epoxy lactone rearrangement



**Scheme 1.** Oxidation of nepetalactone 7 and 9.

The oxidation of **7** with mCPBA afforded **8b** (undesired) as the major isomer (d.r. 7:1).

The epoxidation of **9** installed the correct configuration at C10 for the major isomer **10a** (d.r. 1.5:1).



**Scheme 2.** Tentative mechanism for the ring contraction.

Treatment of **10a** with NaOMe led to a rapid ring contraction of the epoxy lactone moiety into the formyl lactone **11**.

The rearrangement of **8a** into the aldehyde **6** did not take place.

**Resulting from the strain of the trans-bicyclo-[3.3.0]octane scaffold.**

		$\Delta E = E(\text{trans}) - E(\text{cis})$ (kcal/mol)			
Conformers / % abundance		HF/6-31G**	MP2/6-31G**	MP2/6-311G**	Lit.
	100% / 0%	8.01	7.57	7.17	6.4 <sup>a</sup>
	100% / 0%	8.61	8.12	7.77	-
	100% / 0%	12.66	9.47	8.34	-
	100% / 0%	10.95	9.13	8.46	-

<sup>a</sup> Energies of conformers computed at geometries optimized at given level of theory unless otherwise noted.  
<sup>b</sup> Calculated at the MP2/6-31G\* optimized geometries; this last value used to compute %abundance.

Tomas Hudlicky et al. *Synlett*. **2005**, 2911-2914.

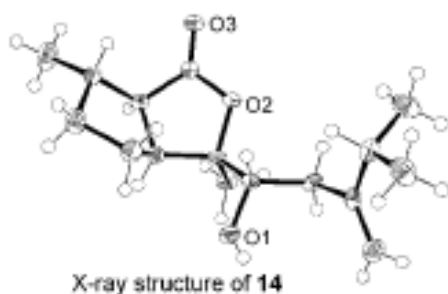
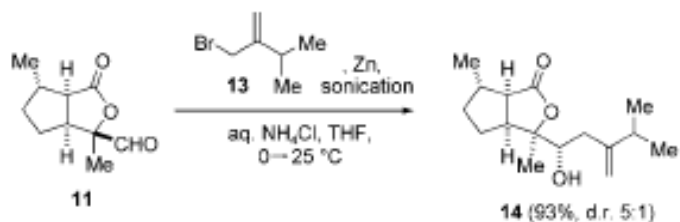
#### Bicyclo[3.3.0]octanones:

It is clear that only cis-fused products would be obtained in all cases regardless of the method used to prepare them;

:The average energy difference is 7.8 kcal/mol.

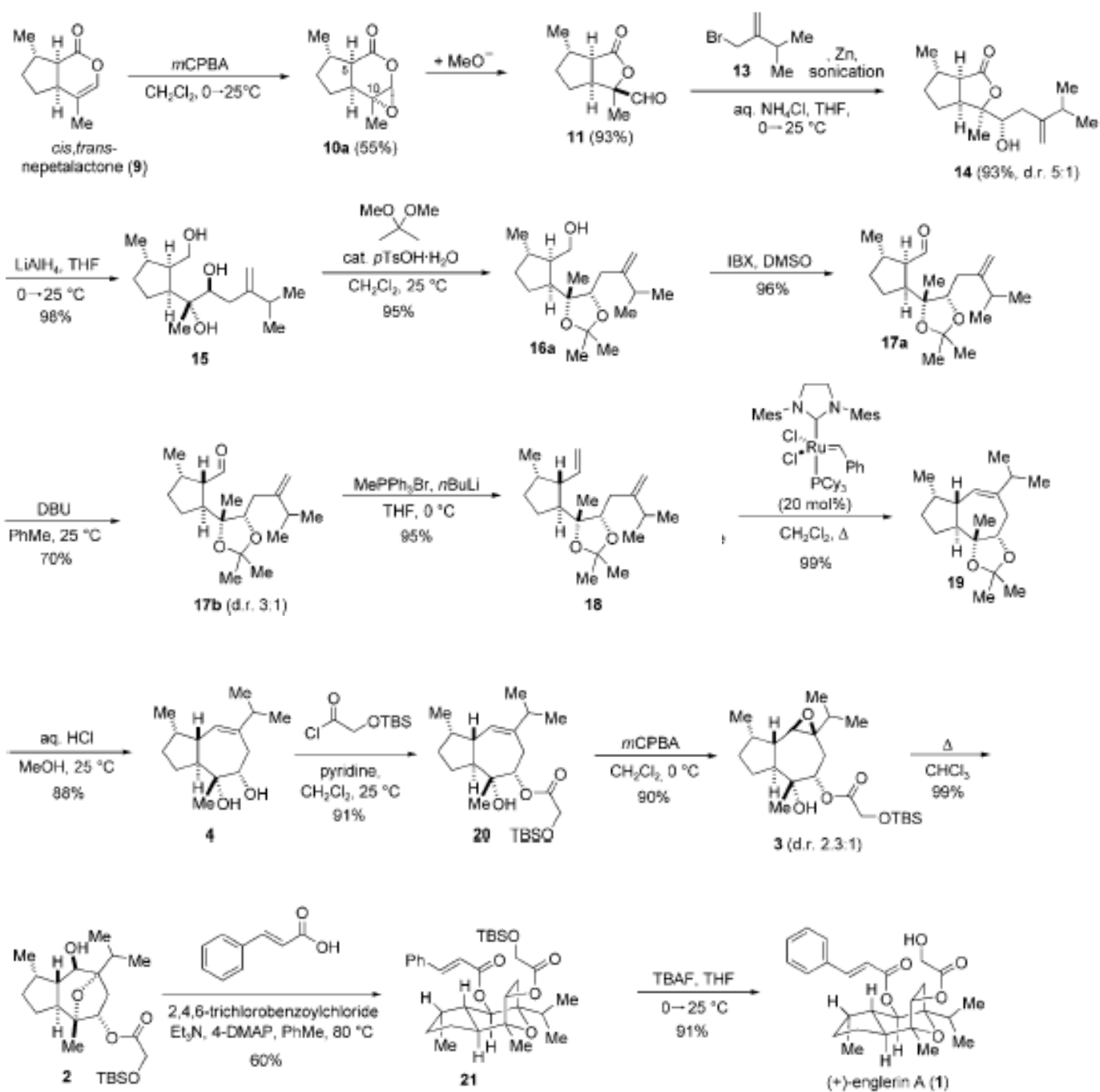
:Any trans-fused compound would isomerize to the cis-isomer immediately.

#### 1.2.2 Diastereoselective Barbier Reaction



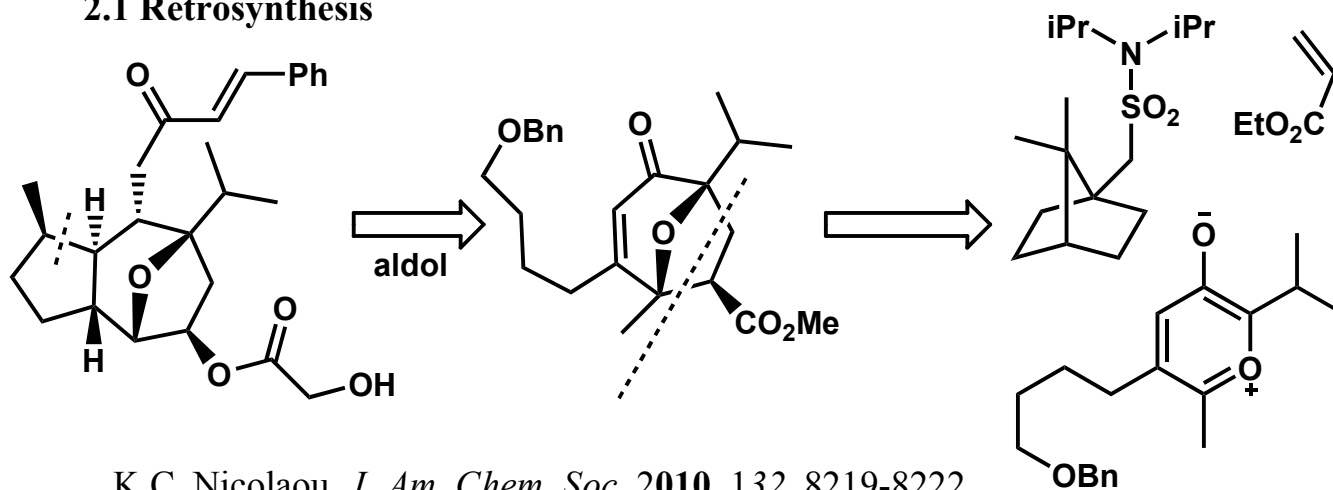
This selectivity results from a minimization of dipole-dipole interactions in the aldehydes reactive conformation.

### 1.3 Total synthesis



## 2. Nicolaou's Total synthesis

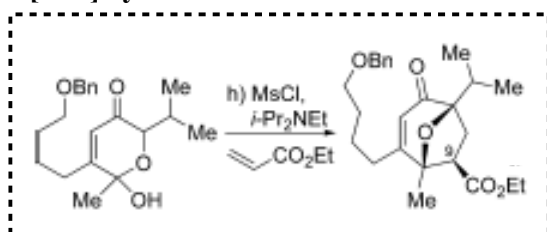
### 2.1 Retrosynthesis



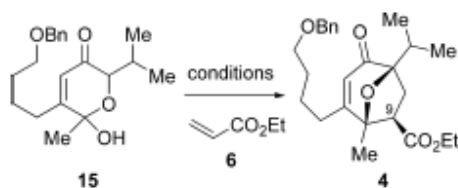
K.C. Nicolaou *J. Am. Chem. Soc.* **2010**, *132*, 8219-8222.

### 2.2 Key Reaction

#### 2.2.1 [5+2] cycloaddition reaction



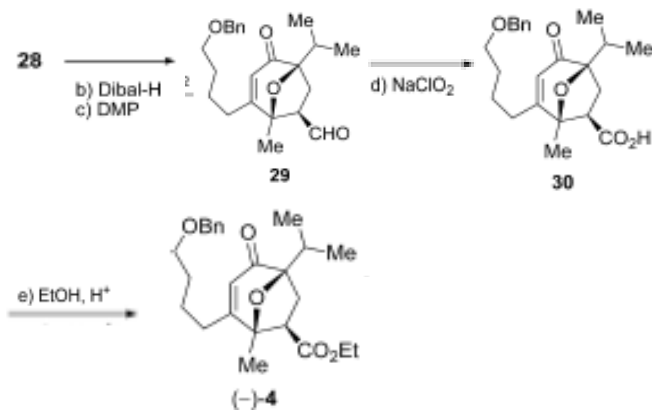
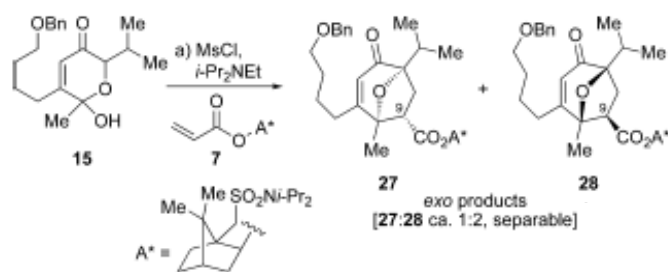
#### ~Racemic Synthesis version~



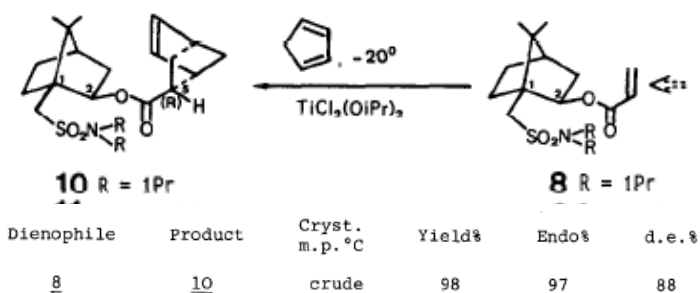
entry	conditions	yield (%) <sup>e</sup>	C <sub>95</sub> :C <sub>97</sub> <sup>f</sup>
1	<i>i</i> -Pr <sub>2</sub> NEt (1.2 equiv), toluene (0.15 M), 3 h	47	5:1
2	<i>i</i> -Pr <sub>2</sub> NEt (1.2 equiv), THF (0.15 M), 3 h	UM <sup>g</sup>	
3	<i>i</i> -Pr <sub>2</sub> NEt (1.2 equiv), CH <sub>2</sub> CN (0.15 M), 3 h	50	1.5:1
4	<i>i</i> -Pr <sub>2</sub> NEt (1.2 equiv), ClCH <sub>2</sub> CH <sub>2</sub> Cl (0.15 M), 3 h	UM <sup>g</sup>	
5 <sup>b</sup>	<i>i</i> -Pr <sub>2</sub> NEt (1.2 equiv), additive (1.0 equiv), toluene (0.15 M), 3 h	UM <sup>g</sup>	
6	<i>i</i> -Pr <sub>2</sub> NEt (1.2 equiv), LiCl (1.0 equiv), toluene (0.15 M), 3 h	25	3.3:1
7 <sup>c</sup>	<i>i</i> -Pr <sub>2</sub> NEt (1.5 equiv), toluene (0.13 M), 3 h	26	5:1
8 <sup>c</sup>	<i>i</i> -Pr <sub>2</sub> NEt (1.5 equiv), CH <sub>2</sub> Cl <sub>2</sub> (0.13 M), 3 h	19	3:1
9 <sup>c,d</sup>	<i>i</i> -Pr <sub>2</sub> NEt (1.2 equiv), toluene (0.13 M), 3 h	49	5:1
10 <sup>c,d</sup>	<i>i</i> -Pr <sub>2</sub> NEt (0.9 equiv), toluene (0.04 M), 3 h	46	8:1

<sup>a</sup> **15** (1.0 equiv), **6** (10.0 equiv), MsCl (1.2 equiv), 23 °C → reflux.  
<sup>b</sup> Yb(OTf)<sub>3</sub>, TiCl<sub>4</sub>, AgOTf, CuCl, and ZnBr<sub>2</sub> were used as additives. <sup>c</sup> A solution of **15** (1.0 M) was added to the reaction mixture at reflux via syringe pump over 1 h, giving a final concentration of 0.13 M (entries 7–9) or 0.04 M (entry 10). <sup>d</sup> 20 equiv of **6** was used. <sup>e</sup> Yields refer to chromatographically and spectroscopically homogeneous materials. <sup>f</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>g</sup> Unidentified mixture.

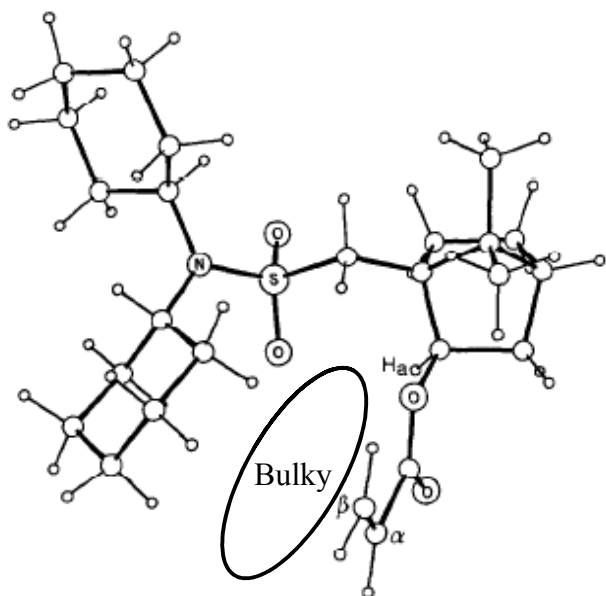
#### ~Asymmetric Synthesis version~



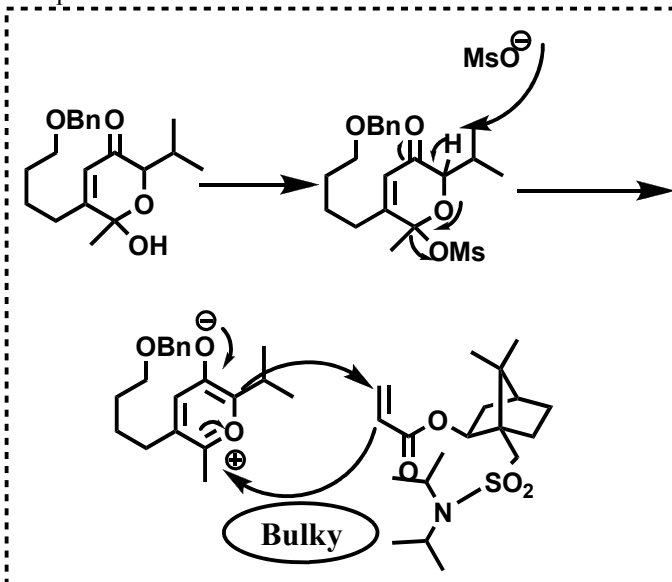
#### Asymmetric cyclization used chiral auxiliaries



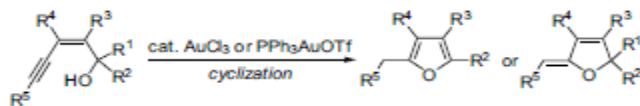
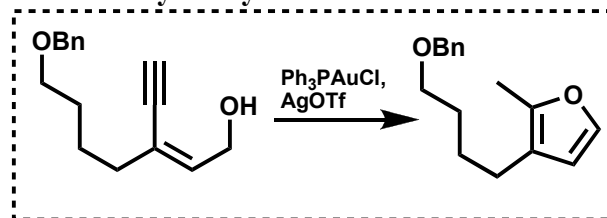
Bernardinelli, G. et al. *Tetrahedron Lett.* **1984**, *25*, 5885.



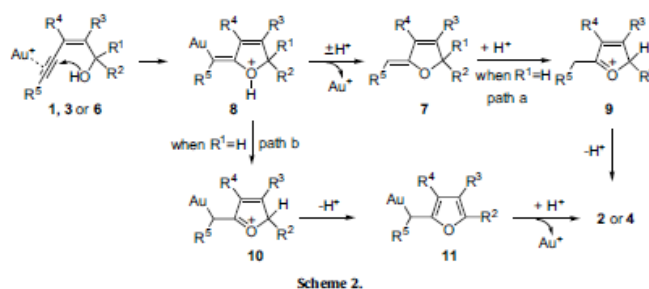
The uncomplexed acrylate adopts in the crystal a strictly antiplanar disposition of the C $\alpha$ ,C $\beta$ - and the C=O bond which in turn is out of the C-Ha-plane by an angle of about 30°. The p lone pair on the planar nitrogen bisects the O-S-O angle ;thus the surface of one cyclohexane ring is projected firmly on top of the olefinic C $\alpha$ -re-face.



## 2.2.2 Gold catalyzed cycladdition



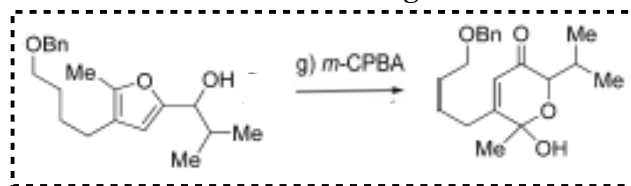
Scheme 1.



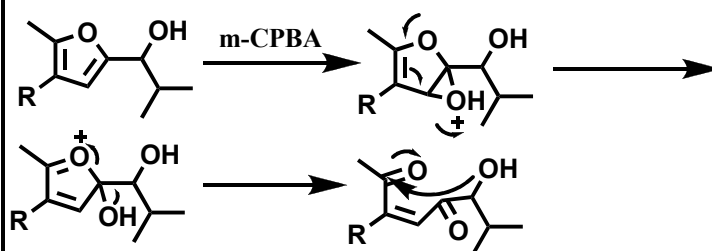
Scheme 2.

Yuanhong Liu, *Tetrahedron* **2009**, *65*, 1839.

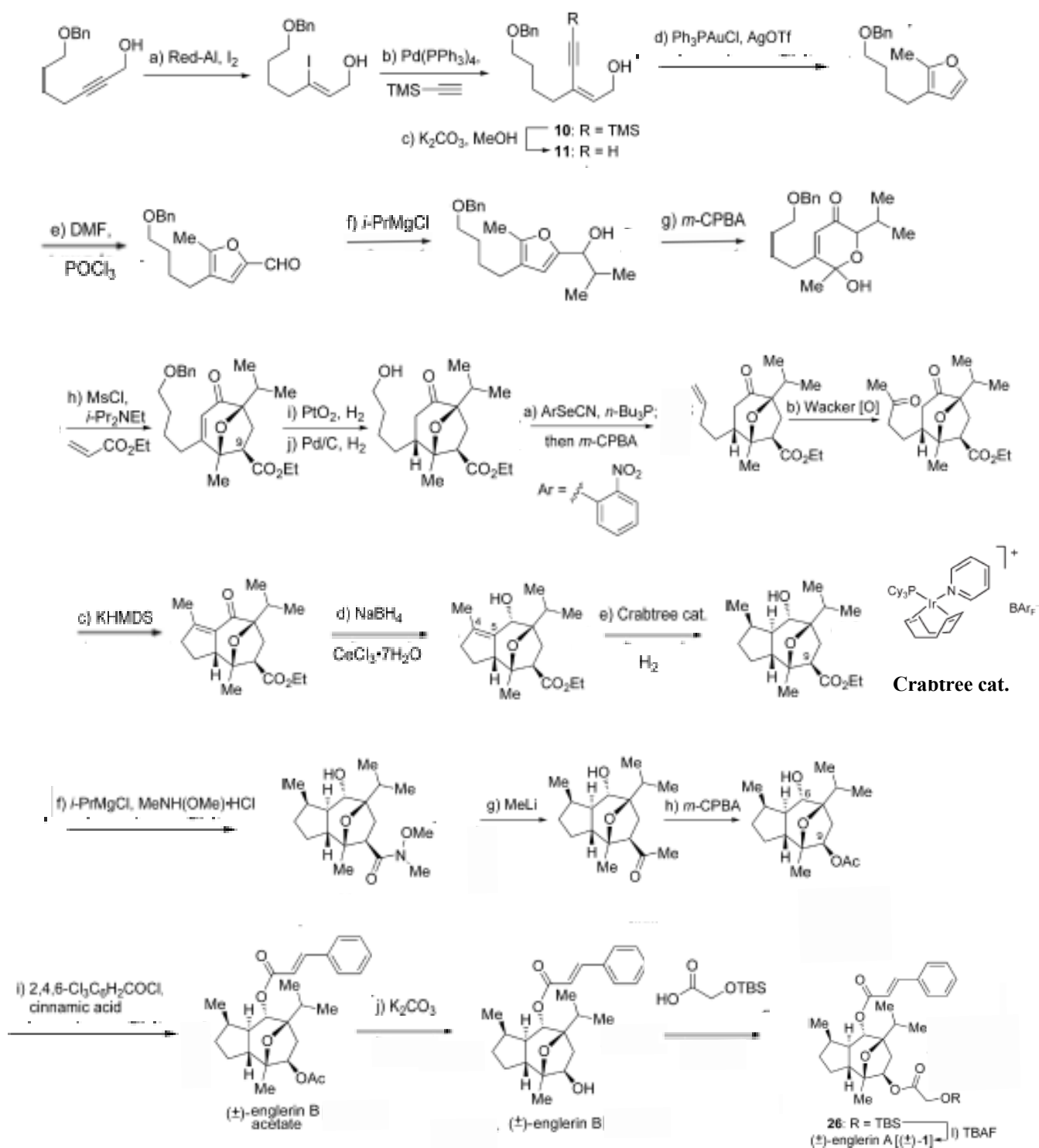
## 2.2.3 Achmatowicz rearrangement



~Mechanism~



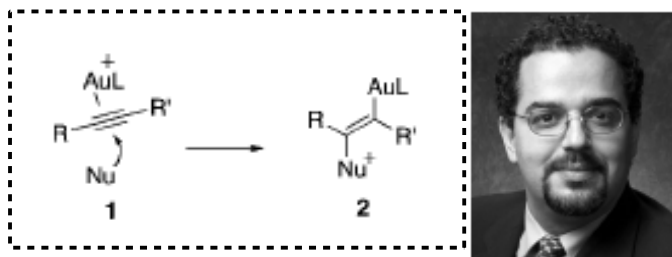
## 2.3 Total synthesis





### 3. Au Catalyzed Cycloaddition Reaction

#### 3.1 Au catalyzed reaction



#### Simplified form

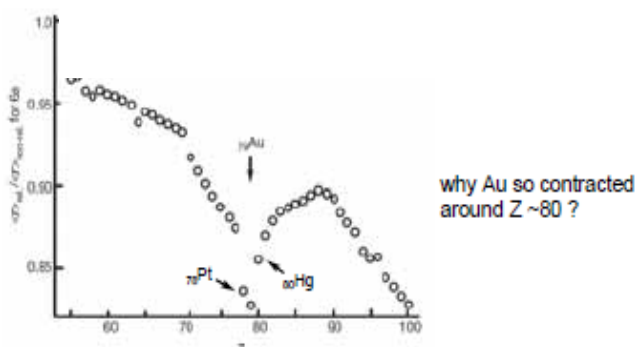
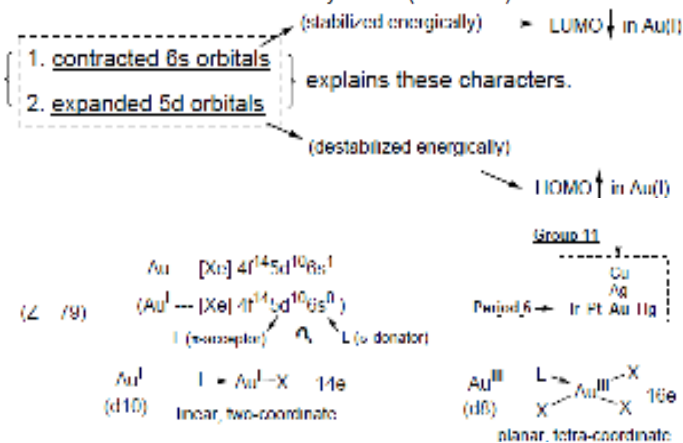
Nucleophilic attack on the [AuL]<sup>+</sup>-activated alkyne proceeds via π complexes 1 to give trans-alkenyl gold complexes of type 2 as intermediates

This high π-acidity is linked to relativistic effects, which reach a maximum in the periodic table with gold.

#### Relativistic effect (detail: see Itano's D2 lit.)

(原子化学の世界において相対性理論を考慮した場合には起こる効果 (s, p, d, f))

should be considered when investigating (calculating) the electronic structure of heavy atoms (> 5th-row)



Box 1 Figure 11 Calculated relativistic contraction of 6s orbital. The relativistic and non-relativistic 6s orbital radii were determined computationally, Notably, Pt, Au and Hg are markedly influenced.

electrons are closer to the nucleus;  
have greater ionization energies.

The d and f orbitals are not contracted.  
(higher angular momentum, seldom descend to nucleus)

Instead better shielded by contracted s and p orbitals  
see a weaker nuclear attraction



Expansion of d and f orbitals

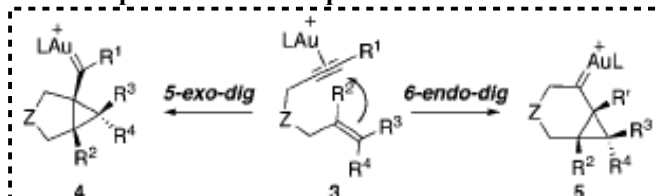


Destabilization of orbital energies

@ With its unique properties strongly influenced by relativistic effects, theoretical chemists have much attention to gold.

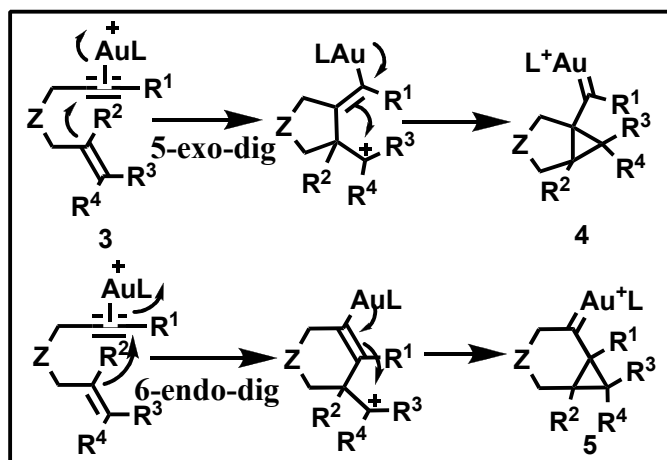
#### 3.2 Au catalyzed Cycloisomerizations

In the case of gold-catalyzed cycloisomerizations of enynes, reactions proceed via π complex 3.

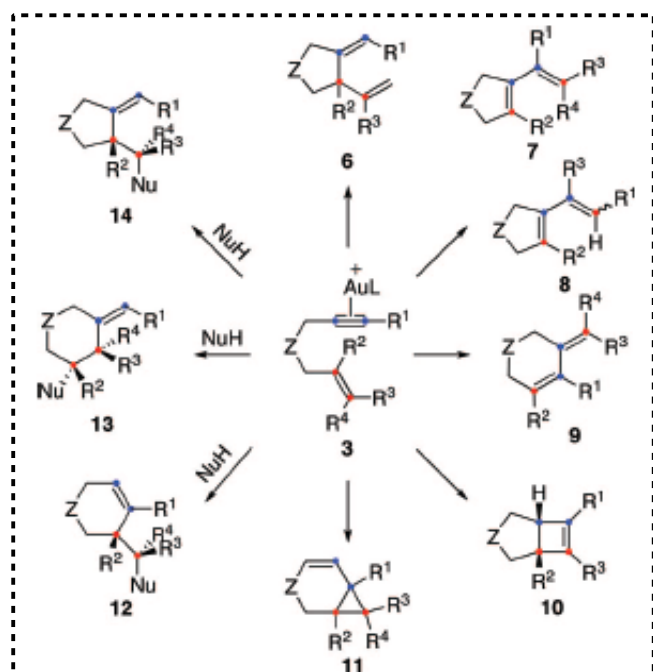


A.M. Echavarren et al. *Chem. Rev.* 2008, 108, 3326-3350

The resulting complex 3 reacts with the alkene by either the 5-exo-dig or 6-endo-dig pathway to form the exo- or endocyclopropyl gold carbene 4 or 5.



However, on occasion, the stronger Lewis acidity of gold complexes can be detrimental in terms of selectivity and because of their low tolerance to certain functional groups. In these instances, the less-strongly Lewis acidic Pt(II) complexes could be the catalysts of choice.



A.M. Echavarren et al. *Chem. Rev.* **2008**, *108*, 3326-3350

Compound 6 is Alder-ene cycloisomerization product that occasionally been found in gold-catalyzed reactions of 1,6-enynes.

Compound 7 and 8 are skeletal rearrangement products. (single and double cleavage).

Compound 9 is endocyclic skeletal rearrangement product.

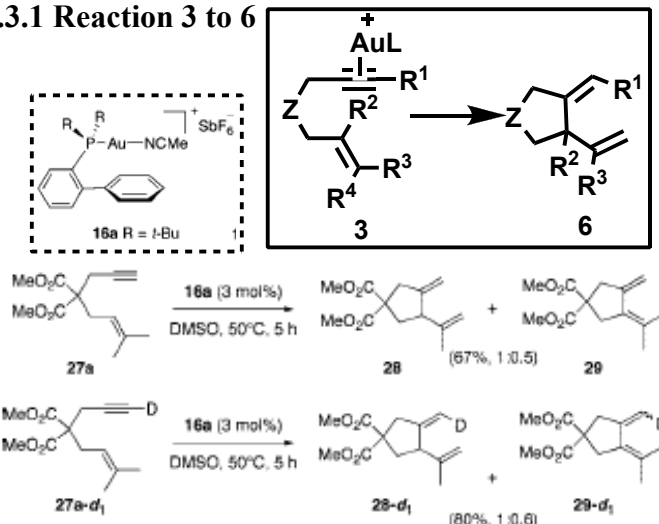
Cyclobutenes 10, and products 11 of intramolecular cyclopropanation have also been obtained.

In the presence of nucleophiles, Compound 12-14 have been obtained in stereospecific processes.

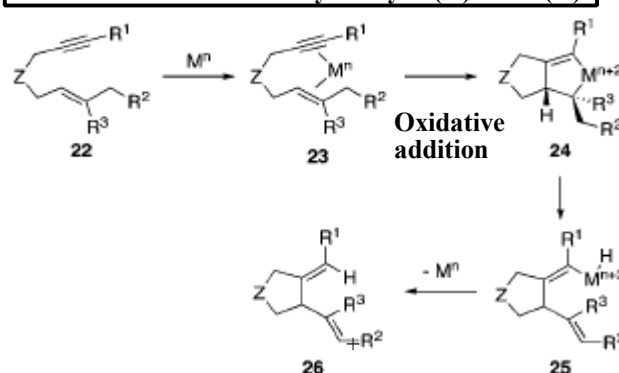
**More-complex transformations starting from more-functionalized enynes are also possible.**

### 3.3 Examples of this type reaction

#### 3.3.1 Reaction 3 to 6



#### Standard mechanism catalyzed by Pt(II) or Ru(II)



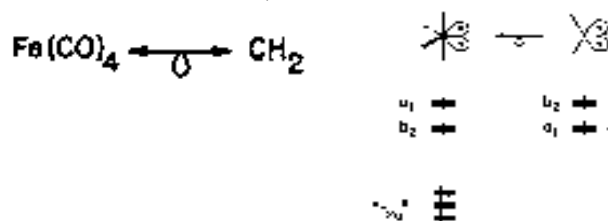
A. M. Echavarren et al. *J. Am. Chem. Soc.* **2001**, *123*, 10511.

$\beta$ -hydrogen elimination occurs from allylic position.  
Pt(II) : trans configuration in starting enyne  
Ru(II): either trans or cis configuration

This type mechanism needs to coordinate to the alkene and the alkyne simultaneously

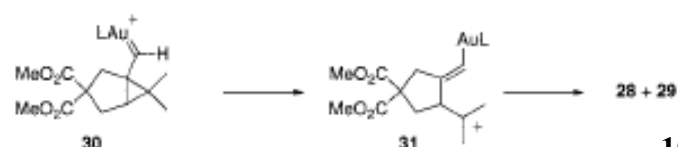
However, the  $[\text{Au}(\text{PR}_3)]^+$ , which is isolobal to  $\text{H}^+$ , cannot coordinate to the alkene and the alkyne simultaneously.

We will call two fragments isolobal if the number, symmetry properties, approximate energy and shape of the frontier orbitals and the number of electrons in them are similar—not identical, but similar.

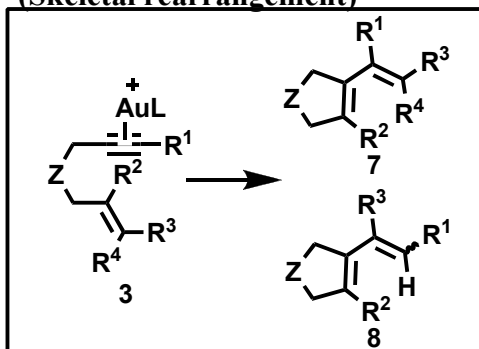


Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 711.724.

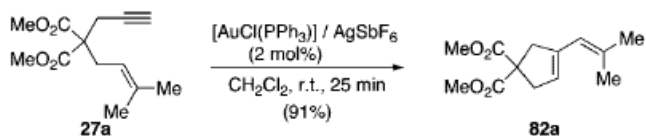
#### Proposed Mechanism



### 3.3.2 Reaction 3 to 7 and 8 (Skeletal rearrangement)

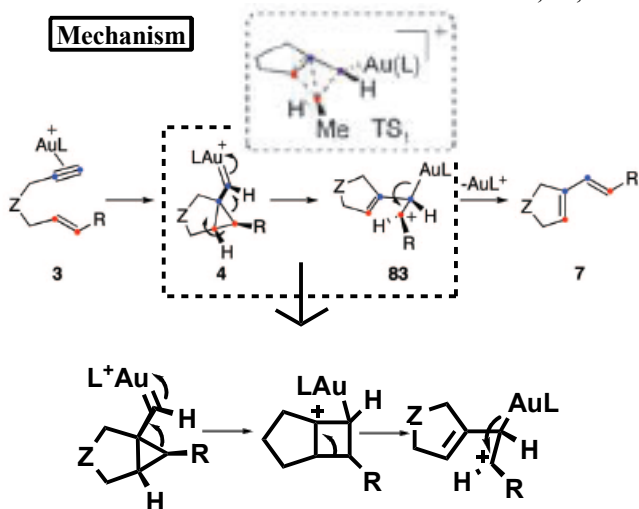


#### Single cleavage rearrangement reaction

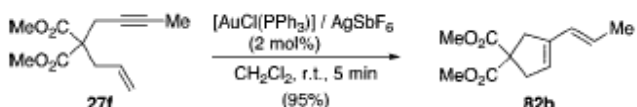


Antonio M. Echavarren et al. *Chem. Eur. J.* **2006**, *12*, 1677.

#### Mechanism

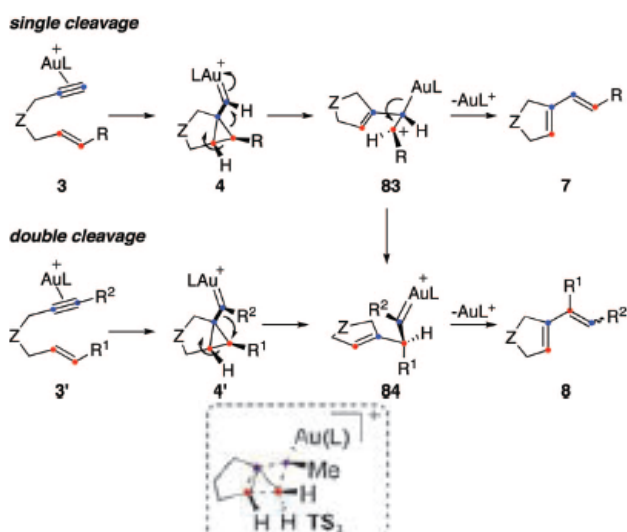


#### Double cleavage rearrangement reaction



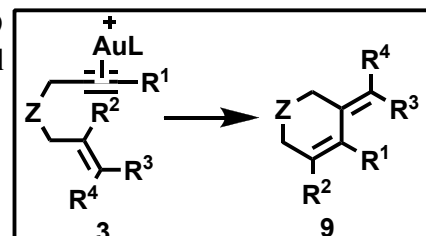
Antonio M. Echavarren et al. *Eur. J. Org. Chem.* **2007**, 4217.

#### Mechanism

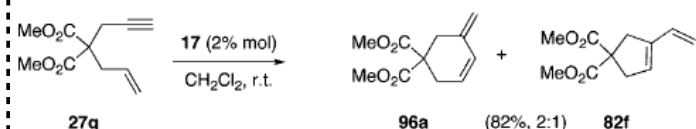


A. M. Echavarren et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146

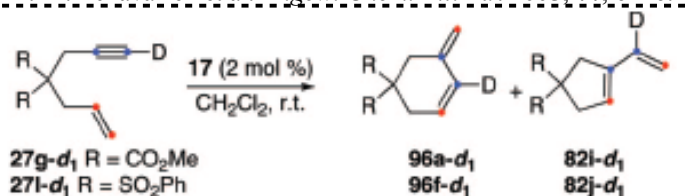
### 3.3.3 Reaction 3 to 9 (Endocyclic Skeletal rearrangement)



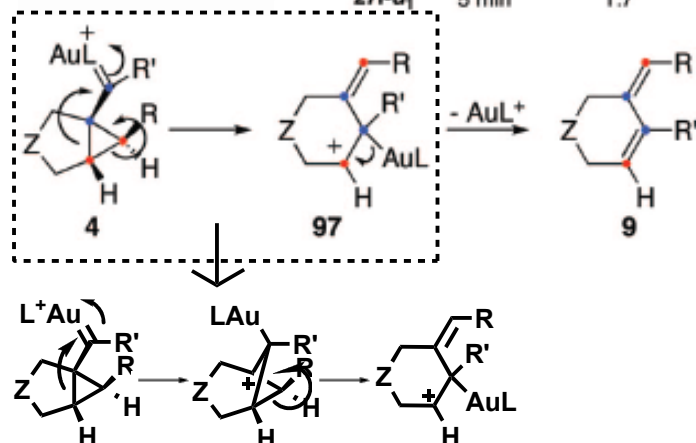
17: [Au(PPh<sub>3</sub>)(NCMe)]SbF<sub>6</sub>



A. M. Echavarren et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146.

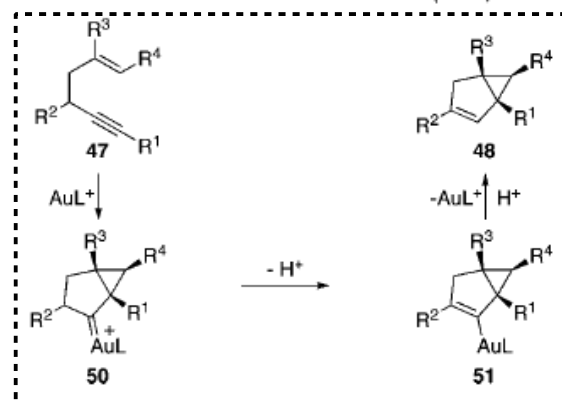
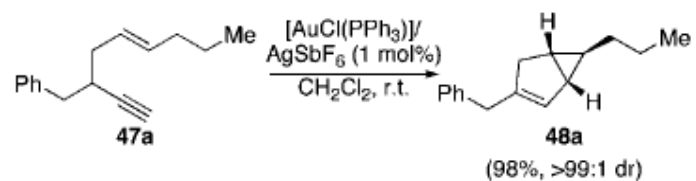


Enyne	Time (min)	Endo/exo ratio
27g-d <sub>1</sub>	20 min	1:2
27f-d <sub>1</sub>	5 min	1:7



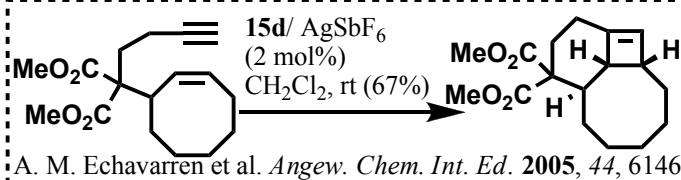
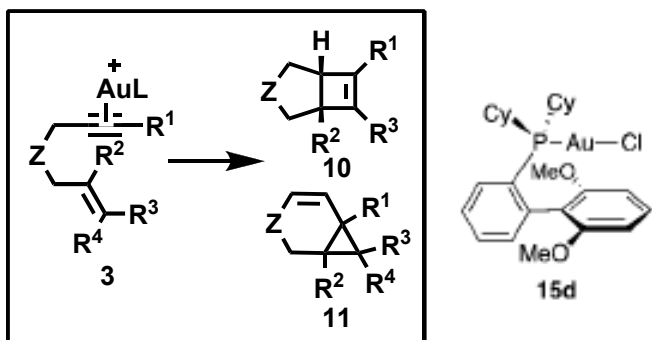
**In the case of 1,6-enynes, the mechanism of this endocyclic rearrangement is just a variation of the single-cleavage rearrangement of 4**

#### In the case of 1,5-enynes

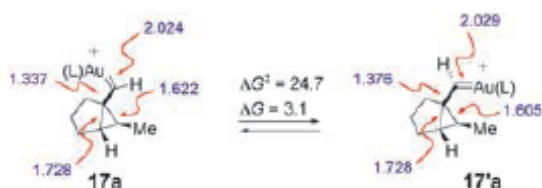


**Exocyclic rearrangement is favorable, because bicyclo[2,1,0]pentane is strained. 11**

### 3.3.4 Reaction 3 to 10 and 11 (Cyclo-propane and butene)

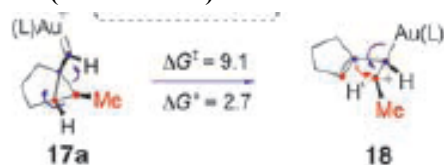


A. M. Echavarren et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146

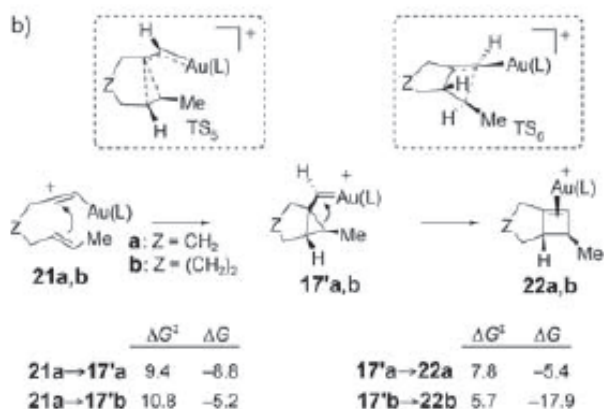


For construction of cyclobutene, the *anti* to *syn* isomerization from **17a** to **17'a** requires a rather high activation energy. (24.7 kcalmol<sup>-1</sup>)

The initially formed *anti* **17a** would undergo a more facile rearrangement (9.1 kcalmol<sup>-1</sup>).

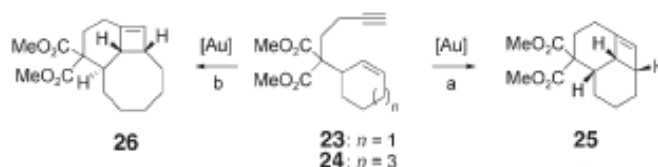


However, an alternative pathway has been found for a more direct formation of complexes **17'a,b** by a *syn*-type attack of the alkene, via **TS5**, to the (alkyne) gold moiety of **21a,b** (Scheme 4).

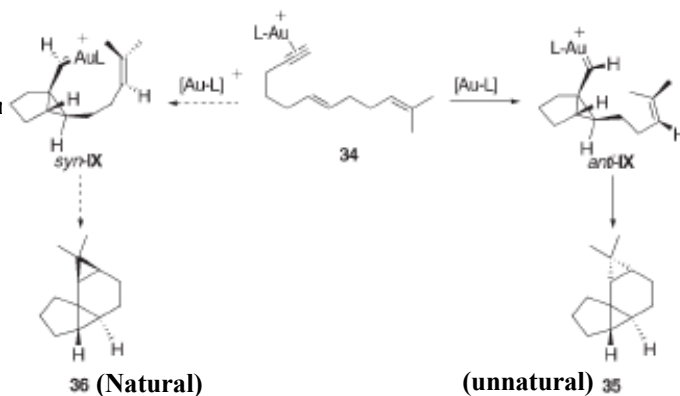
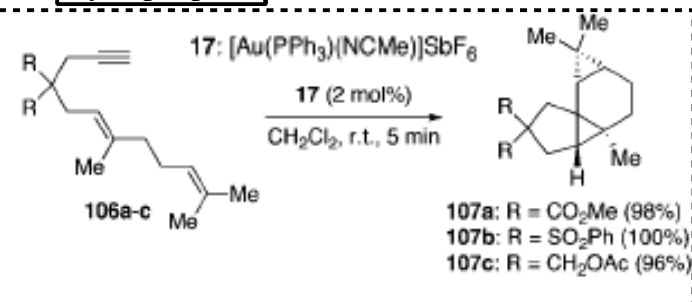


Scheme 4. L =  $\text{PH}_3$ .  $\Delta G$  at 298 K (energies in kcal mol<sup>-1</sup>) and selected bond lengths [Å] for **17'a**, **17'b**, and **TS5**.

The anti attack of the alkene is more favorable, [**7a**] the *syn* attack could compete if substitution at the alkene and/or the alkyne disfavors the skeletal rearrangement. In particular, this should be more favorable for the formation of bicyclo[3.2.0]oct-6-enes from 1,7-enynes, in accordance with the calculations (**17'b** to **22b**, Scheme 4).



### Cyclopropane



Scheme 7. Mechanistic proposal for the stereoselective formation of tetraacycles **32** via *anti*-IX.

Antonio M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1694.

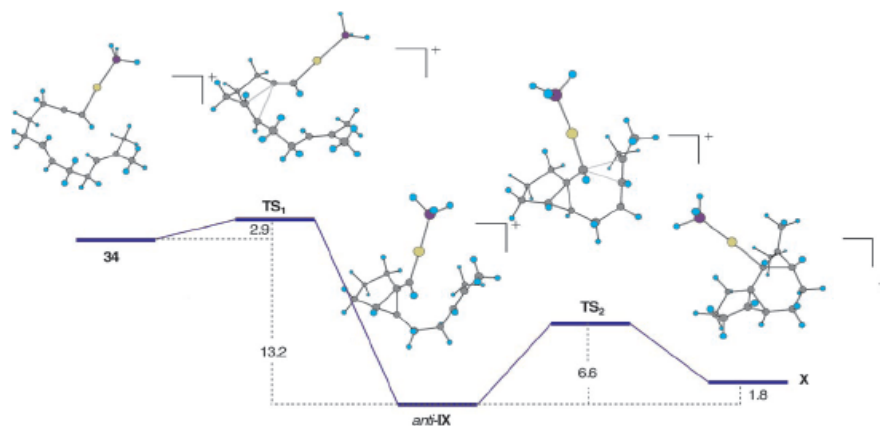


Figure 2. Reaction pathway for the bicyclopropanation from complex **34** calculated at the B3LYP/6-31G(d) (C,H,P), LANL2DZ (Au) level (ZPE-corrected energies are given in kcal mol<sup>-1</sup>). Color code: Au: yellow; C: gray; P: purple; H: turquoise.

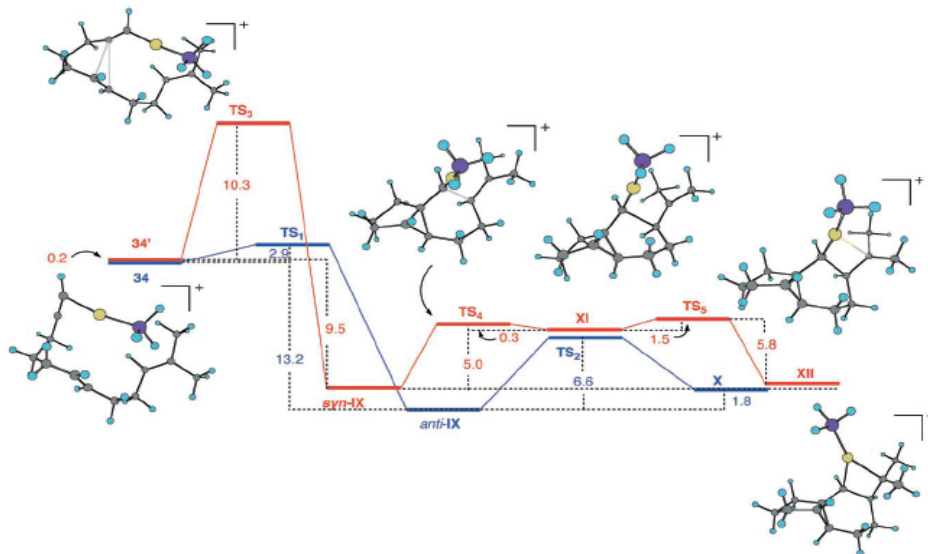
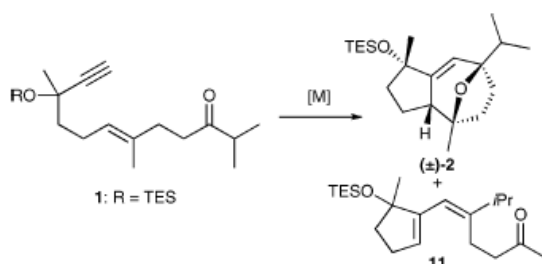


Figure 3. Reaction pathway for the bicyclopropanation from complex **34'** calculated at the B3LYP/6-31G(d) (C,H,P), LANL2DZ (Au) level (ZPE-corrected energies are given in kcal mol<sup>-1</sup>). The bicyclopropanation pathway from complex **34** (blue) is included for comparison. Color code: Au: yellow; C: gray; P: purple; H: turquoise.

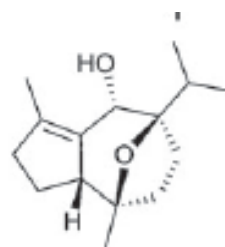
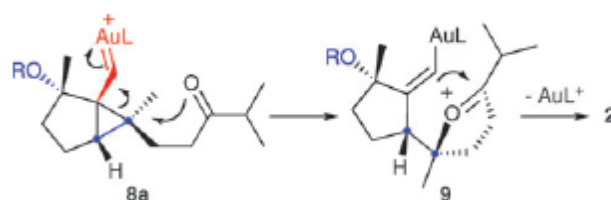
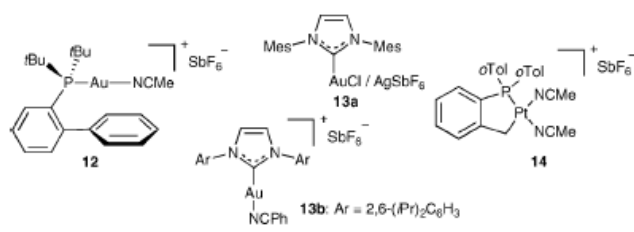
### 3.4 Construct Guaiane sesquiterpene

A.M. Echavarren et al. *Chem. Commun.*, 2009, 7327.



Entry	[M]	<i>t</i>	Products (yield, %)
1	AuCl	24 h	— <sup>b</sup>
2	<b>12</b>	20 min	<b>2</b> (14) + <b>11</b> (34)
3	<b>13a</b>	3 h	<b>2</b> (25) + <b>11</b> (12)
4	<b>13b</b>	3 h	<b>2</b> (65) + <b>11</b> (4)
5 <sup>c</sup>	PtCl <sub>2</sub> /(P <i>o</i> -Tol) <sub>3</sub>	24 h	— <sup>b</sup>
6	<b>14</b>	1 h	<b>2</b> (28) + <b>11</b> (42)

<sup>a</sup> Reactions in CH<sub>2</sub>Cl<sub>2</sub> with 3 mol% catalyst and 4 Å molecular sieves at 23 °C. <sup>b</sup> Starting material was recovered. <sup>c</sup> Reaction in 1,2-dichloroethane at 70 °C.

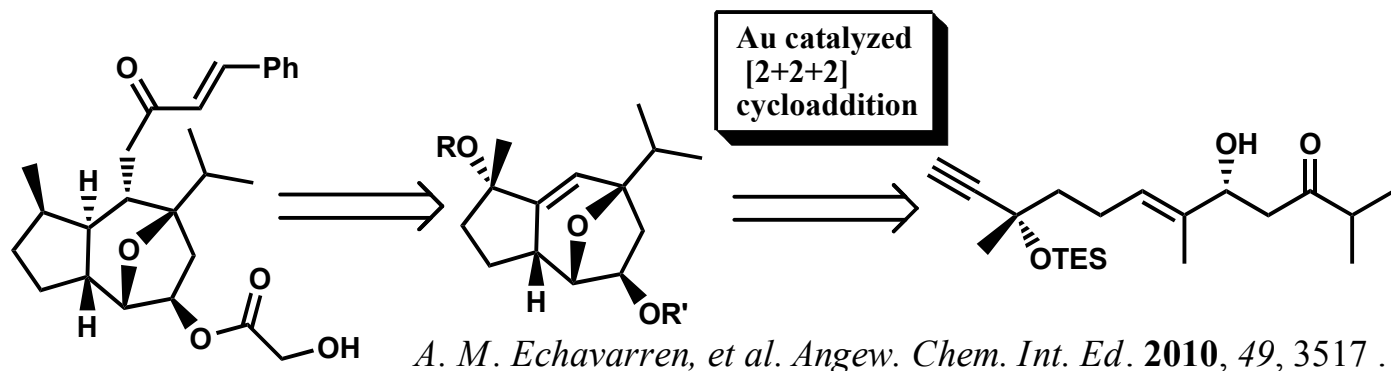


(+)-orientalol F



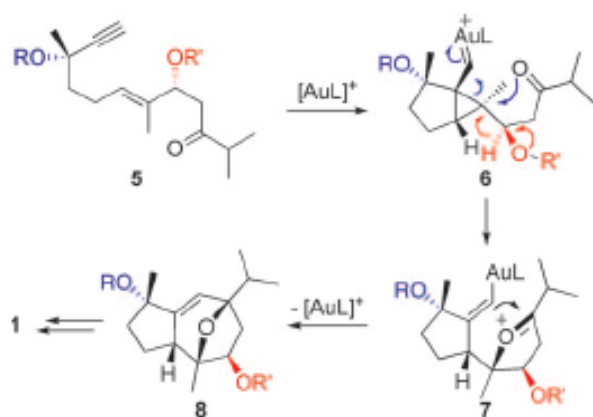
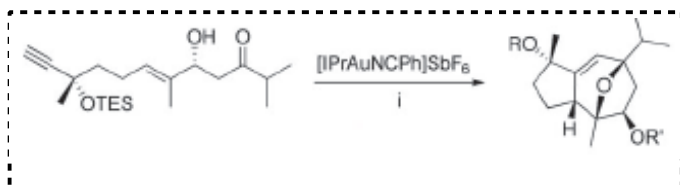
## 4. Echavarren's Total synthesis

### 4.1 Retrosynthetic Analysis



### 4.2 Key Reaction

#### 4.2.1 Au catalyzed [2+2+2] alkyne/alkene/carbonyl cycloaddition reaction



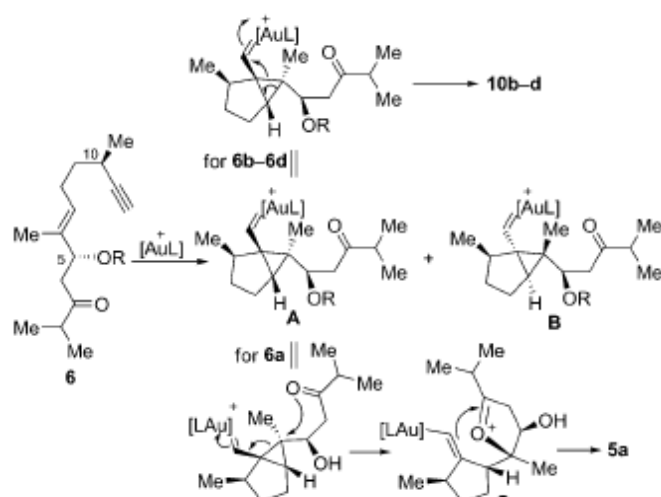
After testing a number of protected derivatives of aldol in gold(I)-catalyzed reactions, they found that the best results were obtained by using unprotected aldol (67 %).

**Table 1:** Gold-catalyzed cyclization of enynes **6**.<sup>[a]</sup>

Entry	R	Catalyst	t [min]	Product (yield [%] <sup>[b]</sup> )
1	TBS	A	30	10b (80)
2	TBS	B	30 <sup>[c]</sup>	10b (40)
3	TES	A	20	10c (90)
4	Me	A	30	— <sup>[d]</sup>
5	Me	B	30 <sup>[e]</sup>	10d (10)
6	H	A	20	5a (48)
7	H	B	20 <sup>[e]</sup>	5a (20)

[a] Reaction conditions: enyne (0.1–0.5 mmol), catalyst (10 mol%), CH<sub>2</sub>Cl<sub>2</sub>, RT; catalyst **A**: AuCl, **B**: [Au(PPh<sub>3</sub>)Cl]/AgSbF<sub>6</sub>; [b] Yield of isolated product, [c] 50% conversion was observed. [d] a complex mixture was obtained. [e] 20% conversion was observed.

Dawei Ma et al. *Angew. Chem. Int. Ed.* 2010, 49, 3513.



The best result is When used R = H

The exclusive formation of monocyclic products from ether substrates **6b**, **6d** could be rationalized by the steric hindrance of their protecting groups, which might prevent the attack of the carbonyl group at the cyclopropanyl ring as indicated for the formation of intermediate **C**.

## 4.2.2 Stereoselective Denmark aldol reaction

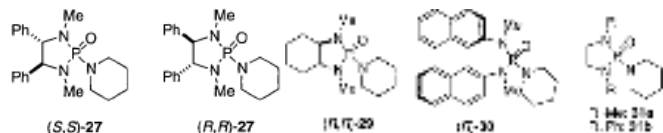
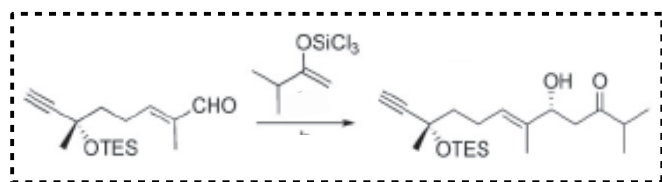
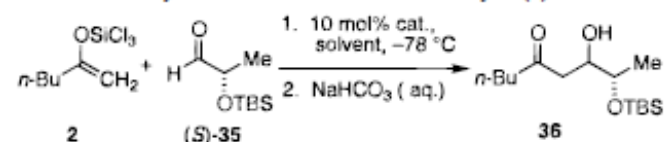


Table 8. Catalyzed Aldol Additions with Aldehyde (S)-35<sup>a</sup>



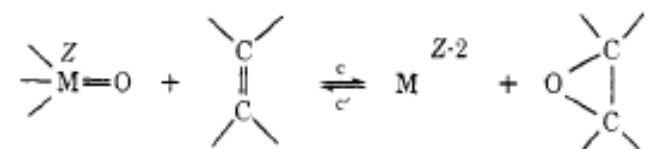
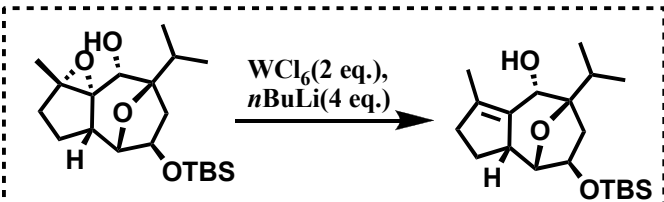
entry	catalyst	solvent	syn/anti <sup>b</sup>	yield, <sup>c</sup> %
1	HMPA	CH <sub>2</sub> Cl <sub>2</sub>	1/1.3	41
2	31b	CH <sub>2</sub> Cl <sub>2</sub>	1/6.7	37
3	(R,R)-29	CH <sub>2</sub> Cl <sub>2</sub>	1/10.1	51
4	(R)-30	CH <sub>2</sub> Cl <sub>2</sub>	1/1.8	54
5	(S,S)-27	CH <sub>2</sub> Cl <sub>2</sub>	2.7/1	47
6	(R,R)-27	CH <sub>2</sub> Cl <sub>2</sub>	1/15.6	50
7	(R,R)-27	Et <sub>2</sub> O	1/9.0	45
8	(R,R)-27	toluene	1/6.7	40
9	(R,R)-27	CH <sub>3</sub> CH <sub>2</sub> CN	1/11.5	43

<sup>a</sup> Reactions performed at 0.5 M for 6 h. <sup>b</sup> Determined by GC analysis.

<sup>c</sup> Chromatographically homogeneous material.

Scott E. Denmark et al. *J. Am. Chem. Soc.* **2000**, *122*, 8837.

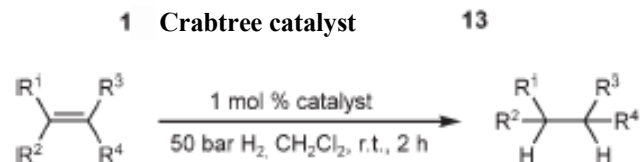
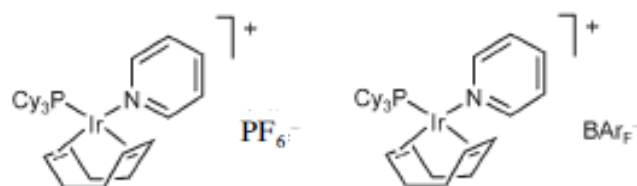
## 4.2.3 Reduction



Epoxide	Yield of olefin, % <sup>a</sup>	% retention of stereochemistry
<i>trans</i> -Cyclododecene oxide	98 (94)	95
	97	
	98	
<i>cis</i> -Cyclododecene oxide	98	94
	89	
	88	
<i>trans</i> -4-Octene oxide	70	98
	99	
	84	
<i>cis</i> -4-Octene oxide	97	>98
	86	
	61	
<i>trans</i> -Stilbene oxide	81	100
	86	
	80	
<i>cis</i> -Stilbene oxide	80	8
Cyclooctene oxide	89	
1-Dodecene oxide	80	
4-Ethylcyclohexene oxide	55	72
	75	
	65	
Geraniol methyl ether bisepoxide	47	
Citronellol methyl ether oxide	37	
Stigmasterol acetate bisepoxide <sup>d</sup>	83	
	(83) <sup>e</sup>	

K. B. Sharpless et al. *J. Am. Chem. Soc.* **1972**, *94*, 6538.

## 4.2.4 Hydrogenation



Entry	Substrates	1 <sup>[b]</sup>	13
1 <sup>[a]</sup>	14	16	91
2 <sup>[a]</sup>	15	> 99	> 99
3 <sup>[a]</sup>	16	31	> 99
4 <sup>[a]</sup>	17	> 99	> 99
5 <sup>[a]</sup>	18	2	6
6 <sup>[a]</sup>	19	> 99	> 99
7 <sup>[a]</sup>	20	27	73
8 <sup>[a,d]</sup>	21	61 (6.0:1 <i>dr</i> )	> 99 (4.0:1 <i>dr</i> )
9 <sup>[a]</sup>	22	0	8

Andreas Pfaltz et al. *Adv. Synth. Catal.* **2008**, *350*, 174.

### 4.3 Total synthesis

