# The Cobalt Way to *dl*-Estrone, a Highly Regiospecific Functionalization of 2,3-Bis(trimethylsilyl)estratrien-17-one

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Yiben Wang

4/3/2012

Funk, R.L. and Vollhardt, K.P.C. *J. Am. Chem. Soc.*, **1979**, *101*, 215.

# Dr. Peter C. Vollhardt

**Education**:

-Vordiplom in Chemistry, University of Munich

-Ph.D. University College London (1972)

-P.J. Garratt

-Post-doctoral: R.G. Bergman – California Institute of Technology

-1974: Assitant Professor at UC Berkeley

-1975: Principal Investigator of the Materials and Chemical Sciences Division at Lawrence Berkeley Lab.

-1978: Promoted to Associate Professor

-1982: Promoted to Full Professor

**Awards:**

-Adolf Windaus Medal of the German Chemical Society (1983).

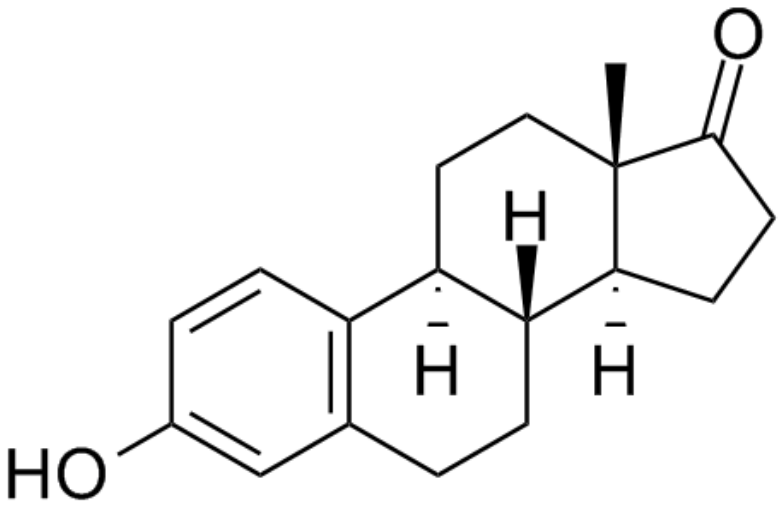
-Chief Editor for Synlett, a journal he launched in 1990.

-Honorary Doctorate from the University of Rome Tor Vergata (2004).

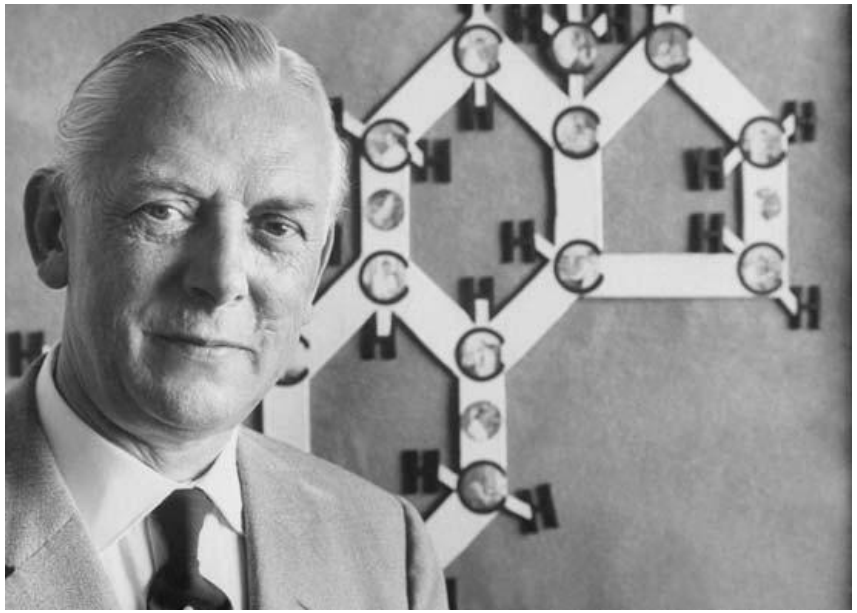
-http://chem.berkeley.edu/faculty/vollhardt/index.php

Estrone:

-an estrogenic hormone
-least abundant compared to estriol and estradiol
-acts as a reservoir for estradiol
-predominant estrogen in postmenopausal women
-synthesized from Androstenedione
-converts to estrone sulfate, which can be used as a prognosis indicator for prostate cancer



Estrone cont:



-discovered by Adolf Friedrich Johann Butenandt

-German biochemist

-Ph.D. in Chemistry at University of Gottingen under Adolf Windaus in 1927

-Awarded the Nobel Prize in Chemistry in 1939

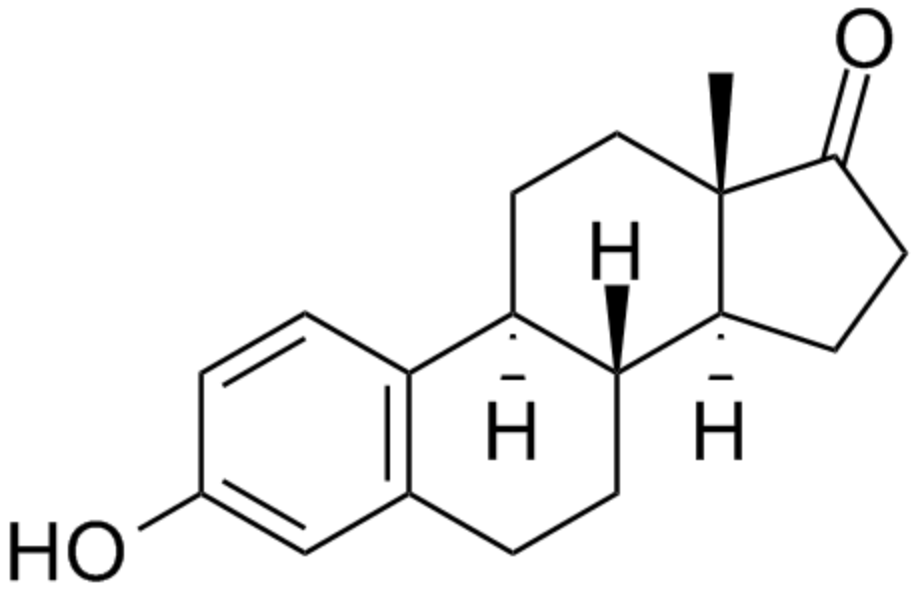
-Initially declined – government policy

-Member of the Nazi party

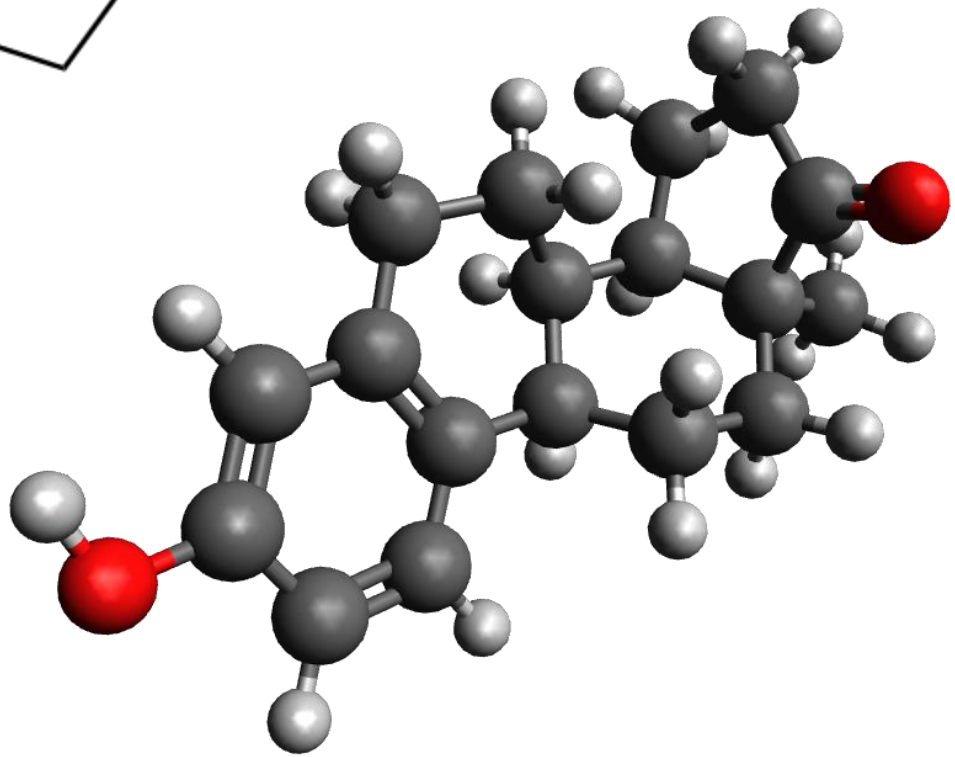
-Accepted it in 1949 – post WWII

-*Kriegsverdienstkreuz* (War Merit Cross) 1942

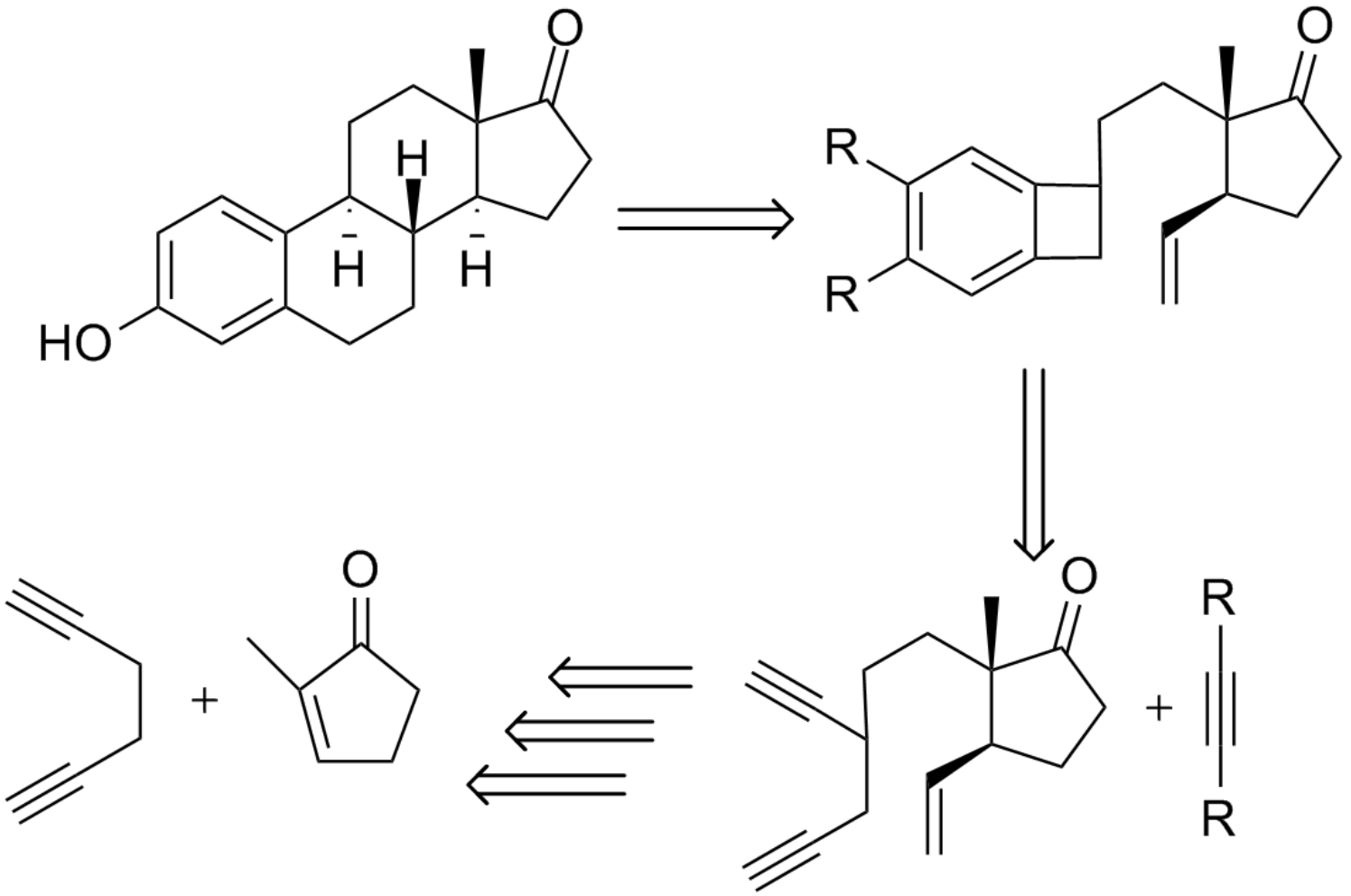
Structure:



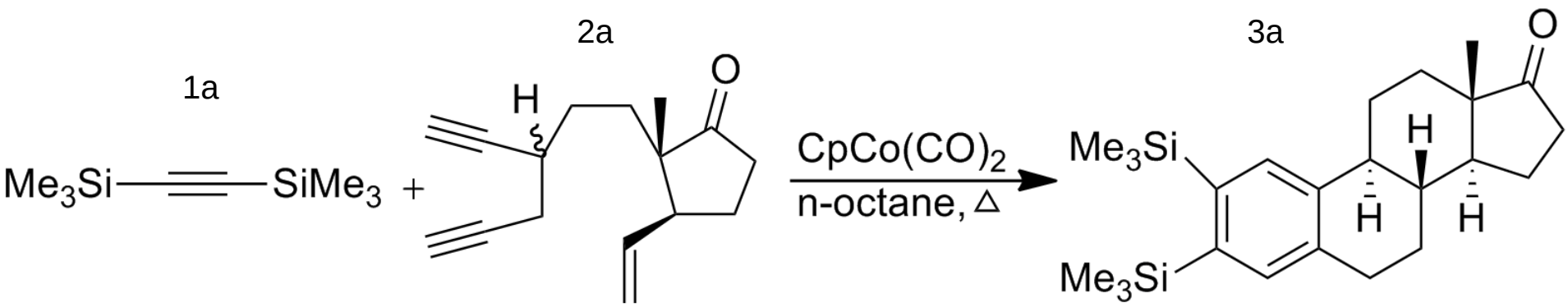

Estrone



Retro:



# Previous Work:




Bis(trimethylsilyl)acetylene (BTMSA)

1,5-hexadiyne derivative

Bis silyl derivative

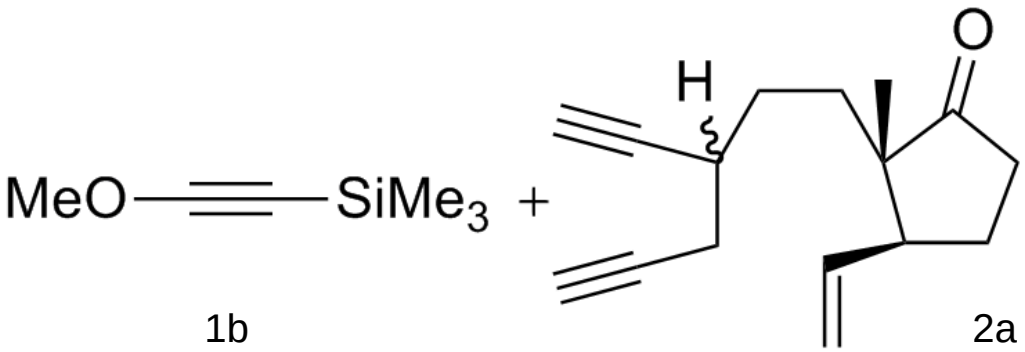
-one step construction of rings ABC of the steroid nucleus w. complete chemo-, regio-, and stereospecificity.
-lack a convenient methodology to convert the silylated steroid into phenolic derivatives.



Funk, R.L. and Vollhardt, K.P.C. *J. Am. Chem. Soc.*, **1977**, *99*, 5483.

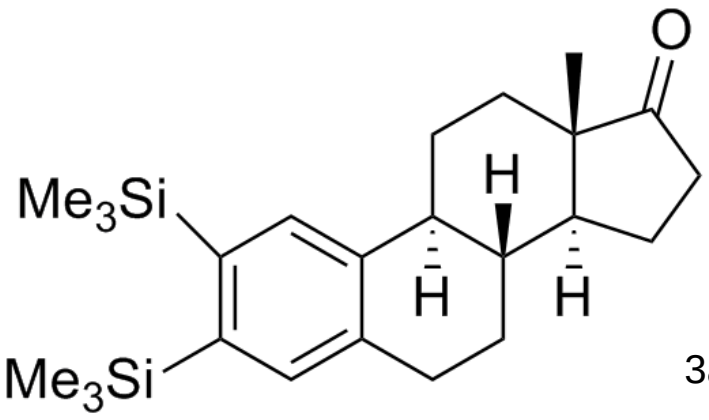
Two Solutions:

1. Based on the cobalt-catalyzed partially regiospecific cotrimerization



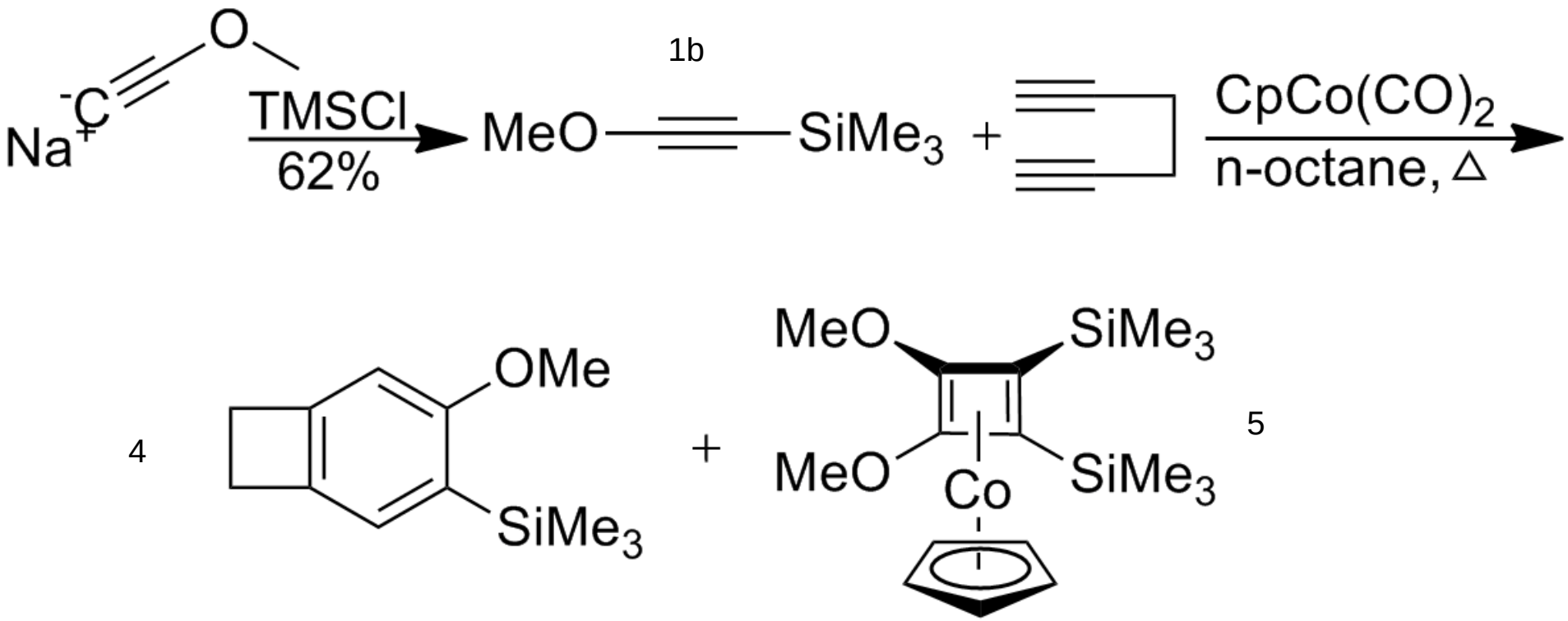

1b 2a

2. Based on the highly regiospecific functionalization of bis silyl derivatives.



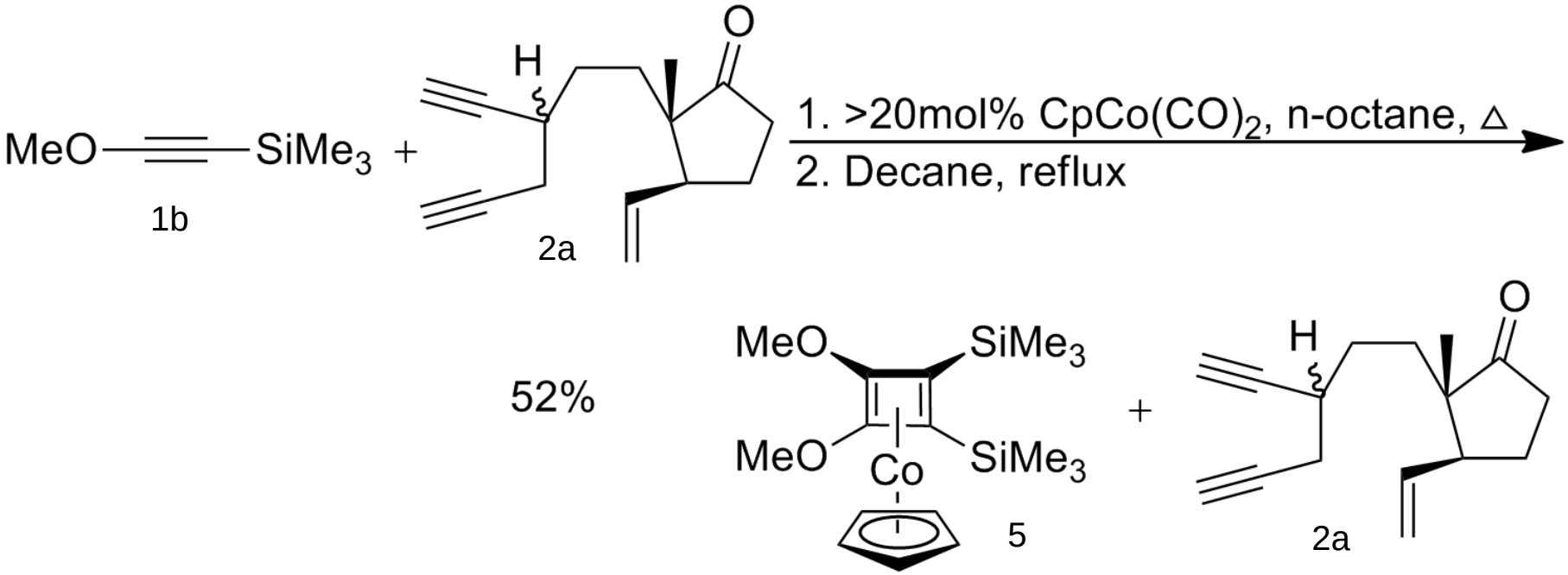

3a

Solution #1:

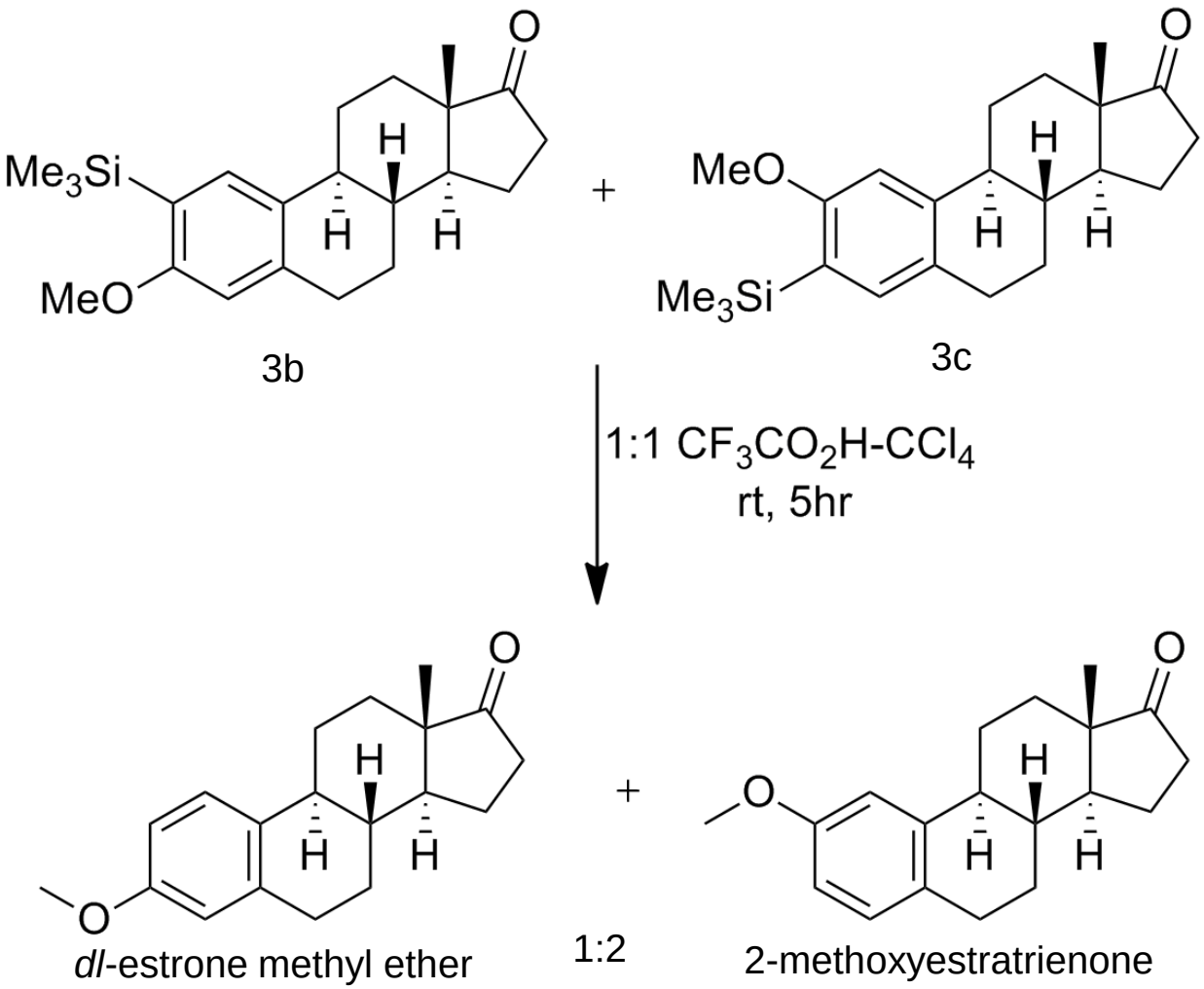



-Neat 1b with 1,5-hexadiyne under the usual conditions => only 5.
-4:1 ratio of 1b:diyne => 4 (15%).

# Solution #1:


MeO
SiMe3
1b
H
O
2a
1. >20mol% CpCo(CO)2, n-octane, Δ
2. Decane, reflux
52%
MeO
SiMe3
MeO
Co
SiMe3
5
+
H
O
2a
Me3Si
MeO
H
H
H
O
3b
+
MeO
Me3Si
H
H
H
O
3c
31%
2:1

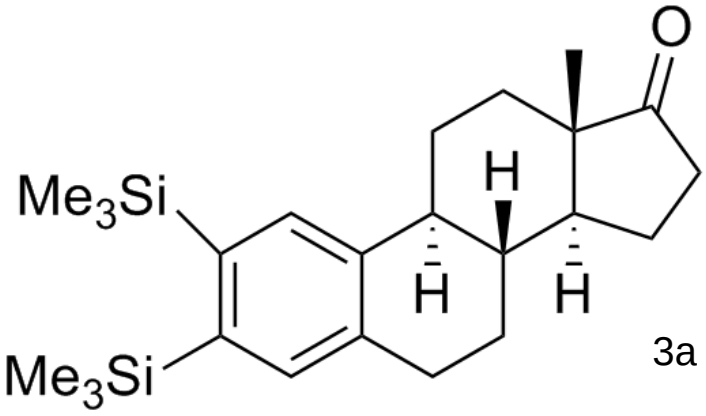
Solution #1:




-Both yield and regioselectivity are unsatisfactory.
-Improvements can be attained: more hindered alkoxyacetylene and a modified diyne precursor.

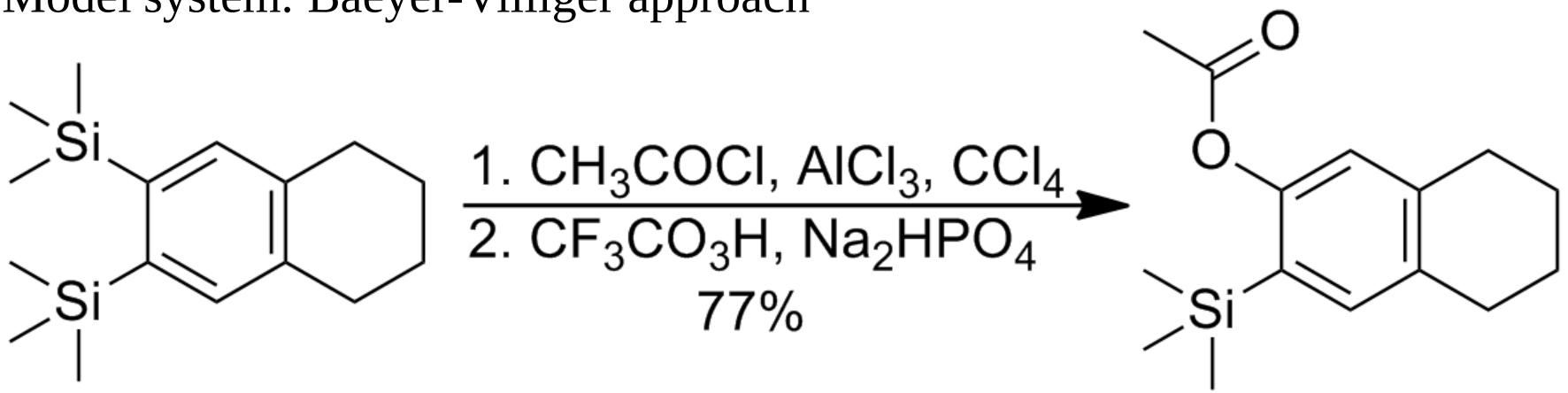
Solution #2:

-Potential estrone precursor: regioselective oxidative phenyl-silicon cleavage




3a

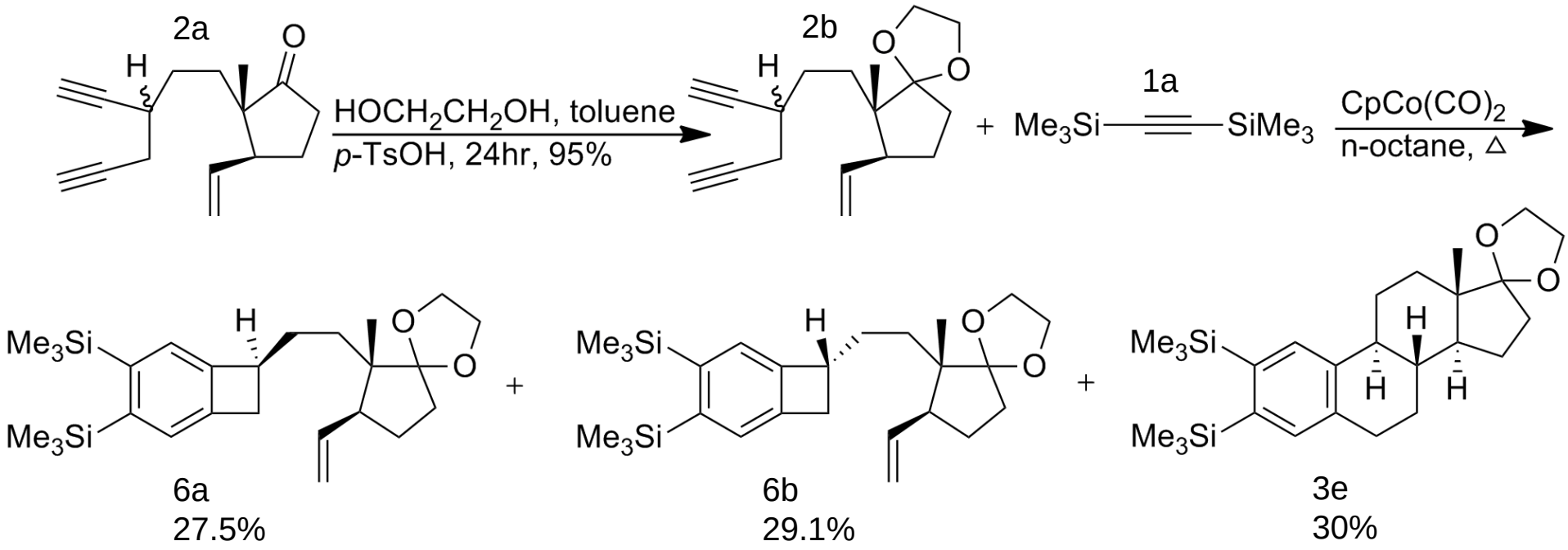
Model system: Baeyer-Villiger approach



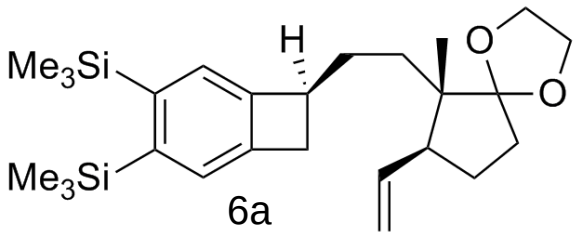

6,7-bis(trimethylsilyl)tetralin

6-trimethylsilyl-7-acetoxytetralin

# Solution #2:

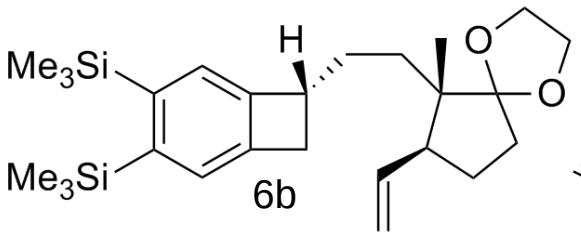

2a
H
O
HOCH2CH2OH, toluene
p-TsOH, 24hr, 95%
2b
H
O
O
1a
+ Me3Si
SiMe3
CpCo(CO)2
n-octane, Δ
Me3Si
Me3Si
H
O
O
6a
27.5%
+
Me3Si
Me3Si
H
O
O
6b
29.1%
+
Me3Si
Me3Si
H
H
H
O
O
3e
30%

# Solution #2:



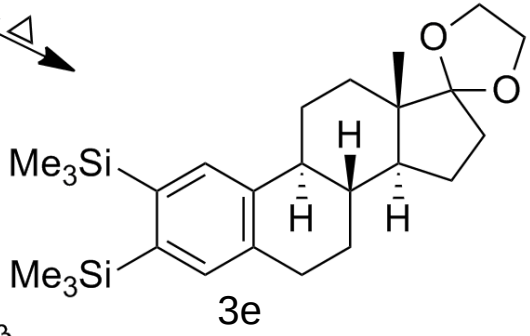

6a

or



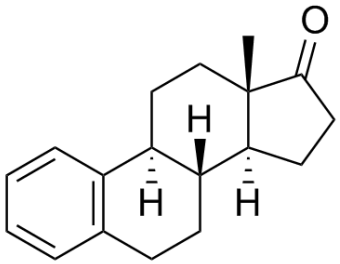

6b

Decane, Δ




3e

$CF_3CO_2H$, $H_2O$

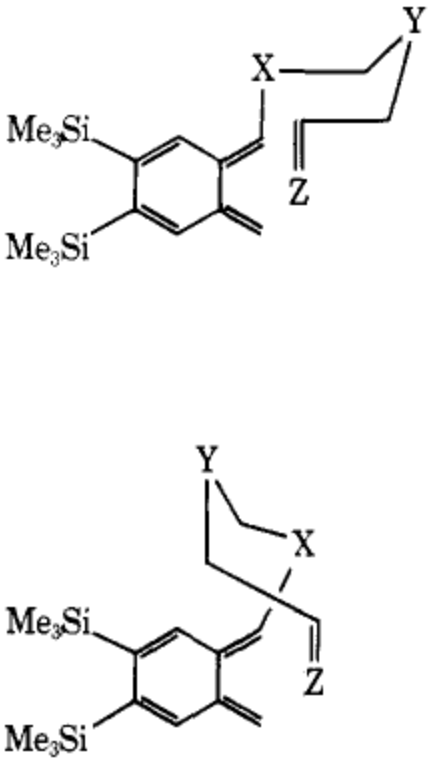



Estra-1,3,5(10)-trien-17-one

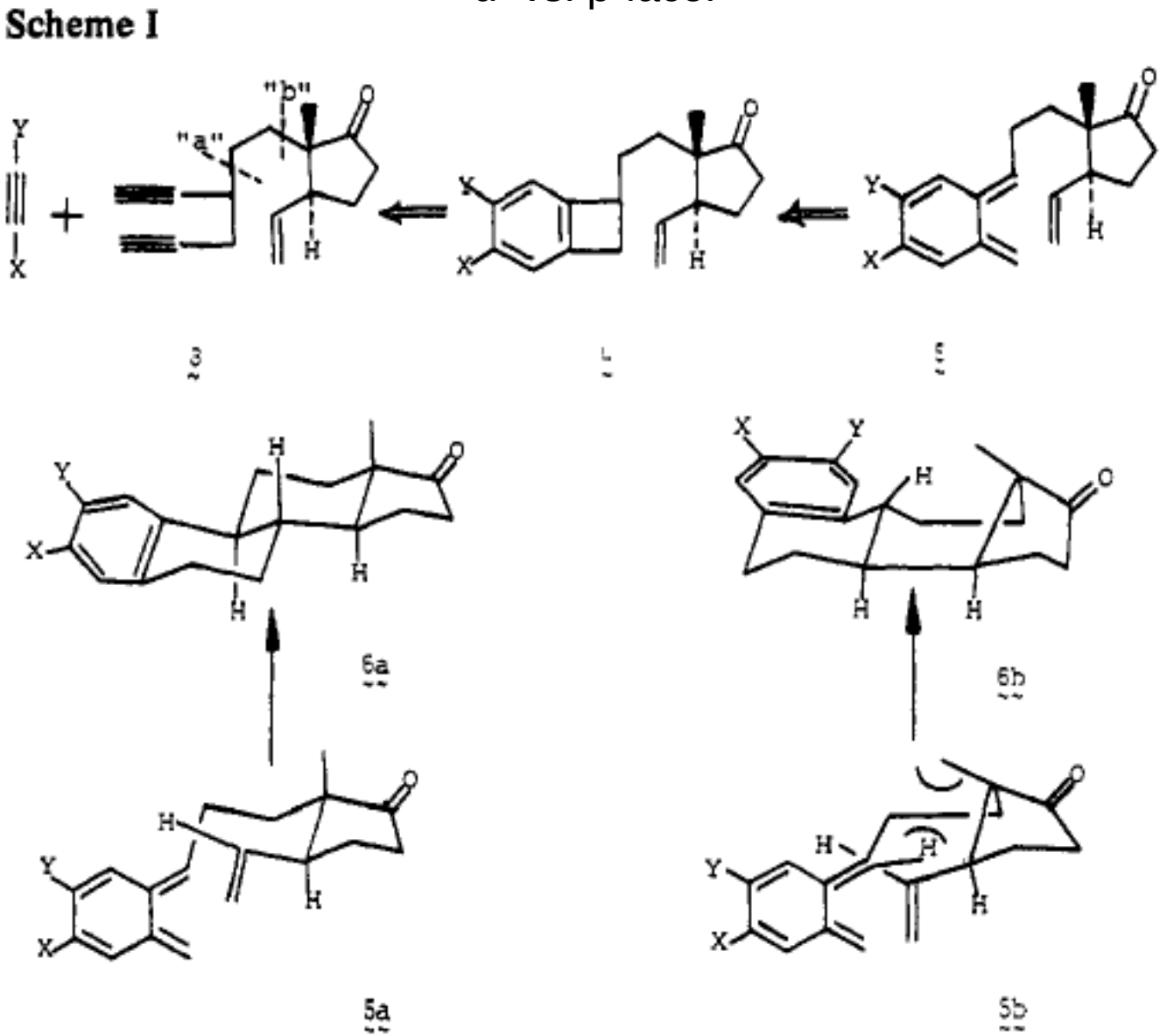
$CH_3COCl$, $AlCl_3$

Complex mixture of products.

Endo vs. Exo:



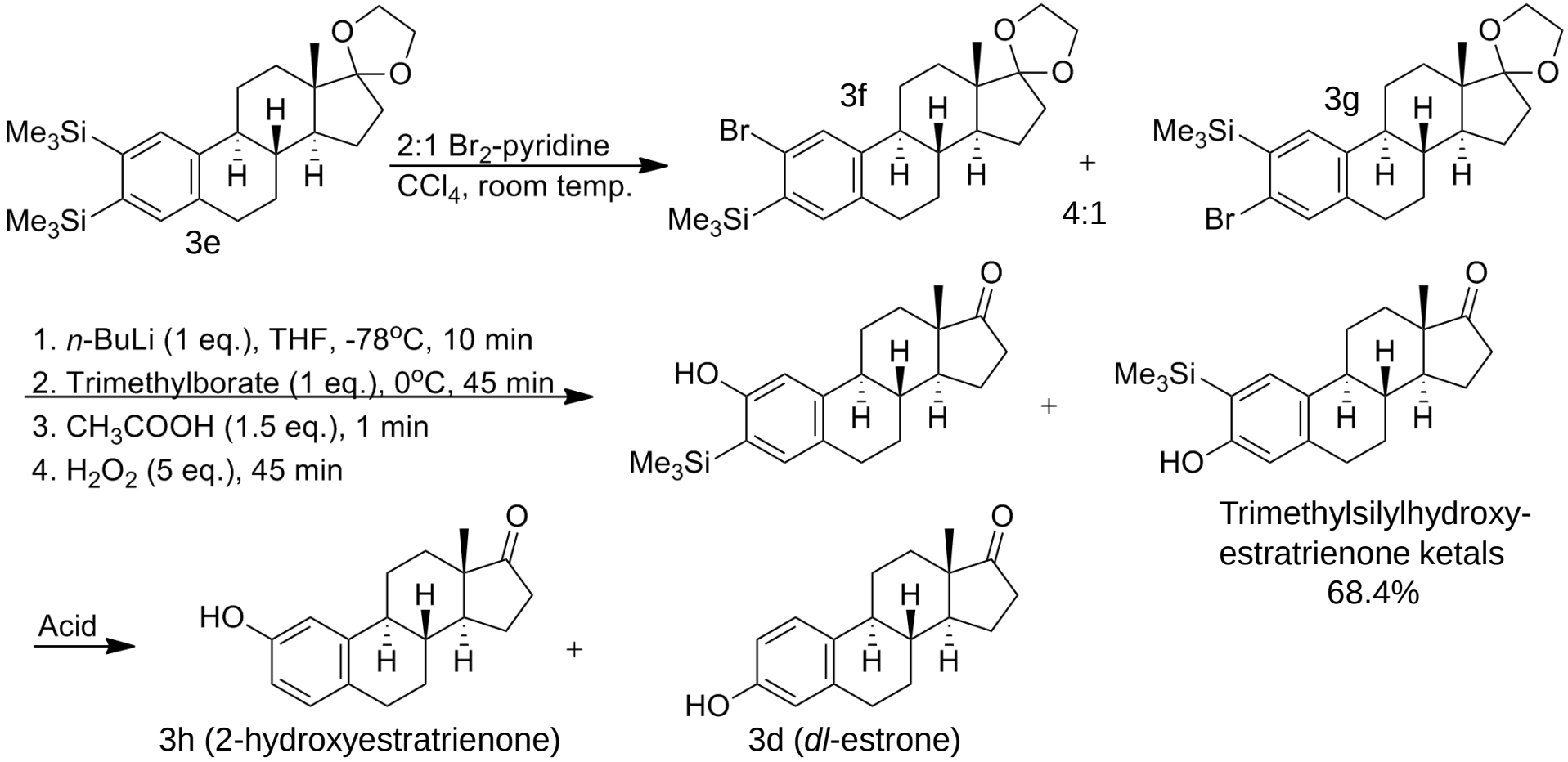

α- vs. β-face:



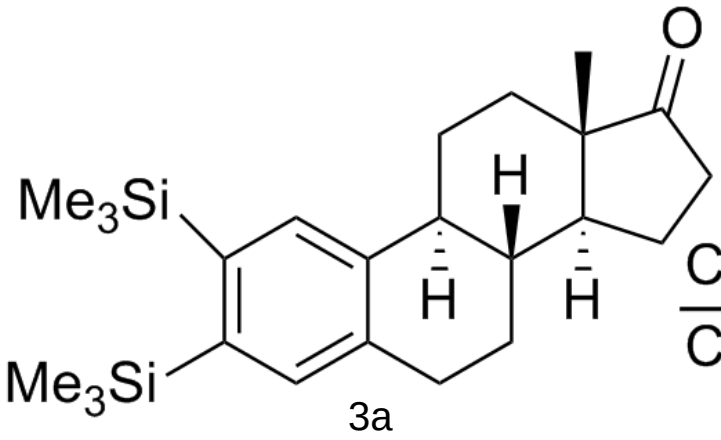

Funk, R.L., Vollhardt, P.C. *J. Am. Chem. Soc.*, **1976**, *98*, 6755-6757.

Funk, R.L., Vollhardt, P.C. *J. Am. Chem. Soc.*, **1980**, *102*, 5253-5261.

# Solution #2:


Me3Si
Me3Si
H
H
H
O
O
3e
2:1 Br2-pyridine
CCl4, room temp.
3f
Br
Me3Si
+
4:1
3g
Me3Si
Br
1. n-BuLi (1 eq.), THF, -78°C, 10 min
2. Trimethylborate (1 eq.), 0°C, 45 min
3. CH3COOH (1.5 eq.), 1 min
4. H2O2 (5 eq.), 45 min
HO
Me3Si
+
Me3Si
HO
Trimethylsilylhydroxy-
estratrienone ketals
68.4%
Acid
HO
+
HO
3h (2-hydroxyestratrienone)
3d (dl-estrone)

# Solution #2:

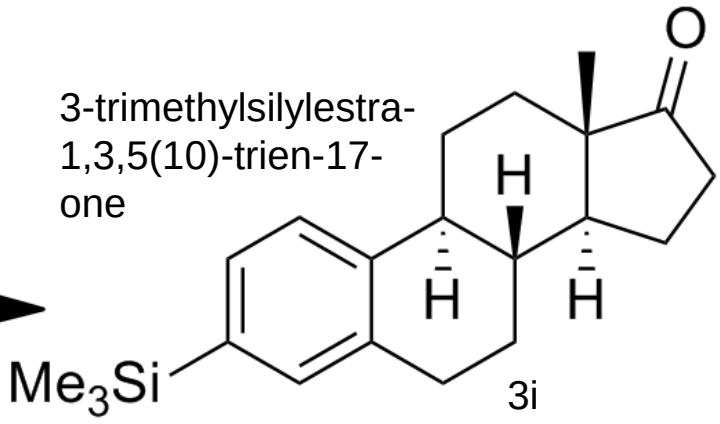



3a

$CF_3CO_2H$

$CDCl_3$-$CCl_4$, -30°C

3-trimethylsilylestra-1,3,5(10)-trien-17-one

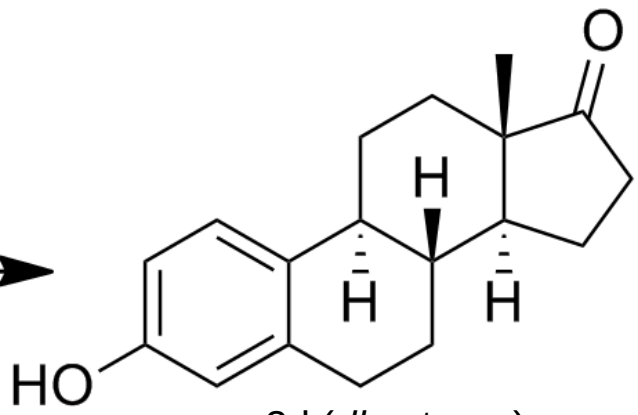



3i

9:1 (select)

90%

Lead tetrakis(trifluoroacetate)




3d (*dl*-estrone)

# Conclusions

- Shorest racemic estrone synthesis to date.*
  - Monocyclic precursor:
    - 2-methylcyclopentenone – five steps in 24% yield.
  - Acylic precursor:
    - 1,5-hexadiyne – seven steps in 17% yield
- The Cobalt-catalyzed approach to form steroid nucleus is readily applicable to A-ring phenolic derivatives.
- Synthesis of optically active steroids by this method requires:
  - Asymmetric synthesis of precursor 2
  - Modified synthetic methodology: cyclization of achiral substrates to chiral polycycles mediated by chiral and optically active metal complexes.
- 1980: Total synthesis
  - Funk, R.L., Vollhardt, P.C. *J. Am. Chem. Soc.*, **1980**, *102*, 5253-5261.