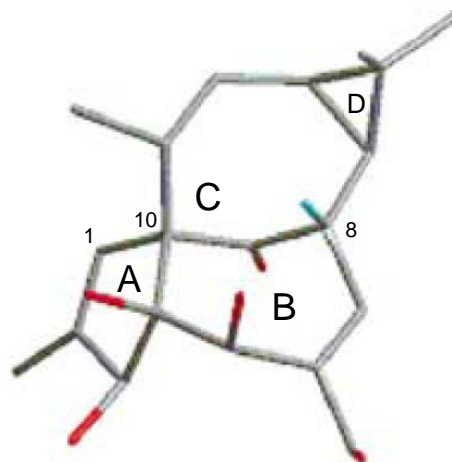
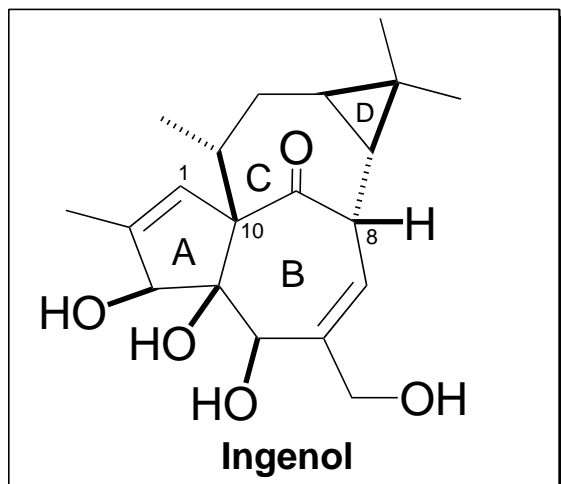


## Total Synthesis of Ingenol



### contents

1. Introduction
2. What's In/Out chemistry?
3. Synthesis of Ingenane core
4. Tanino & Kuwajima's total synthesis
5. Summary

## 1. Introduction

### Structural Features and Synthetic Challenges

- 1) Trans-fused bicyclo[4,4,1]undecane ring
- 2) Highly strained inside-outside intrabridgehead stereochemistry of the BC ring
- 3) *cis*-triol segment located on upper face

### Comparison of Ingenol and Isoingenol (in-H) (out-H)

	Ingenol	Isoingenol
Structure		
$\Delta E_{rel}$ (kcal/mol)	5.9	0
First total synthesis (yeah)	2002	1988 (Paquete, L. A.)
Biological activity	tumor promoting etc.	no activity

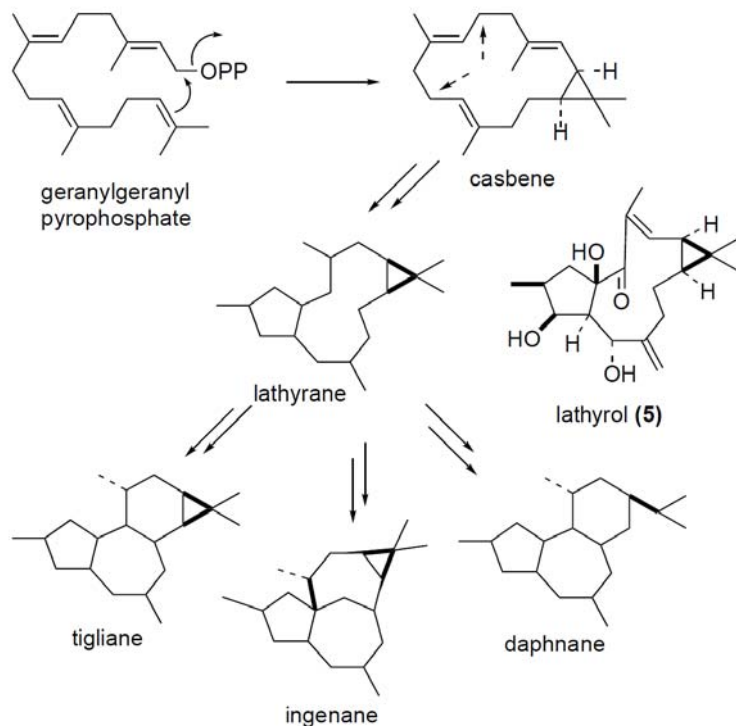
## Natural source

*Euphorbia Ingens* (Hecker, E. *et al.*, *Cancer Res.* **1968**, 28, 2338)

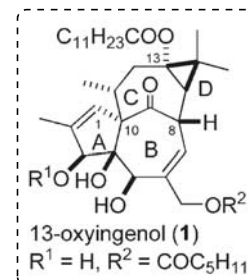
## Bioactivity

Tumor promoting, antileukemic, and anti-HIV properties (activation of PKC)

## Biosynthesis



Although no details are known, a 1,2-alkyl shift (ex. Wagner-Meerwein rearrangement) connects tiglanes to ingenanes.



## History

1) Ingenol was isolated by Hecker, E. and co-workers in 1968

2) Zeckmeister, K. and co-workers determined its structure by X-ray crystallography in 1970

3) Synthetic approach to Ingenol

Funk, R. .... 1993(*J. Org. Chem.*)  
Rigby, J. H. .... 1998(*Tetrahedron, Lett.*)

4) Total synthesis of Ingenol

Winkler, J. D. .... 2002(*J. am. Chem. Soc.*)  
Tanino, K. and Kuwajima, I. .... 2002(*J. am. Chem. Soc.*)  
Kigoshi, H. (formal synthesis) ..... 2004(*J. Org. Chem.*)  
Wood, J. L. .... 2004(*J. am. Chem. Soc.*)

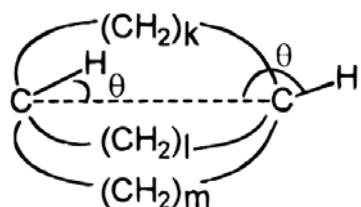
5) Synthetic Studies toward 13-Oxyingenol  
Kigoshi, H.

..... 2011(*Org. Lett.*)

now (2011)

## 2. What's In/Out chemistry?

Alder, R. W. *et al.*, *Chem. Rev.* **1996**, 96, 2097

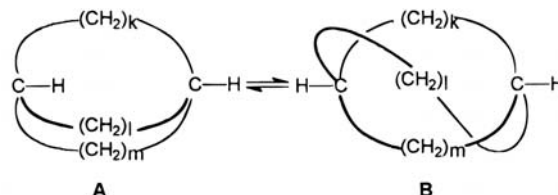
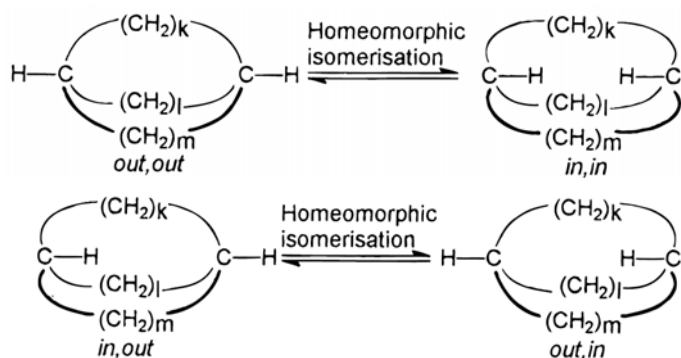


### Angle Definition

C-H in :  $0^\circ < \theta < 90^\circ$

C-H out :  $90^\circ < \theta < 180^\circ$

**Figure 2.** Homeomorphic isomerisation



**Figure 3.** An *in,out*-bicyclic compound (A) at equilibrium with an intertwined *out,out* conformation (B).<sup>34</sup>

Half-twist

**Table 1.** MM2 Calculated Steric Energies of Lowest Energy Conformations of Bicyclic Hydrocarbons (in kcal/mol)<sup>a</sup>

bicyclic hydrocarbon	<i>out,out</i>	<i>in,out</i>	<i>in,in</i>
bicyclo[3.2.2]nonane	24.25	81.43	
bicyclo[3.3.1]nonane	18.26	64.43	
bicyclo[4.2.1]nonane	24.36	68.04	
bicyclo[5.1.1]nonane	46.75	87.44	
bicyclo[3.3.2]decane	29.95	66.78	130.17
bicyclo[4.2.2]decane	29.60	67.14	
bicyclo[5.2.1]decane	30.10	50.90	
bicyclo[4.3.1]decane	24.20	48.30	
bicyclo[3.3.3]undecane	37.28	70.17 <sup>b</sup>	119.57
bicyclo[4.3.2]undecane	37.26	56.15	107.83
bicyclo[5.2.2]undecane	38.22	53.96	
bicyclo[4.4.1]undecane	27.19	37.52	62.23
bicyclo[5.3.1]undecane	26.19	37.52	63.93
bicyclo[4.3.3]dodecane	48.60	55.80	93.45
bicyclo[4.4.2]dodecane	44.09	51.43	84.68
bicyclo[5.3.2]dodecane	43.75	48.47	86.46
bicyclo[5.4.1]dodecane	32.98	33.99	48.02
bicyclo[6.3.1]dodecane <sup>c</sup>	43.43	50.53	
bicyclo[4.4.3]tridecane	58.35	54.81	82.43
bicyclo[5.3.3]tridecane	56.46	52.43	78.20
bicyclo[5.4.2]tridecane	48.00	46.51	67.33
bicyclo[5.5.1]tridecane	36.55	37.45	41.55
bicyclo[7.3.1]tridecane <sup>c</sup>	32.50	31.34	
bicyclo[4.4.4]tetradecane	68.66	56.45	71.92
bicyclo[5.4.3]tetradecane	63.21	53.01	69.21
bicyclo[5.5.2]tetradecane	53.43	48.84	55.97
bicyclo[6.5.1]tetradecane	42.16	40.18	42.44
bicyclo[5.4.4]pentadecane	64.86	55.03	63.61
bicyclo[6.6.1]pentadecane	48.36	44.06	46.35
bicyclo[7.5.1]pentadecane	41.83	41.78	41.48
bicyclo[5.5.4]hexadecane	63.79	54.77	57.08
bicyclo[5.5.5]heptadecane	60.83	54.16	49.78
bicyclo[6.5.5]octadecane	57.88	50.81	45.61
bicyclo[6.6.6]eicosane	47.42	43.62	36.4

*out,out*-isomers are strongly preferred for smaller bicyclic system

← Ingenol

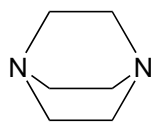
*in,out*-isomers become the most stable

*in,in*-isomers is most stable

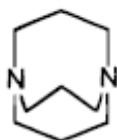
Due to nonbinding interactions between methylene groups in the bridges, *out,out*-isomer is itself usually severely strained.

<sup>a</sup> All data is taken from reference 36 unless otherwise stated.  
<sup>b</sup> Calculation by present authors. <sup>c</sup> Data from ref 77.

## Amines



**41**  
lone pair  
out/out



**43**  
flat nitrogen  
atom



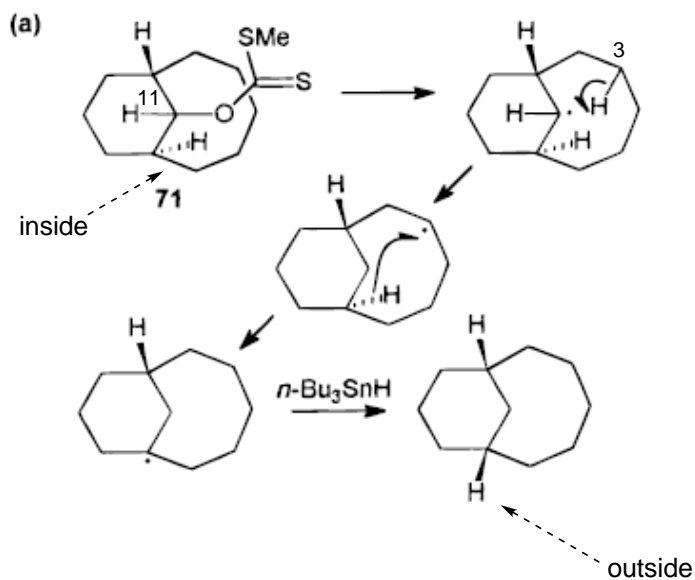
**10**  
lone pair  
in/in

1,4-diazabicyclo-[2,2,2]-octane (DABCO, **41**)

1,5-diazabicyclo-[3,3,3]-undecane (**43**)

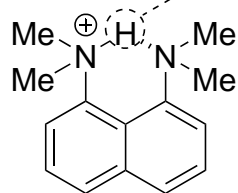
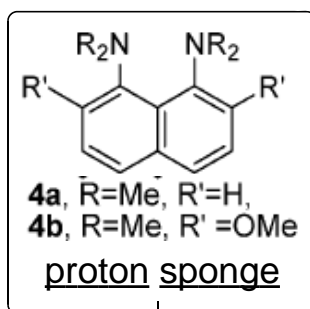
1,6-diazabicyclo-[4,4,4]-tetradecane (**10**)

## Transannular interactions involving inside functionally

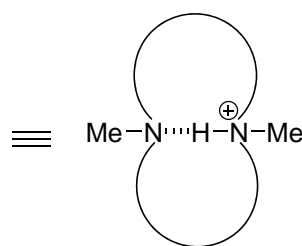
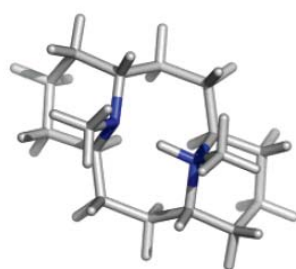
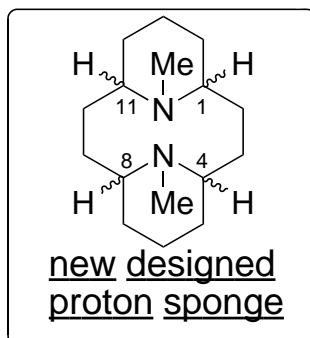


By Barton-McCombie deoxygenation of in/out-substrate, unusual rearrangement was discovered.

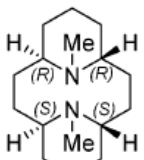
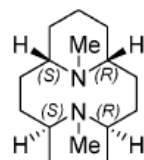
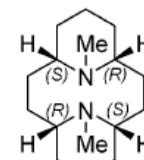
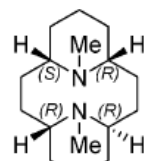
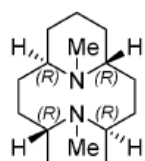
in/out  $\longrightarrow$  out/out

**Table 1.** Calculated (B3LYP/6-311+G\*\*//B3LYP/6-31G\*) PA and  $pK_a$  Values

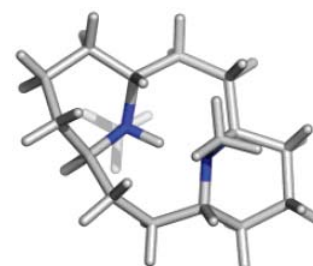
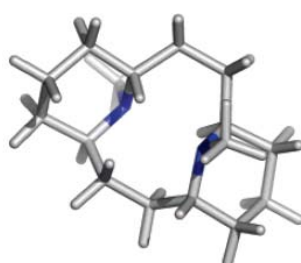
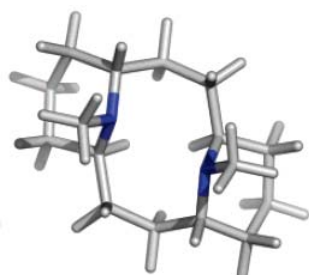
diamine	gas-phase PA (kJ mol <sup>-1</sup> )	$pK_a$ (H <sub>2</sub> O) <sup>a</sup>	$pK_a$ (MeCN) <sup>b</sup>	$\Delta E(i)$ (kJ mol <sup>-1</sup> )	$\Delta E(ii)$ (kJ mol <sup>-1</sup> )
<b>4a</b>	1028	11.9	18.1		
<b>4b</b>	1089	20.1	23.2		

<sup>a</sup> Relative to Me<sub>3</sub>N,  $pK_a = 9.81$ . <sup>b</sup> Relative to Me<sub>3</sub>N,  $pK_a = 17.61$ .

Inside-monoprotonated ion could not be deprotonated easily.

**Table 2.** Calculated (B3LYP/6-311+G\*\*//B3LYP/6-31G\*) PA and  $pK_a$  Values for diastereomers of 15,16-dimethyl-15,16-diazatricyclo[9.3.1.1<sup>4,8</sup>]hexadecane

diamine	gas-phase PA (kJ mol <sup>-1</sup> )	$pK_a$ (H <sub>2</sub> O) <sup>a</sup>	$pK_a$ (MeCN) <sup>b</sup>	$\Delta E(i)$ (kJ mol <sup>-1</sup> )	$\Delta E(ii)$ (kJ mol <sup>-1</sup> )
<i>syn-RRRR</i>	1105	23.6	30.4	43	-23
<i>anti-RRRR</i>	1022	9.8	16.7	16	33
<i>Syn-RRRS</i>	1091	21.4	28.0	36	-18
<i>Anti-RRRS</i>	1025	10.4	16.9	13	24
<i>Syn-RSRS</i>	1082	19.9	26.5	41	-3
<i>Anti-RSRS</i>	1071	19.1	25.4	45	13
<i>Syn-RRSS</i>	1107	24.5	30.9	93	24
<i>Anti-RRSS</i>	1031	10.9	17.8	2	7
<i>Syn-RSSR</i>	1093	21.5	28.9	59	2
<i>anti-RSSR</i>	1014	9.5	16.1	-1	22

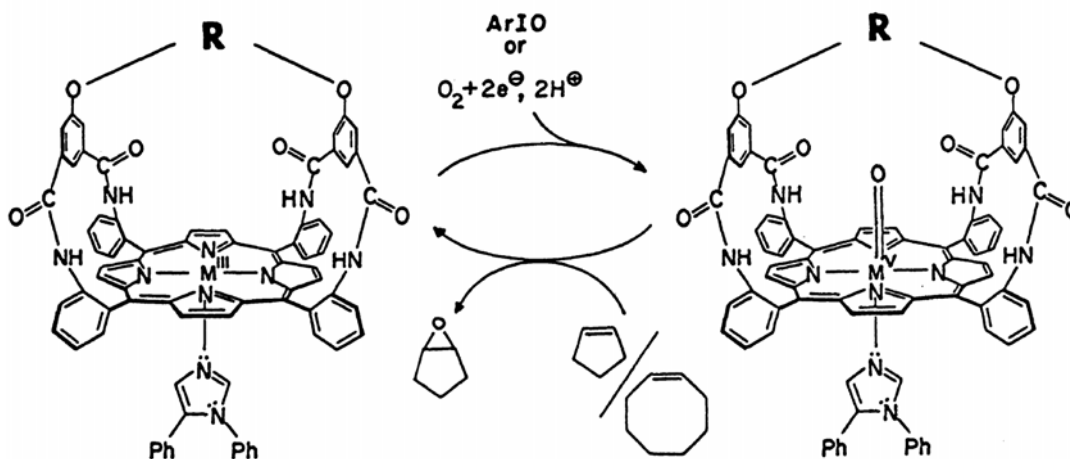
<sup>a</sup> Relative to Me<sub>3</sub>N,  $pK_a = 9.81$ . <sup>b</sup> Relative to Me<sub>3</sub>N,  $pK_a = 17.61$ .

# Enantioselective epoxidation by threitol-strapped Manganese porphyrin

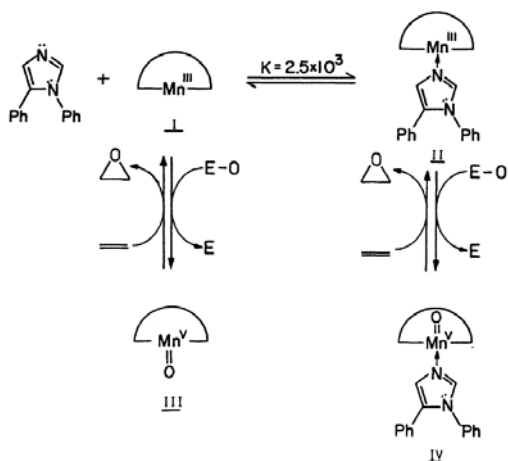
Background

Collman, J. P. *et al.*, *Bull. Chem. Soc. Jpn.*, **1988**, 61, 47

## The "picnic-Basket" Strategy

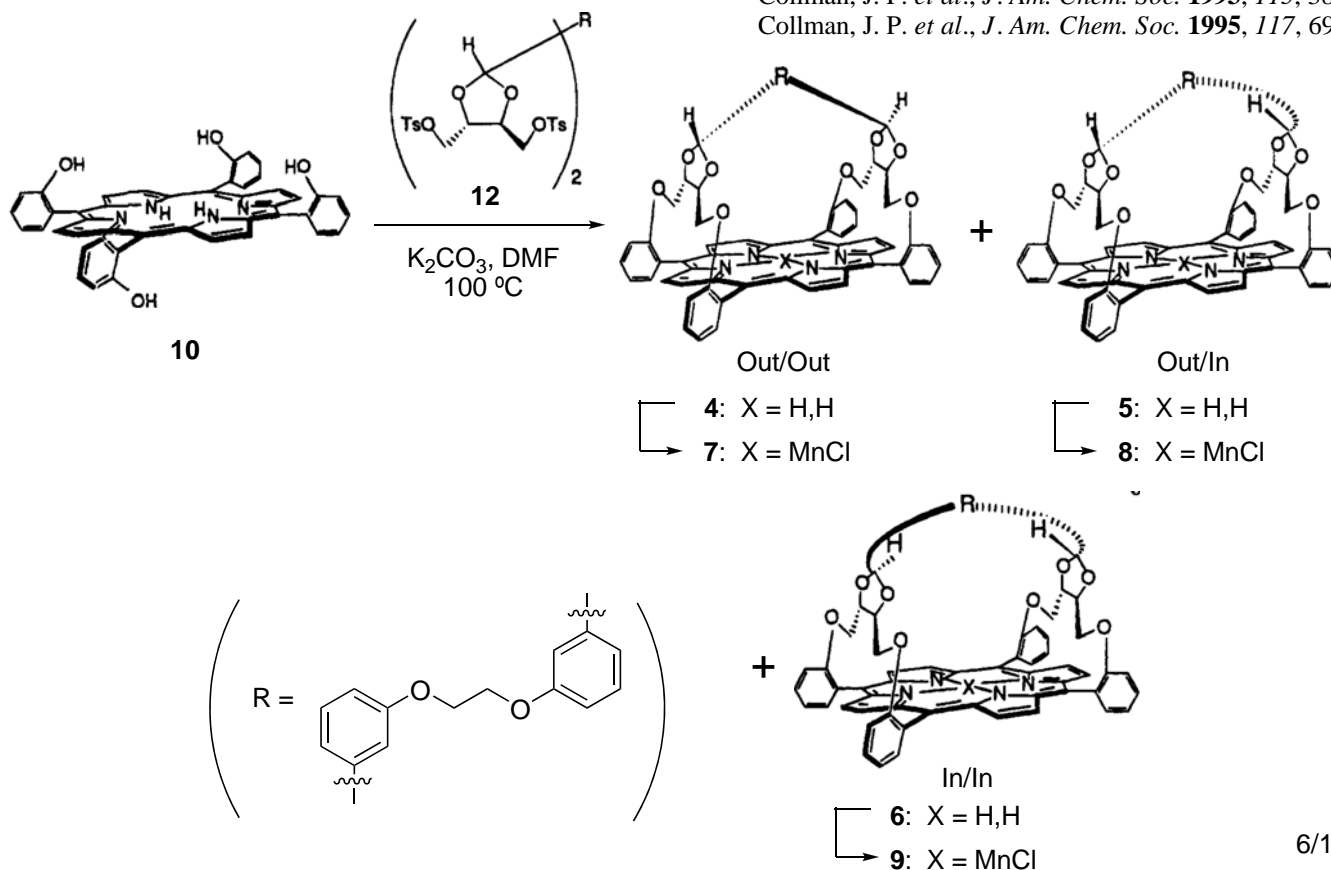


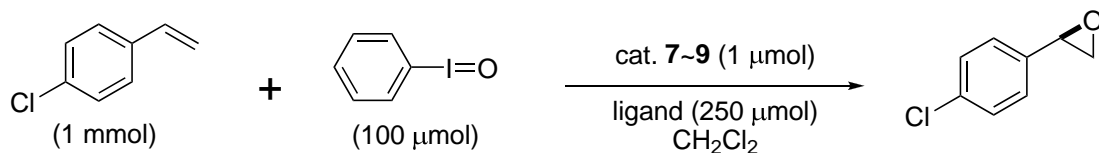
Scheme 1. Strategy for catalysis by "picnic-basket" porphyrins.



1,5-dicyclohexylimidazole binds to the unhindered face of the manganese porphyrin

Collman, J. P. *et al.*, *J. Am. Chem. Soc.* **1993**, 115, 3834  
 Collman, J. P. *et al.*, *J. Am. Chem. Soc.* **1995**, 117, 692

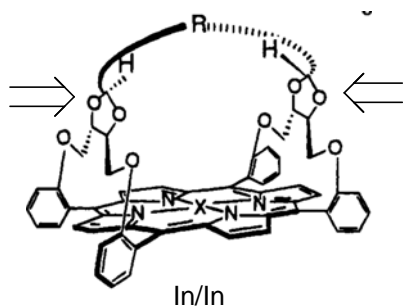




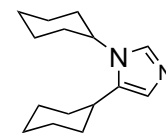
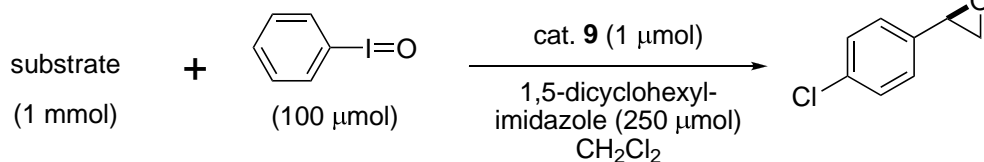
**Table 3.** % ee from the Asymmetric Epoxidation of 4-Chlorostyrene and *cis*- $\beta$ -Methylstyrene Catalyzed by Manganese Threitol-Strapped Porphyrins: Effect of Added Pyridine or 4-*tert*-Butylpyridine<sup>a</sup>

catalyst	4-chlorostyrene			<i>cis</i> - $\beta$ -methylstyrene		
	blank	Pyridine	4- <i>tert</i> -BuPyridine	blank	Pyridine	4- <i>tert</i> -BuPyridine
Out/Out <b>7</b>	36	17	34	22	5	23
Out/In <b>8</b>	55	34	50	58		
In/In <b>9</b>	58	32	58	59	34	61

In three catalyst, in/in - isomer **9** is the most effective asymmetric catalyst.

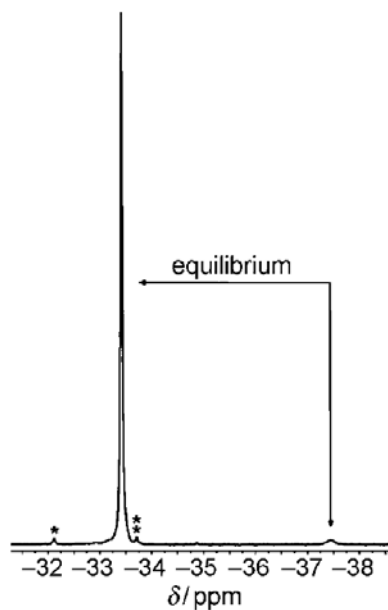
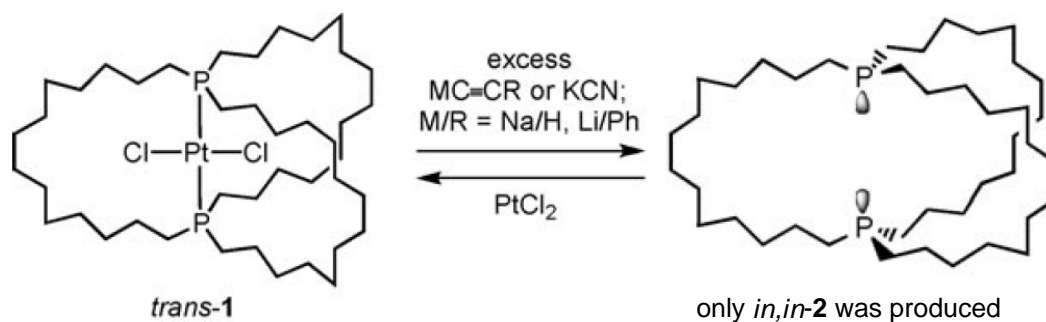


The function of the bridge is to pull the threitol rings closer to the center of the macrocycle.



**Table I.** Asymmetric Epoxidation of Aromatic Olefins with **9** (Yields are based upon iodobenzene.)

substrate	reaction T, °C	yield, % <sup>b</sup>	ee, % <sup>c</sup>	configuration <sup>d</sup>	best reported ee, % <sup>e</sup>
	25	86	69	R(+)	57 <sup>f</sup>
	25	82	70	R(+)	51 <sup>g</sup>
	25	65 <sup>h</sup>	79	(-) <sup>i</sup>	16 <sup>g</sup>
	25	89	77	1R,2S(-)	92 <sup>j</sup>
	0	76	80	1R,2S(-)	
	25	85	84	1R,2S(+)	
	0	67	87	1R,2S(+)	83 <sup>k</sup>
	-10	26	88	1R,2S(+)	
	25	81	21	1S,2S(-)	56 <sup>k</sup>



$^{31}\text{P}$  NMR and  $^{31}\text{P}$  EXCY experiment established that the species responsible for the two signals are in equilibrium.

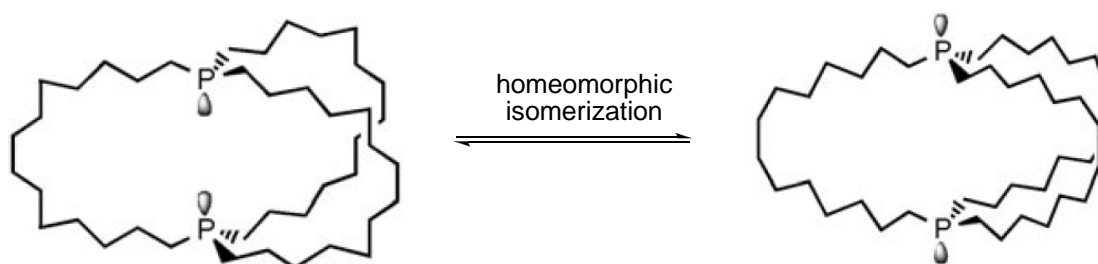
↓

Lonpair inversion in simple trialkylphosphines require 29-36 kcal/mol, which corresponds to very slow process at room temperature.

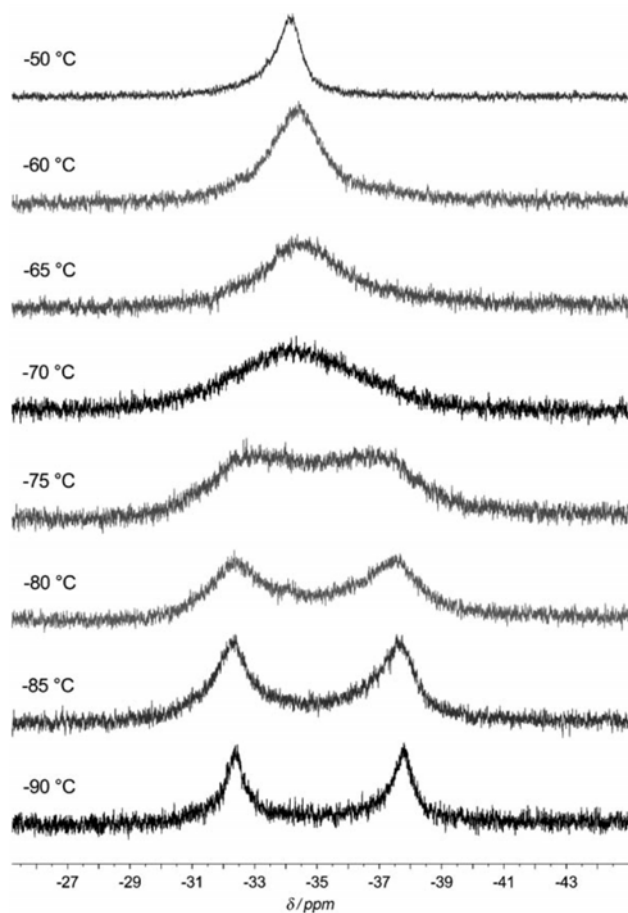
↓

(strong peak: *in,in*-  $\rightleftharpoons$  weak peak: *out,out*-)

**Figure 1.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum of **2** in  $[\text{D}_8]$ toluene at  $-80^\circ\text{C}$  (the arrows denote exchanging species; \* and \*\* denote unknown and known impurities, respectively).

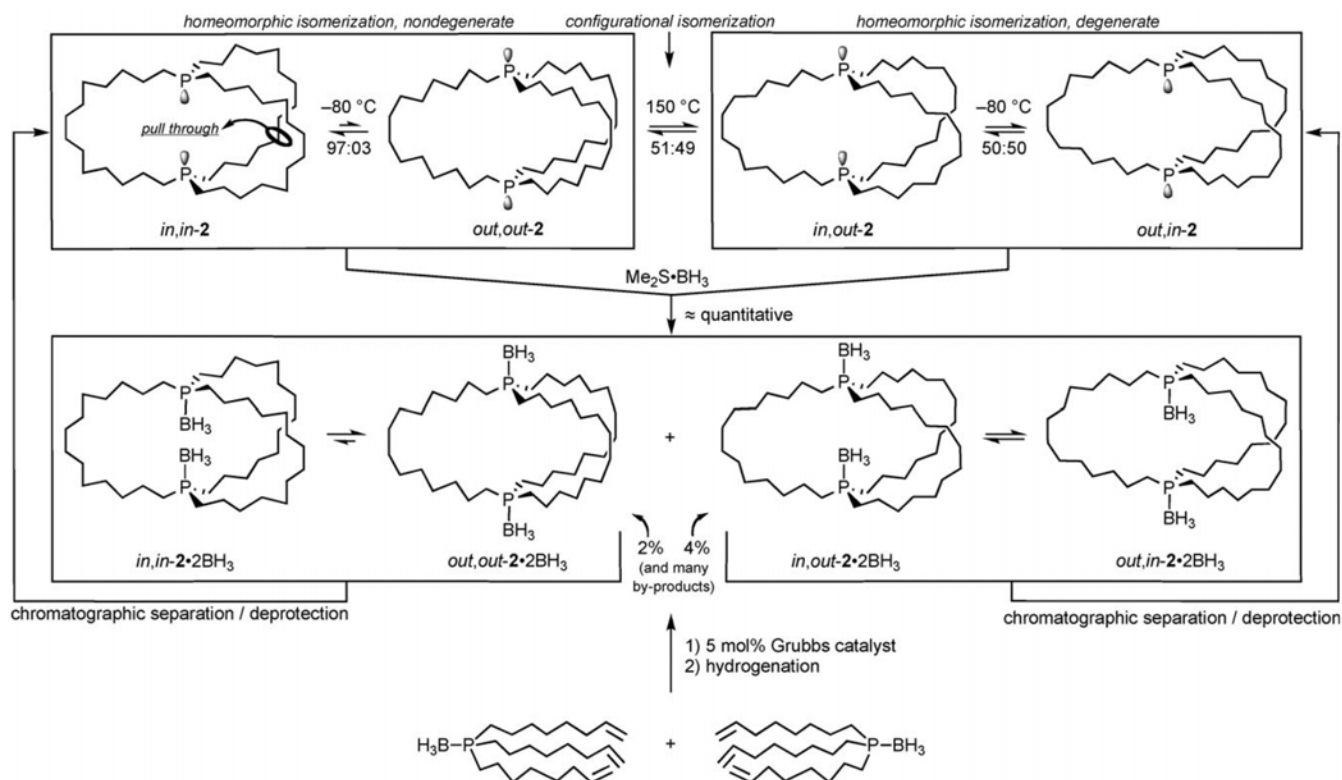




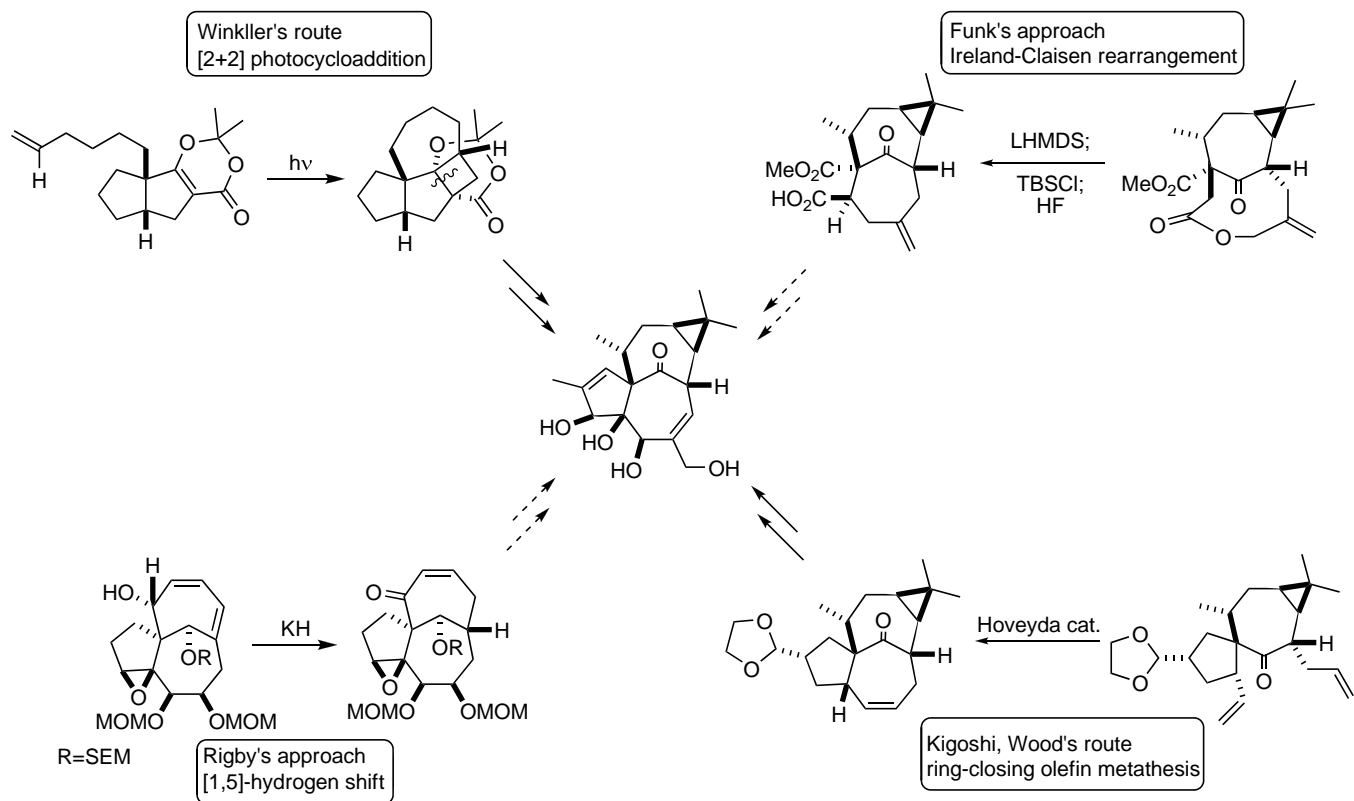


*in,out-2* exhibited a single signal in the  $^{31}\text{P}$  NMR spectrum at  $-50\text{ }^\circ\text{C}$ . But at  $-90\text{ }^\circ\text{C}$ , two signals were observed. This implies that a degenerate *in,out/out,in* homeomorphic isomerization is rapid on the NMR time scale.

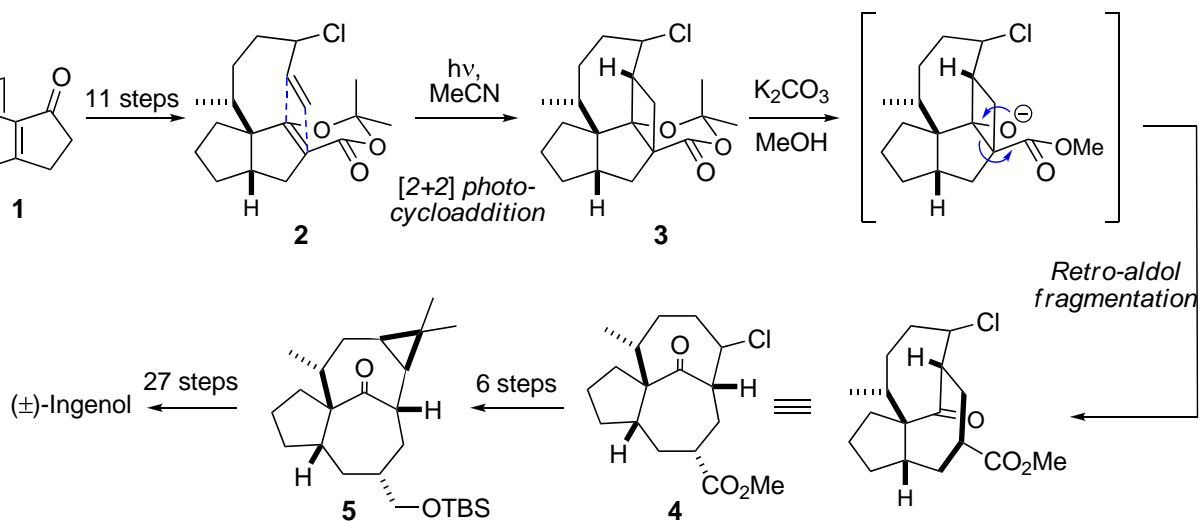
Figure 2. Low-temperature  $^{31}\text{P}\{^1\text{H}\}$  NMR spectra of *in,out-2*.



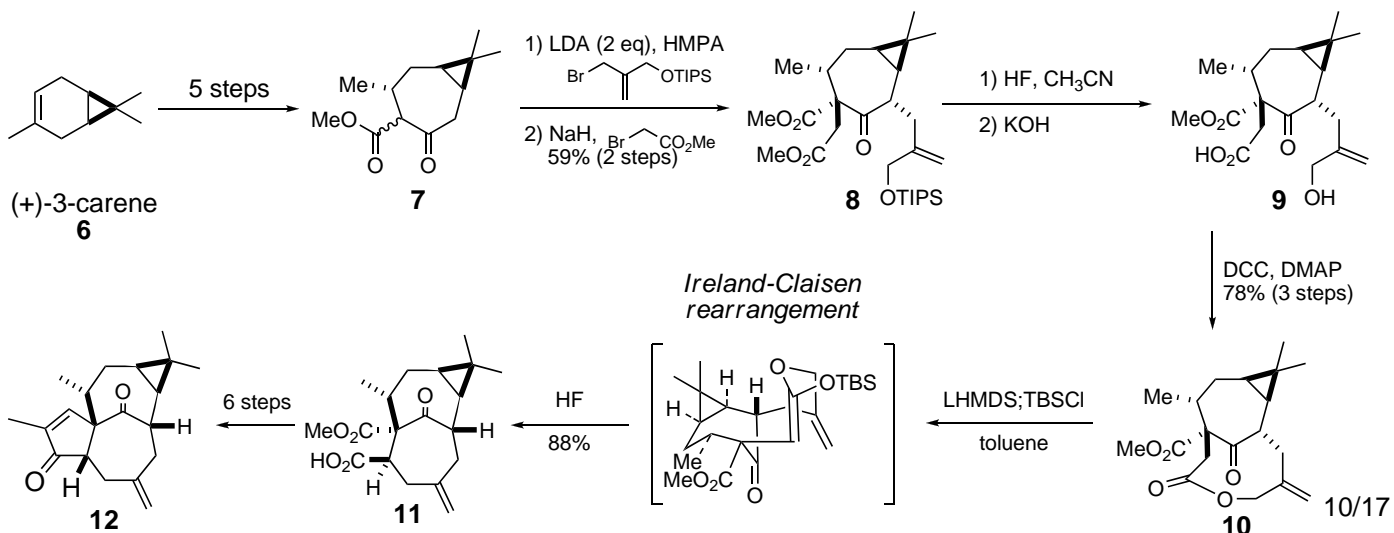
### 3. Synthesis of Ingenane core



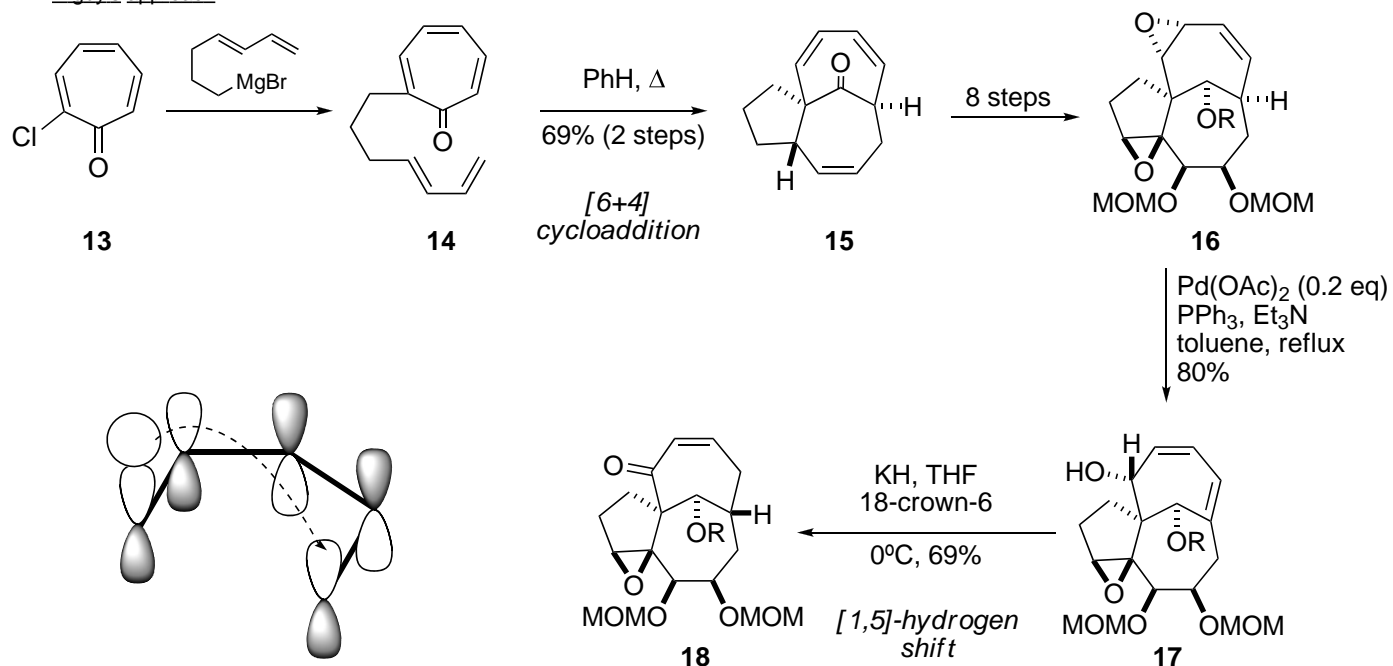
#### Winkler's route



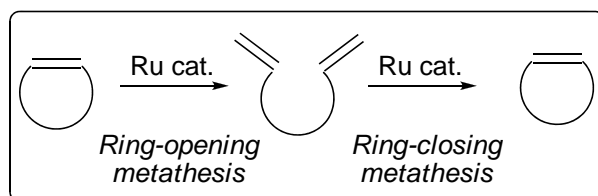
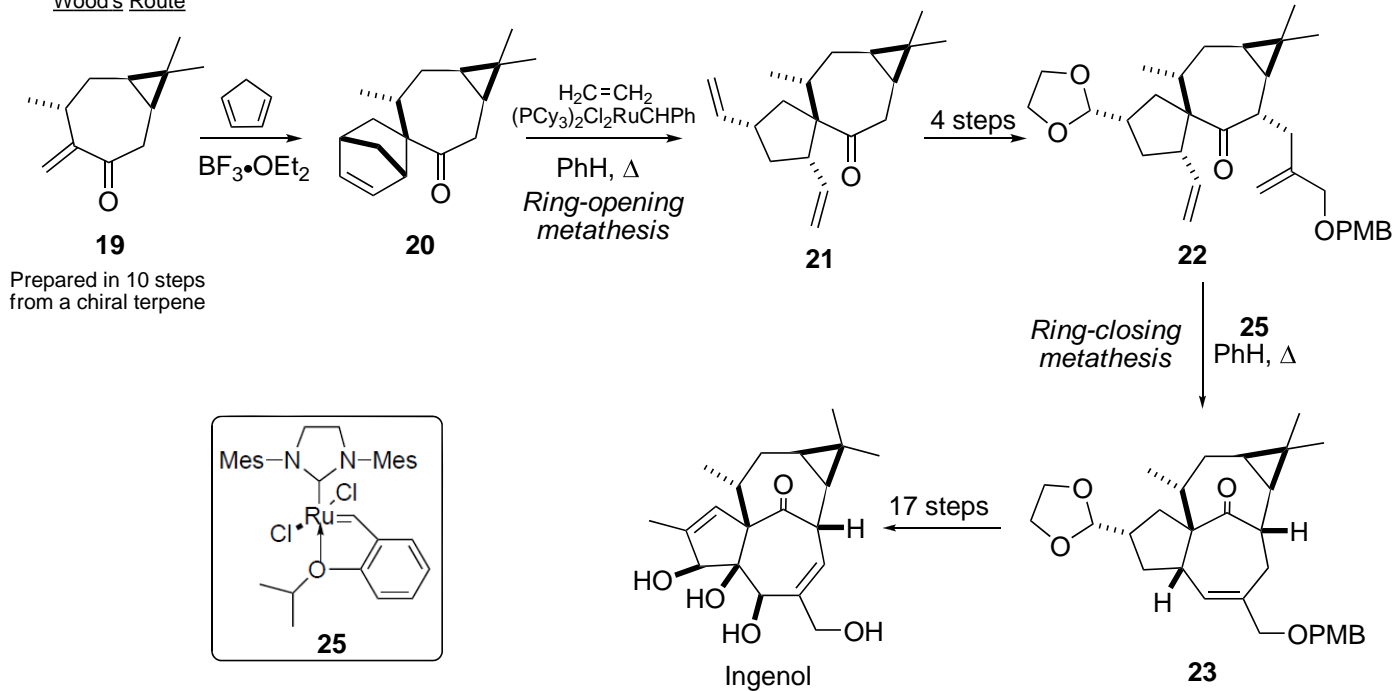
#### Funk's approach



Rigby's approach

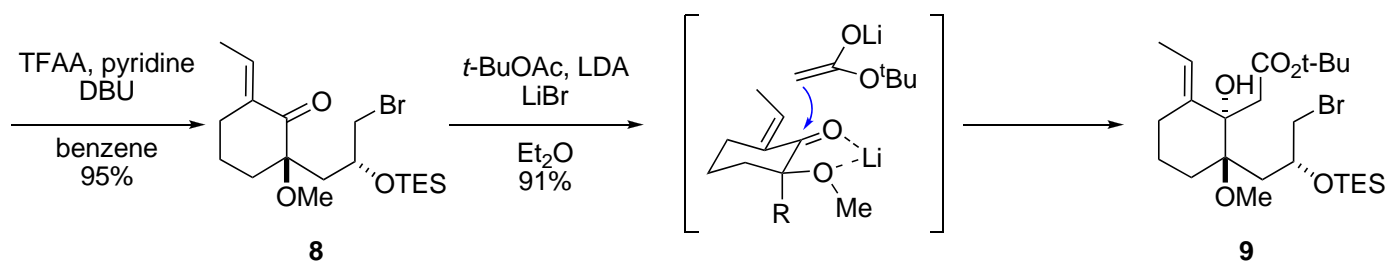
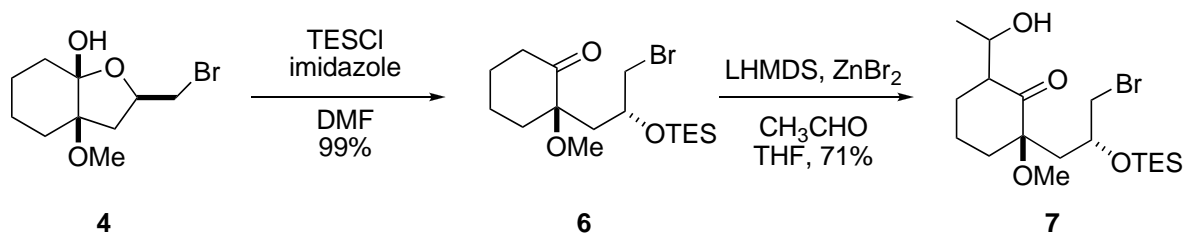
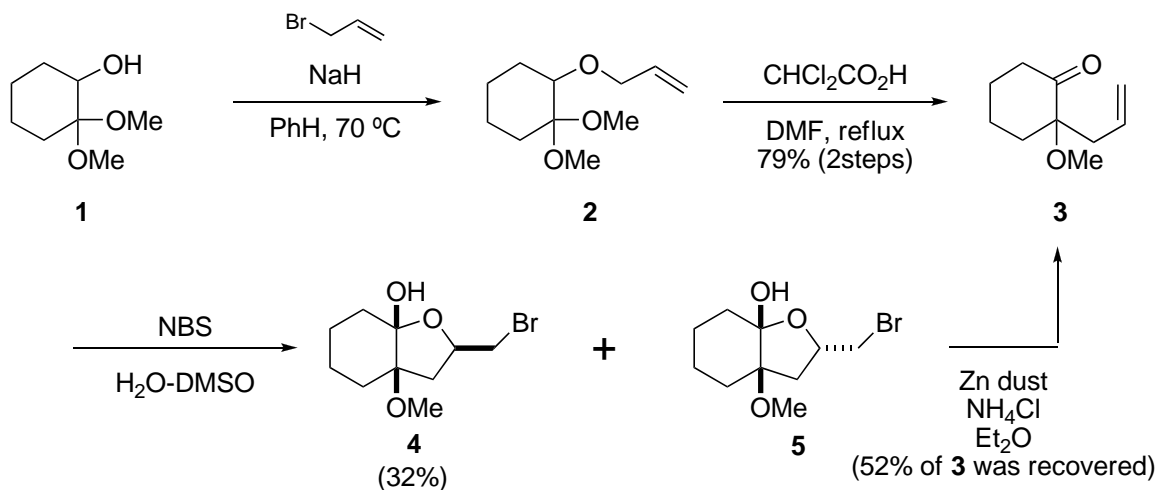
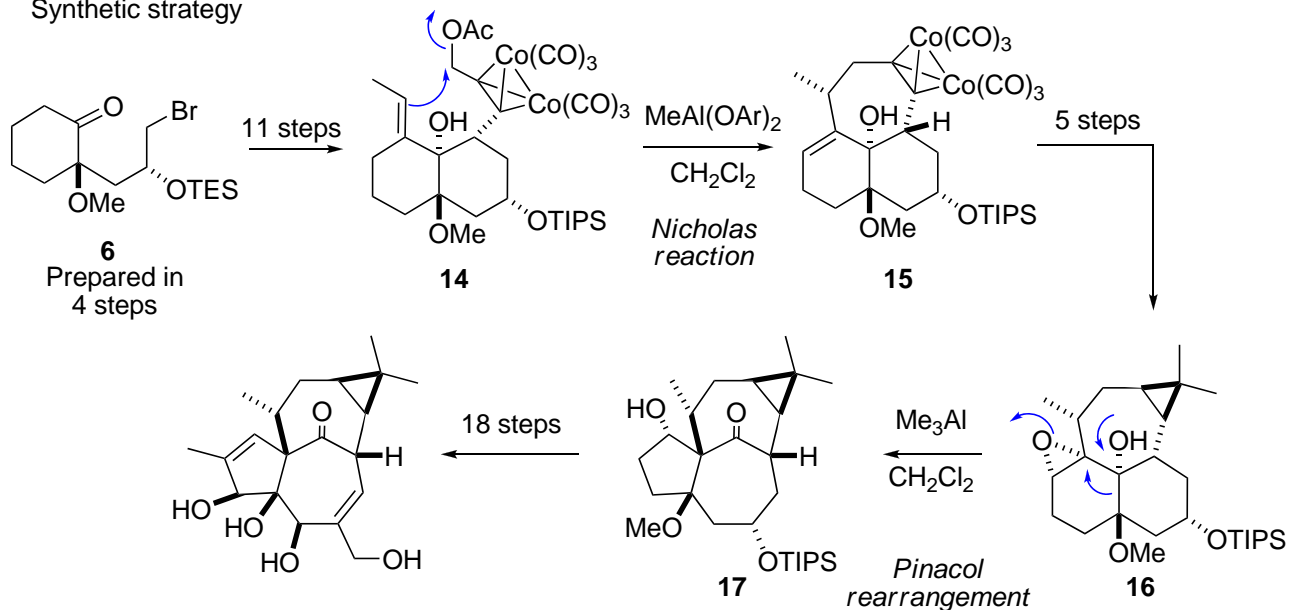


Wood's Route

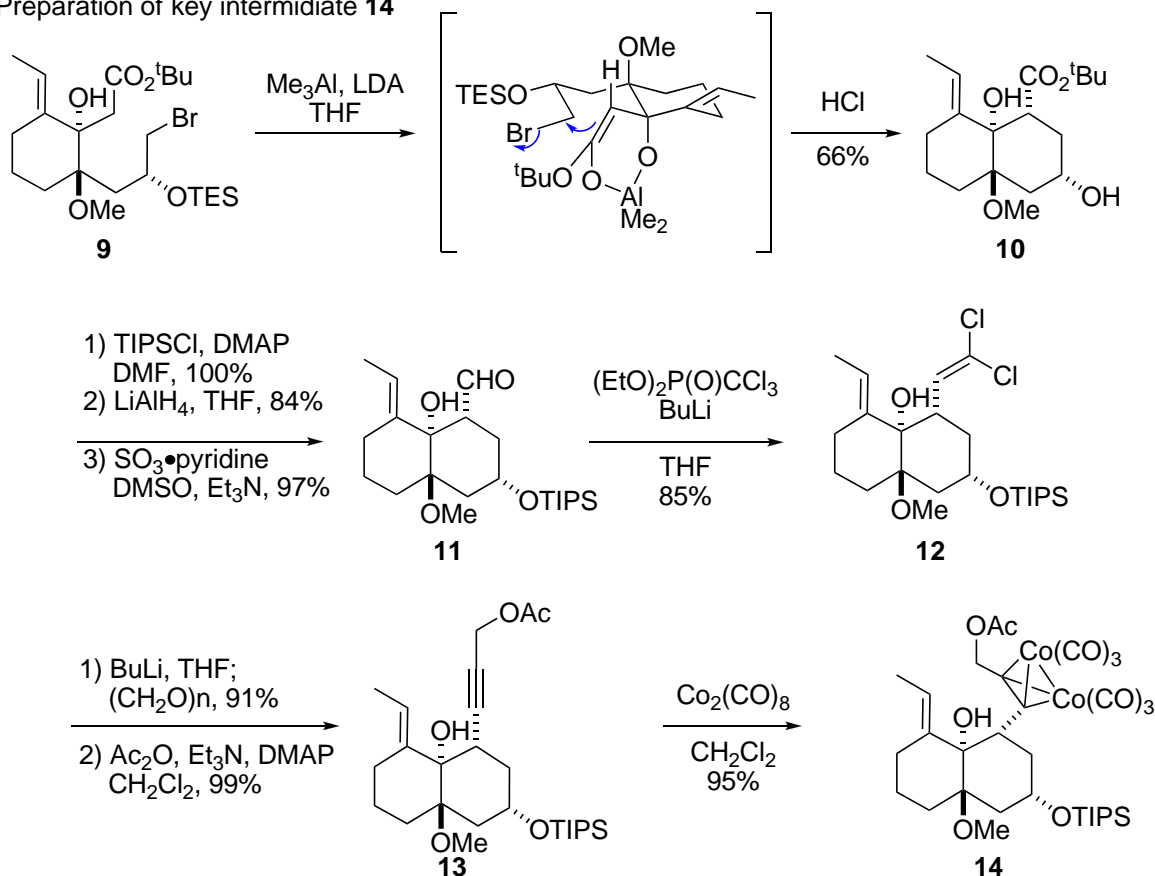


## 4. Tanino & Kuwajima's total synthesis of Ingenol

Synthetic strategy



Preparation of key intermediate **14**



Dicobalt hexacarbonyl complex

(i) Introduction

Saito (M1) Literature seminar(2010)

Omae *et al.*, *Appl. Organometal. Chem*, **2007**, 21, 318

Organocobalt compounds in organic synthesis have three characteristic reactions.

- A high affinity to C-C  $\pi$ -bonds or C-N  $\pi$ -bonds.
- A high affinity to carbonyl groups.
- Easily tending to form square-planar bipyramidal six-coordination structures at the square-planar position, and to bond with one or two carbon atoms at axial position.

Nicholas reaction, Pauson-Khand reaction and [2+2+2] cyclization are based on character A.  
 (Pauson-Khand reaction is also based on character B)

(ii) Nicholas reaction (character A)

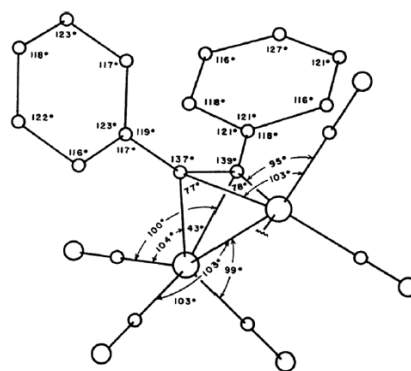
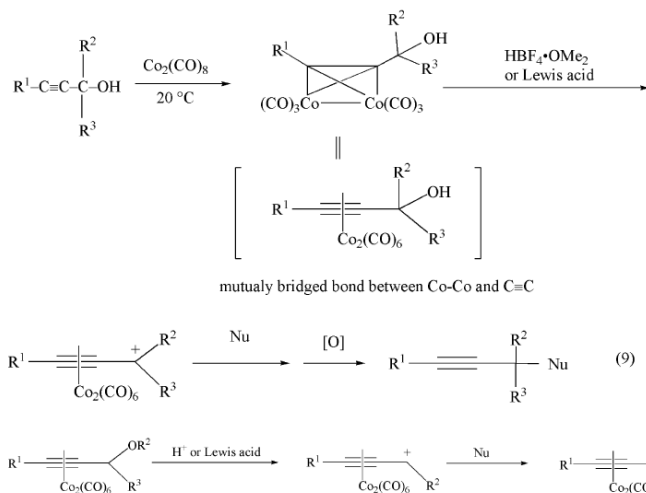
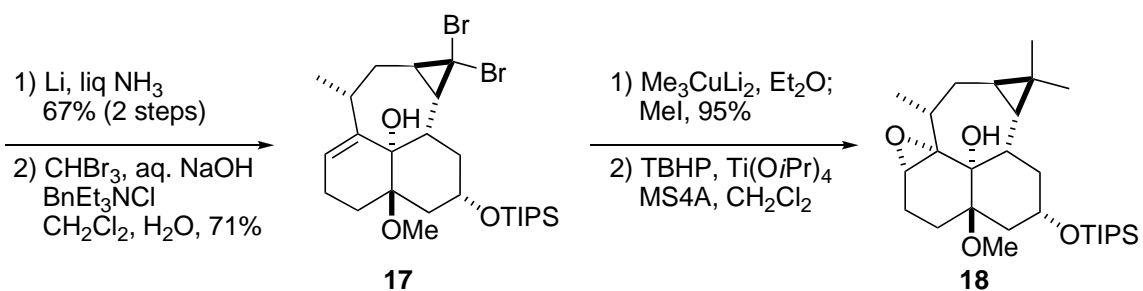
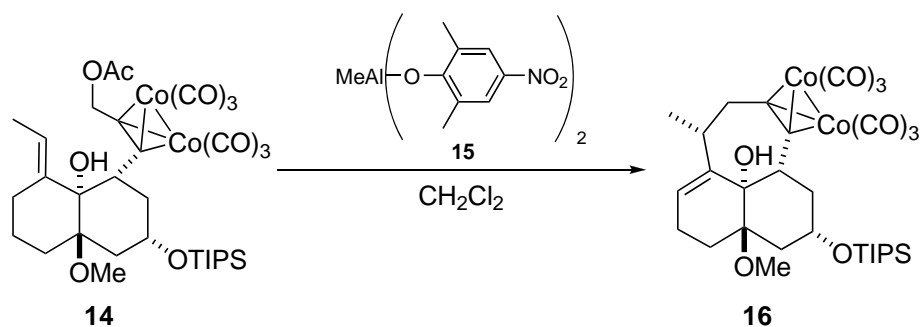
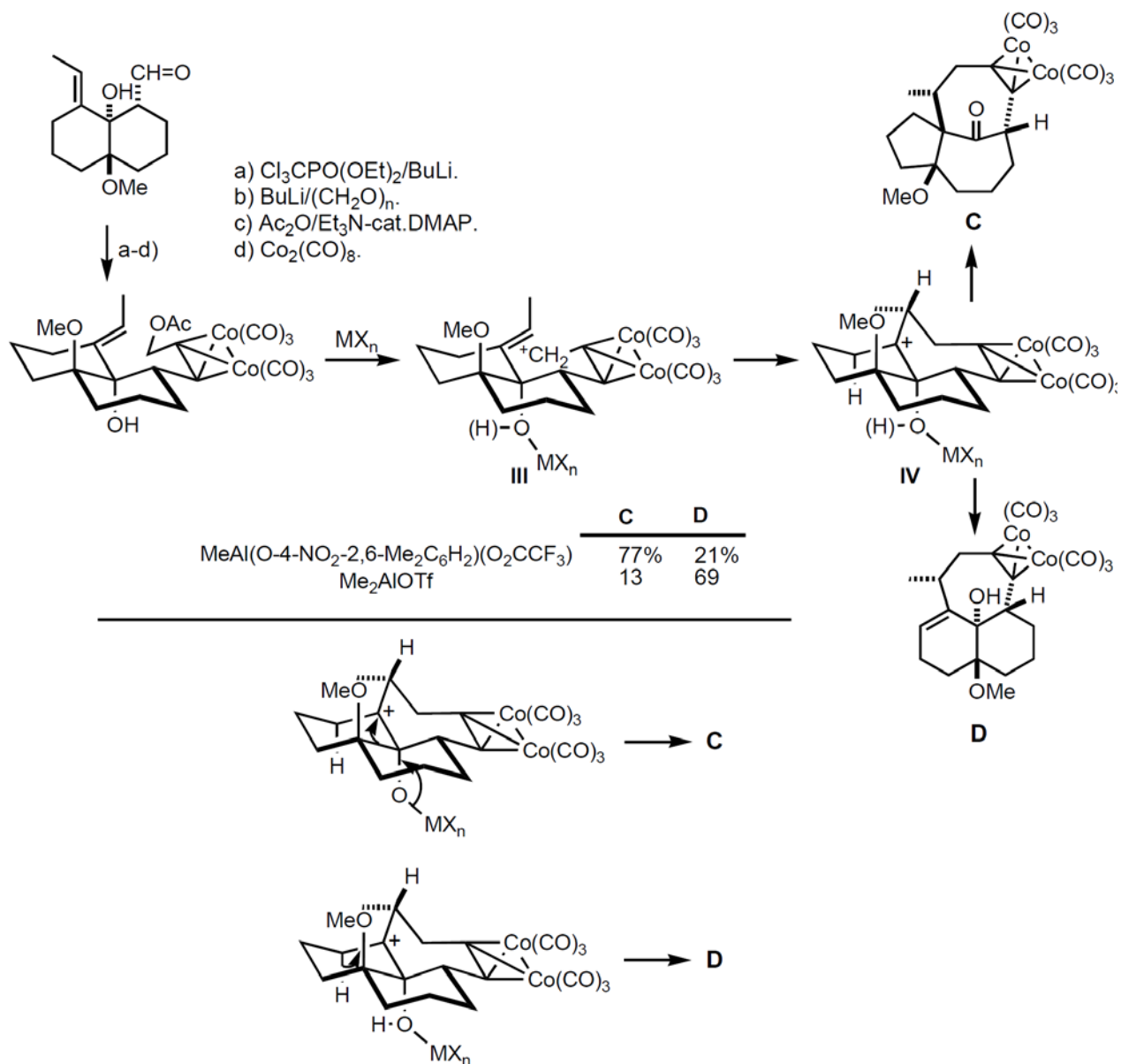


Figure 1. Structure of dicobalt hexacarbonyl diphenylacetylene.<sup>69</sup>

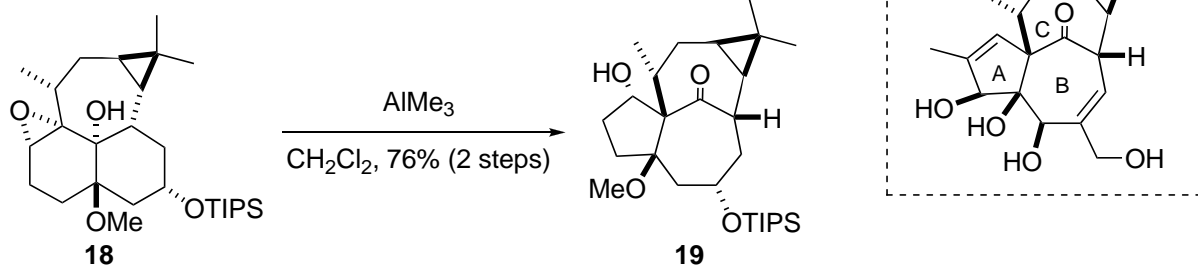
The cation at the  $\beta$ -position of the cobalt is stabilized by dicobalt hexacarbonyl acetylene moiety.

Ref : Mayr *et al.*, *JACS*, **1998**, 120, 900

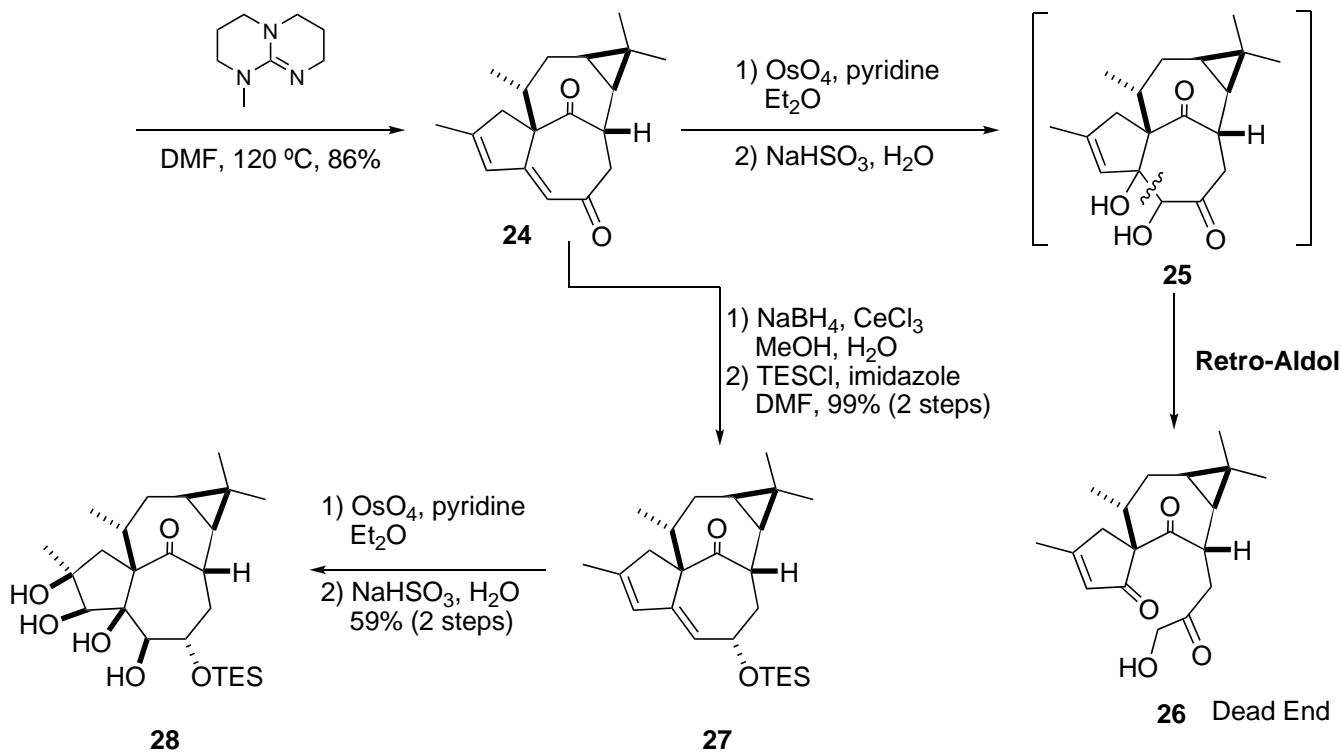
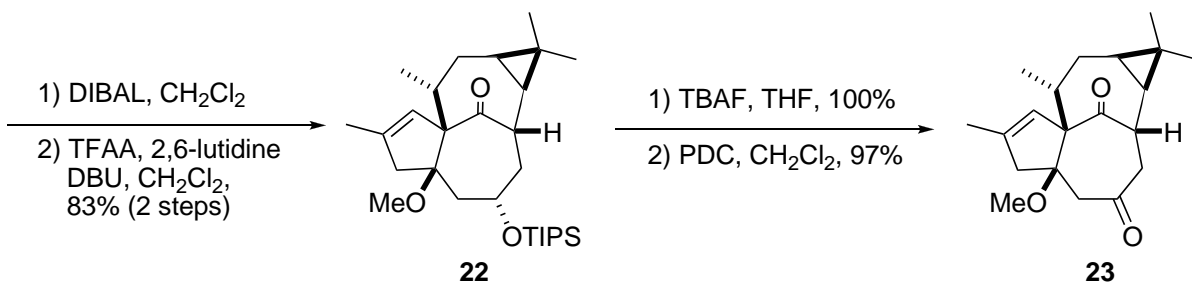
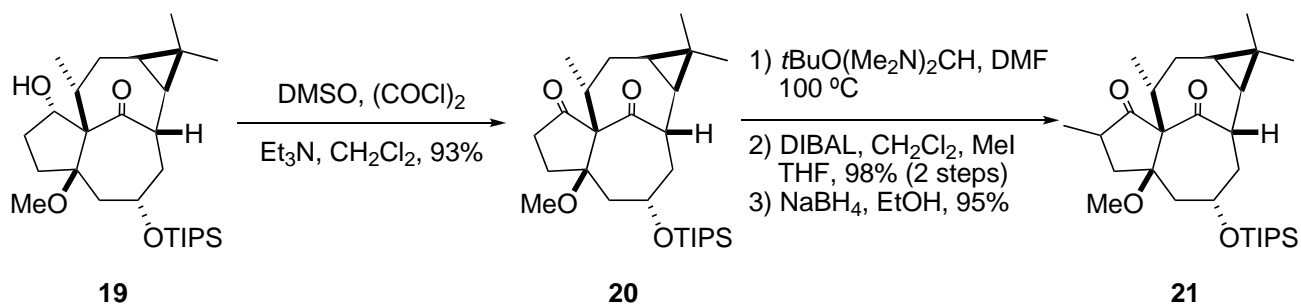
Model study of Nicholas reaction

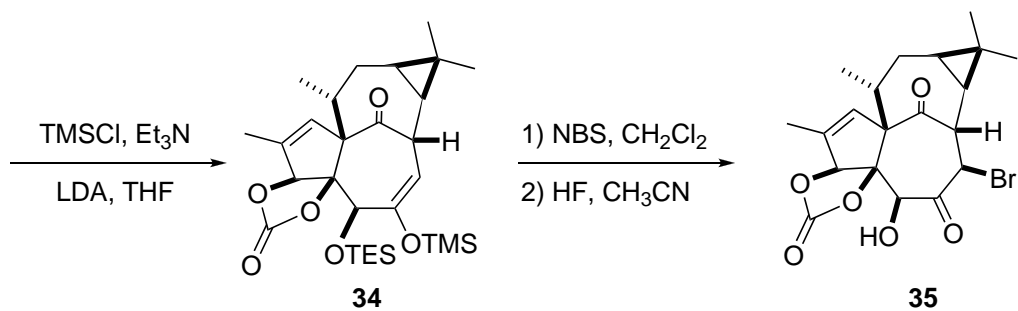
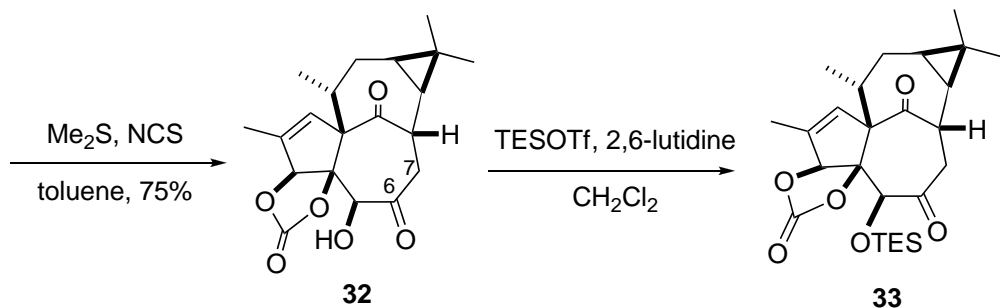
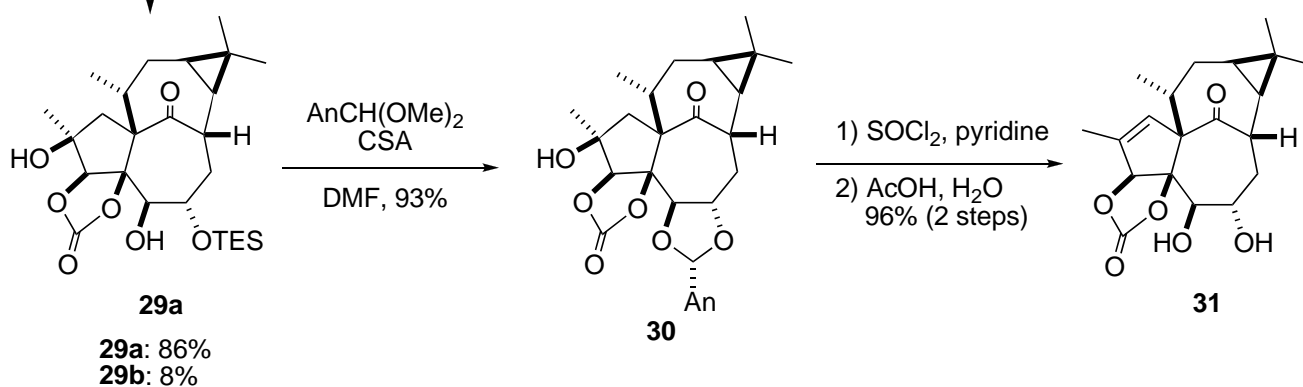
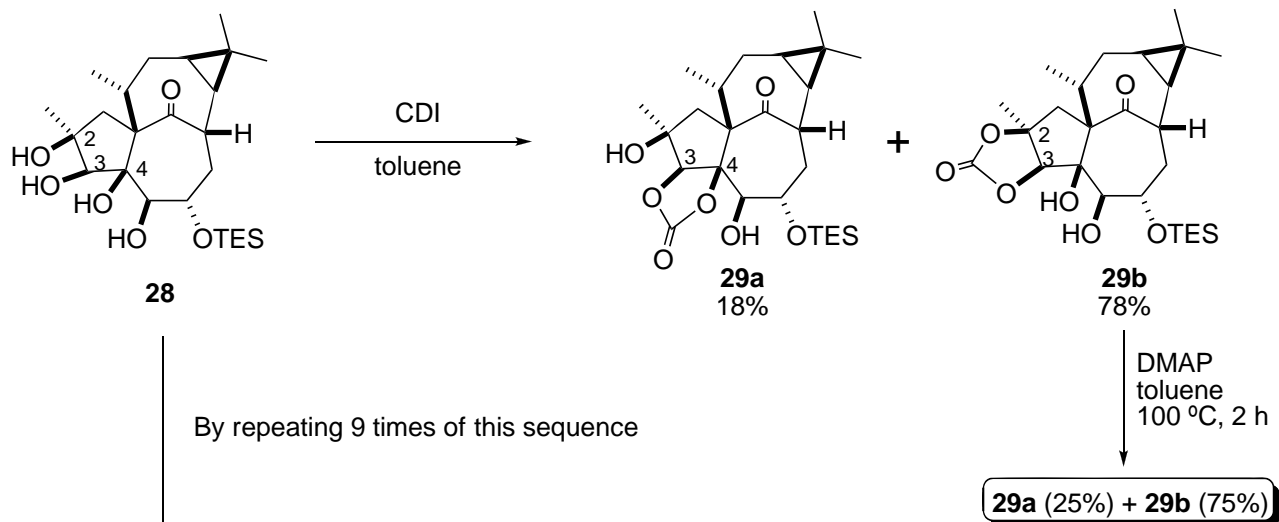


Construction of ABCD ring by pinacol rearrangement

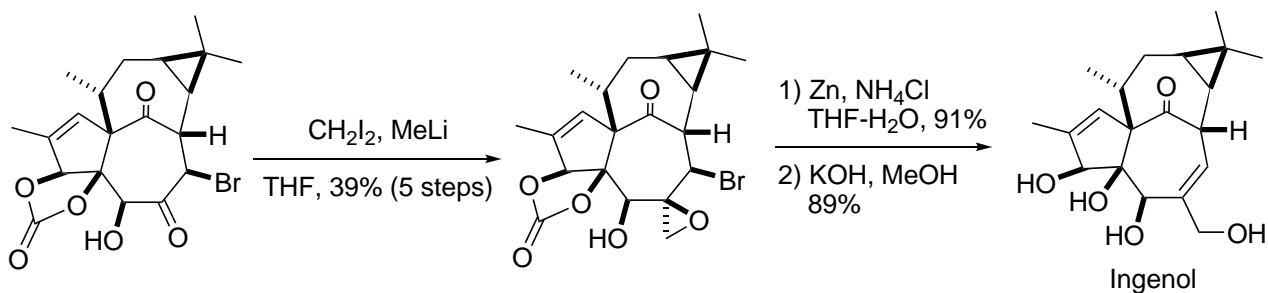


Introduction of hydroxyls for tetraol **28**









## 5. Summary

Total synthesis of Ingenol

Winkler, J. D. .... [2+2]-photocycloaddition  
 racemic total synthesis - 43 steps, 0.007% yield

Tanino, K. and Kuwajima, I. .... Nicholas reaction and pinacol rearrangement  
 racemic total synthesis - 45 steps, 0.03% yield

Wood, J. L. .... ring-closing metathesis  
 asymmetric synthesis - 35 steps, 0.002% yield