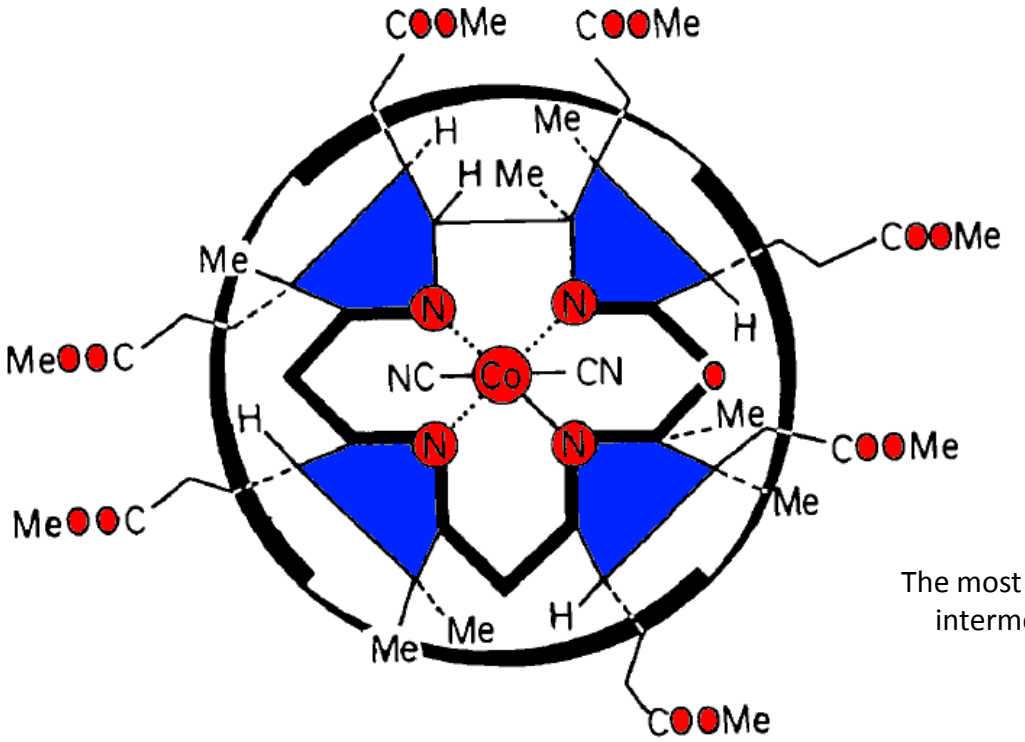
The Total Synthesis of Vitamin B12



The most advanced synthetic intermediate as of 1968

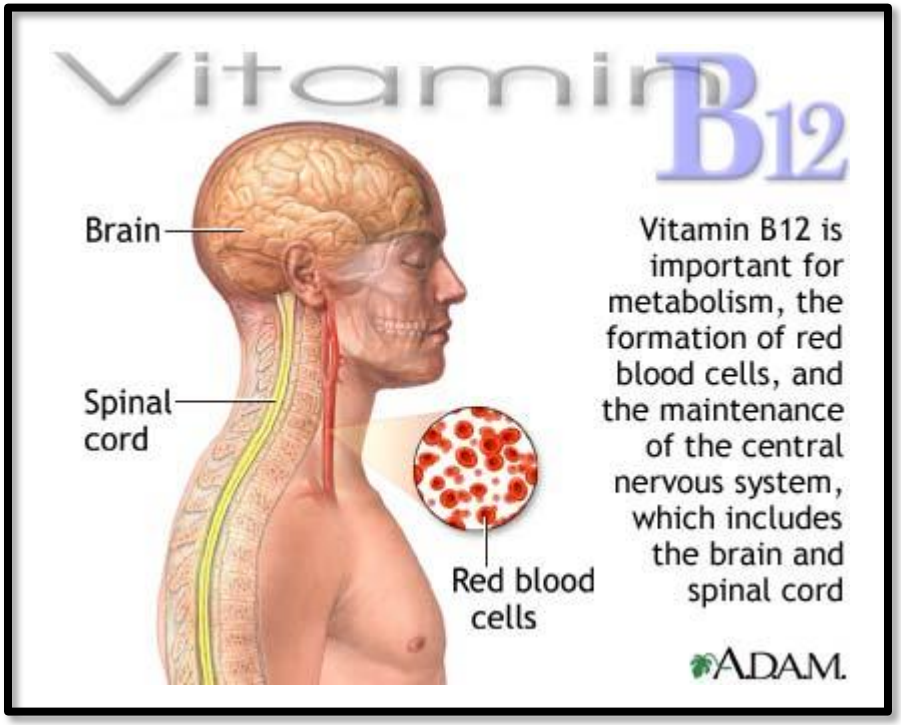
Nathan S. Werner

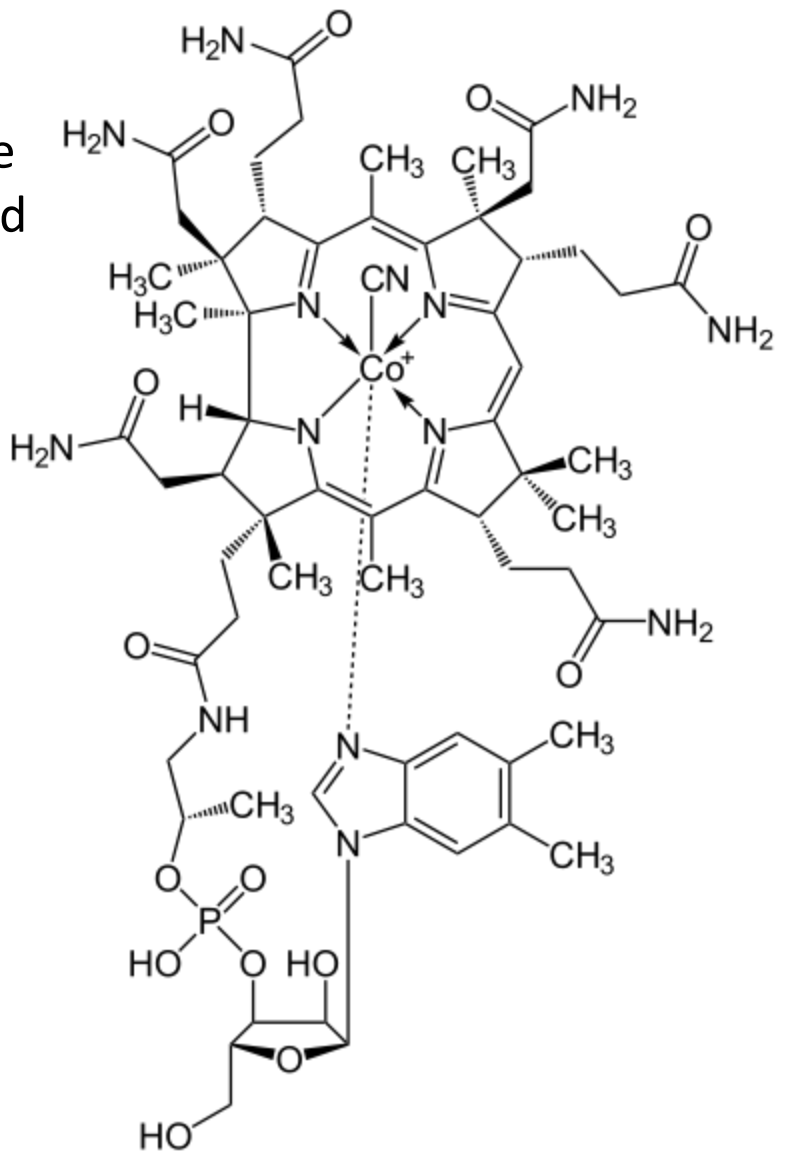
Denmark Group Meeting

September 28th, 2010

Biology of Vitamin B_{12}

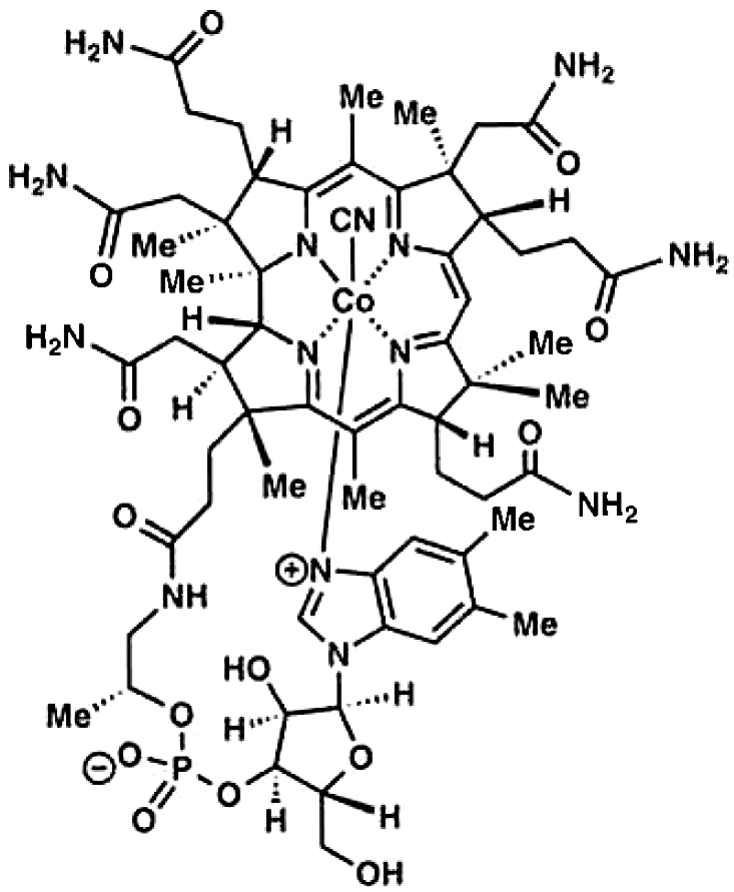
- Vitamin B_{12}, common name cobalamin, is a water soluble molecule produced by bacteria and algae
- It is involved in the metabolism of every cell of the human body, especially affecting DNA synthesis and regulation
- Vitamin B_{12} deficiency can potentially cause sever and irreversible damage to the nervous system





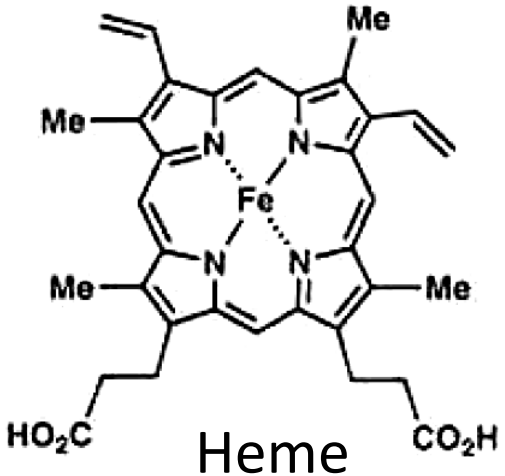
Brown, K. L. *Chem. Rev.* **2005**, 2075–2149

The Pigments of Life



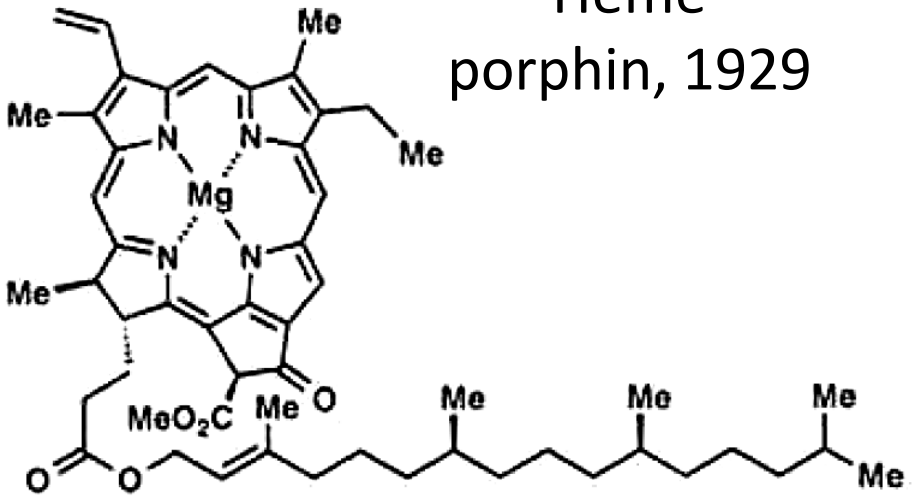
Vitamin B_{12}
corrin, 1973

Woodward, R.B. *Pure Appl. Chem.* **1973**, 145–177



Heme
porphin, 1929

Fischer, H. et al. *Justus Liebigs Ann. Chem.* **1929**, 468

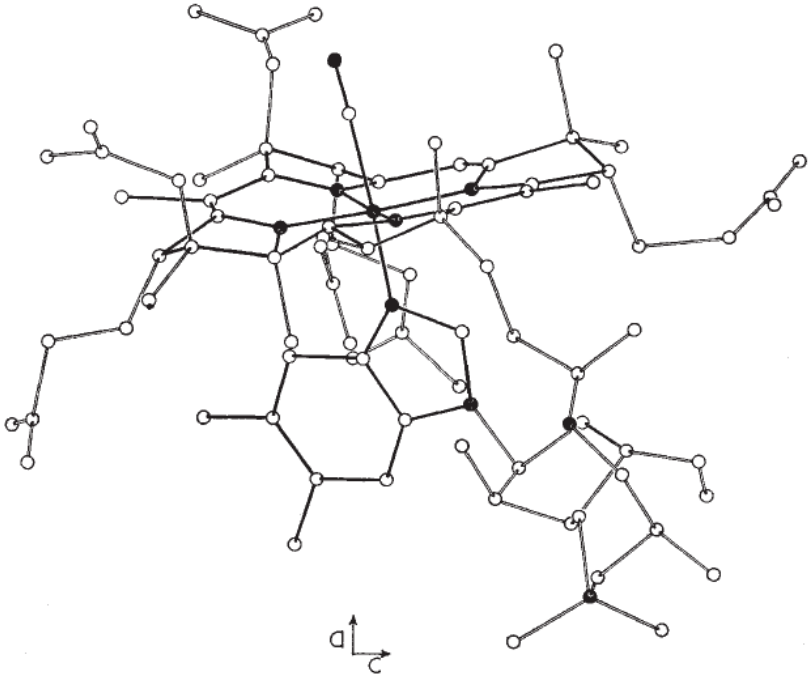


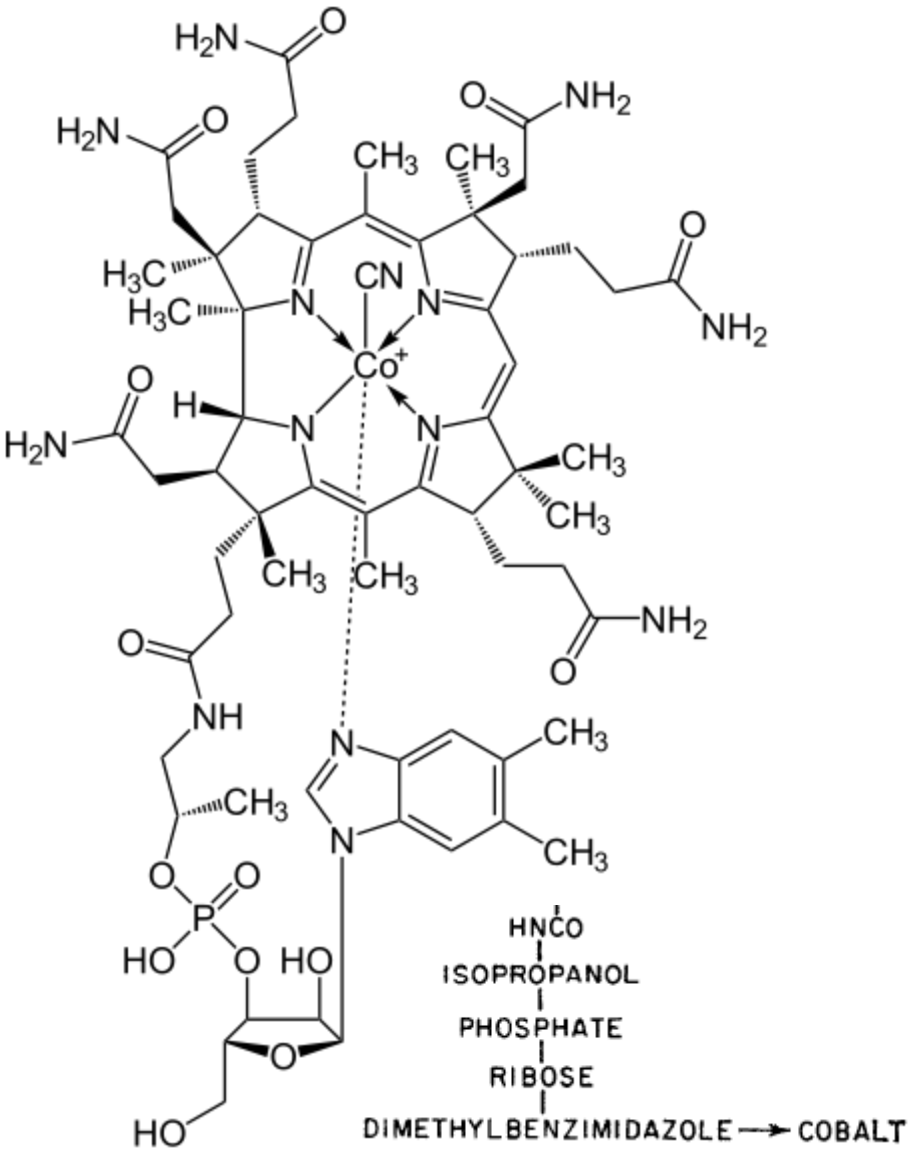
Chlorophyll A
chlorin, 1960

R. B. Woodward et al. *J. Am. Chem. Soc.* **1960**, 3800

X-Ray Crystal Structure

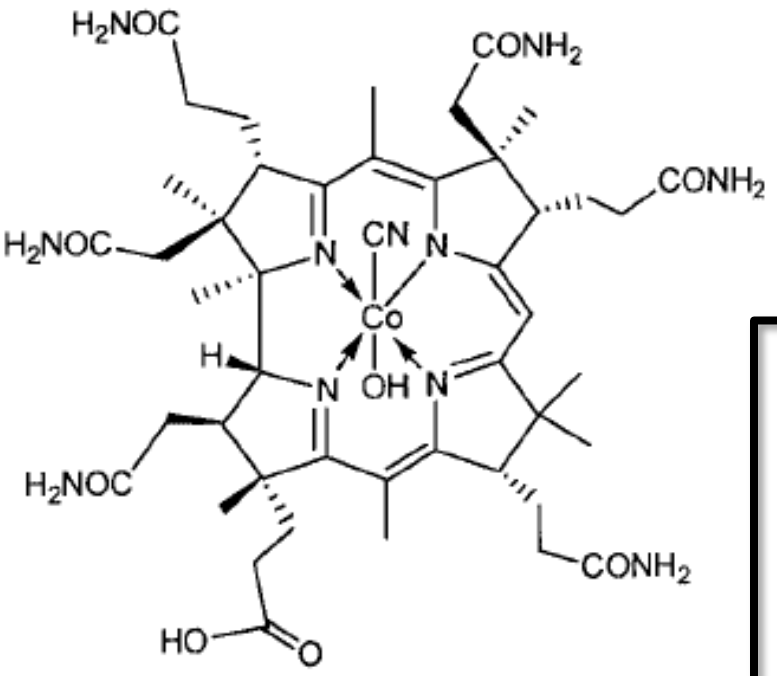
X-Ray Crystal Structure
Solved 1956



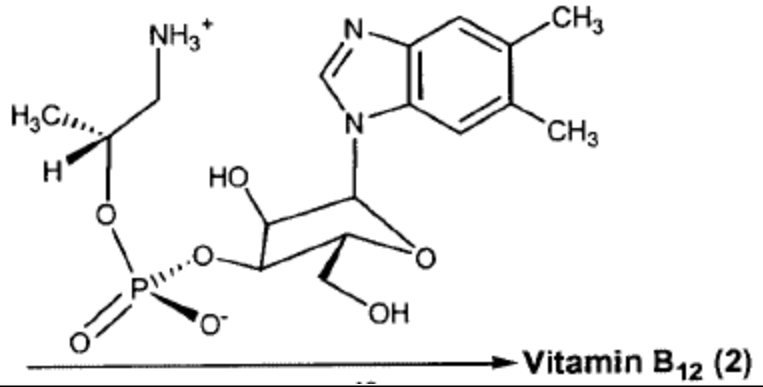


Hodgkin, D. C.; et al. *Nature* **1956**, 1032–1033

Structural Analysis



Cobyric Acid (1)



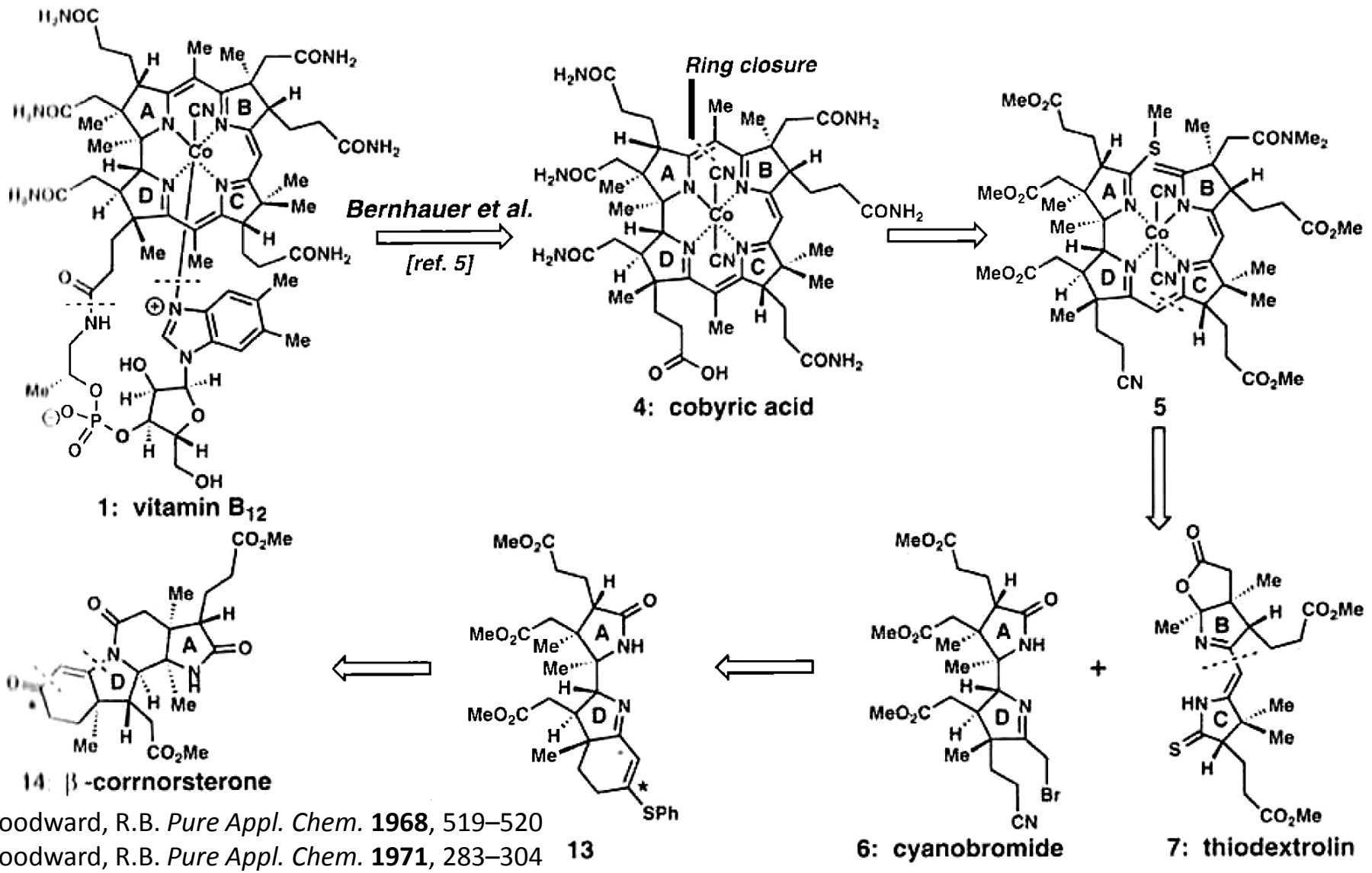
Vitamin B_{12} (2)

- Cobalt complex
- 15-membered macrocycle
- 4 heterocyclic rings
- 9 stereogenic centers
- 6 contiguous stereogenic centers
- 4 quaternary carbon atoms
- 6 amide side chains
- 1 carboxylic acid side chain
- Direct linkage between A-D rings

Mulzer, J. *Eur. J. Org. Chem.* **2005**, 30–45

Bernhauer, K.; et al. *Helv. Chim. Acta* **1960**, 704–712

Retrosynthetic Analysis



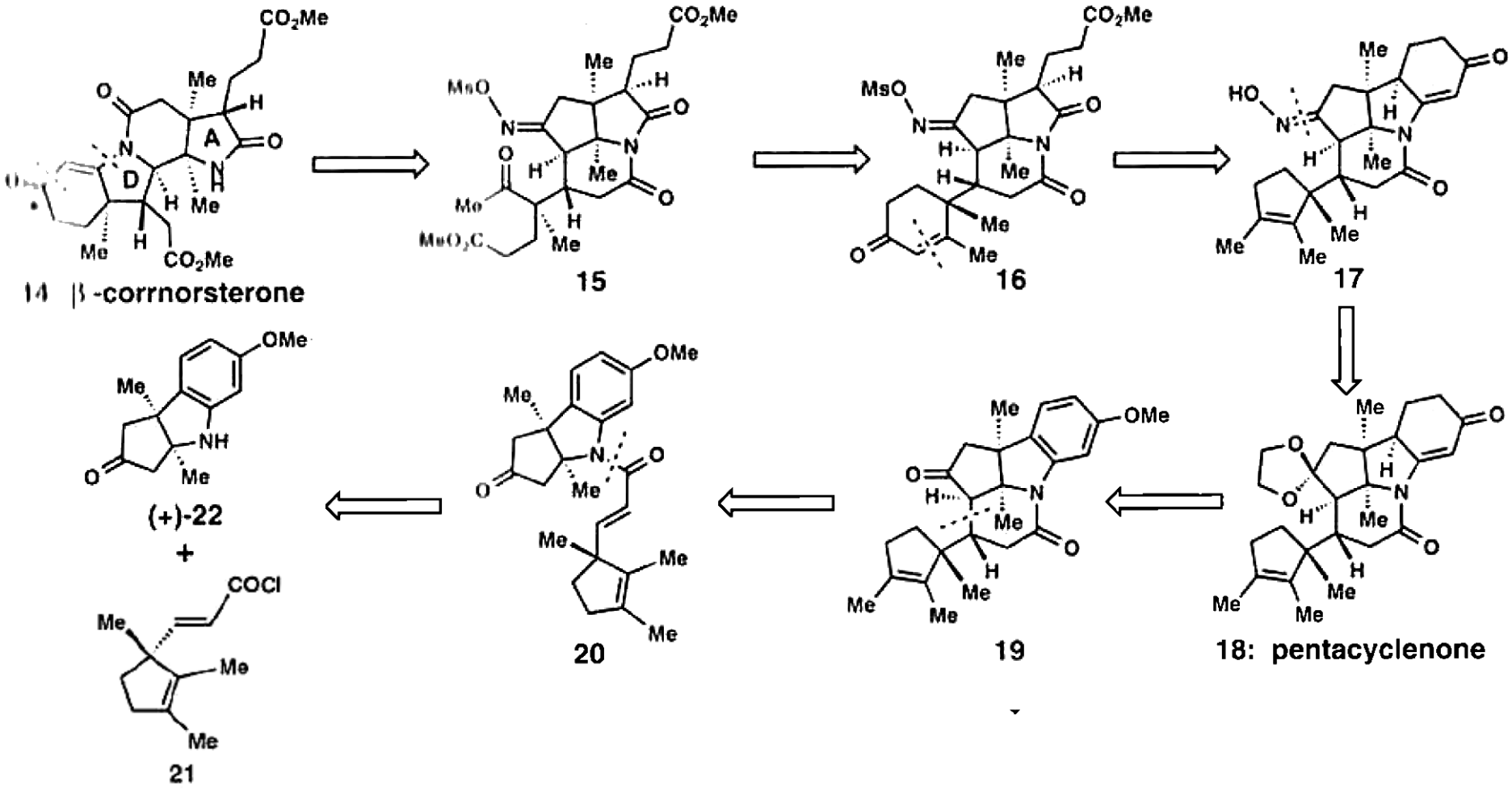
Woodward, R.B. *Pure Appl. Chem.* **1968**, 519–520

Woodward, R.B. *Pure Appl. Chem.* **1971**, 283–304

Woodward, R.B. *Pure Appl. Chem.* **1973**, 145–177

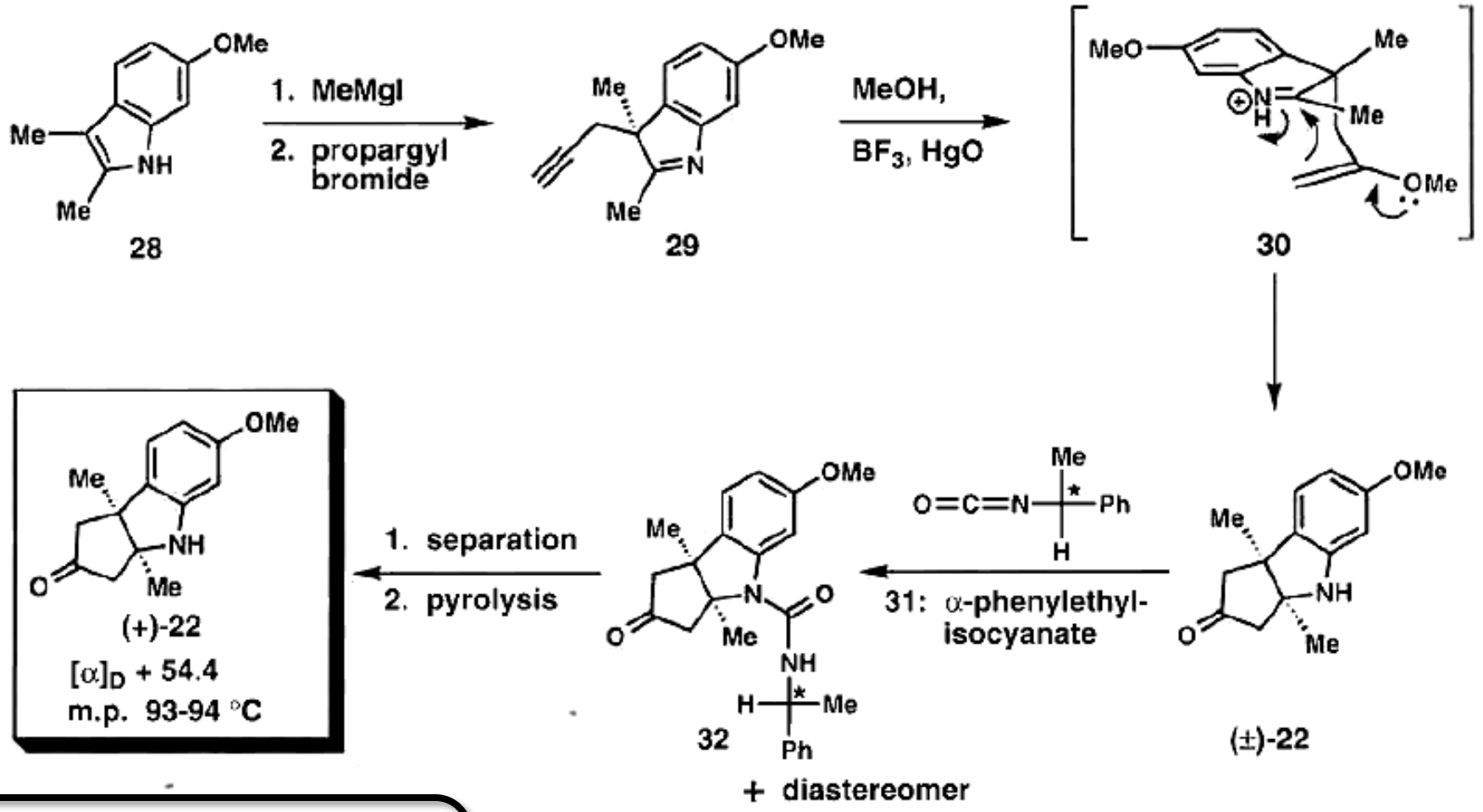
Bernhauer, K.; et al. *Helv. Chim. Acta* **1960**, 704–712

β-Corrnorsterone Retrosynthetic Analysis



Woodward, R.B. *Pure Appl. Chem.* **1968**, 519–520

Woodward's Western Fragment Synthesis

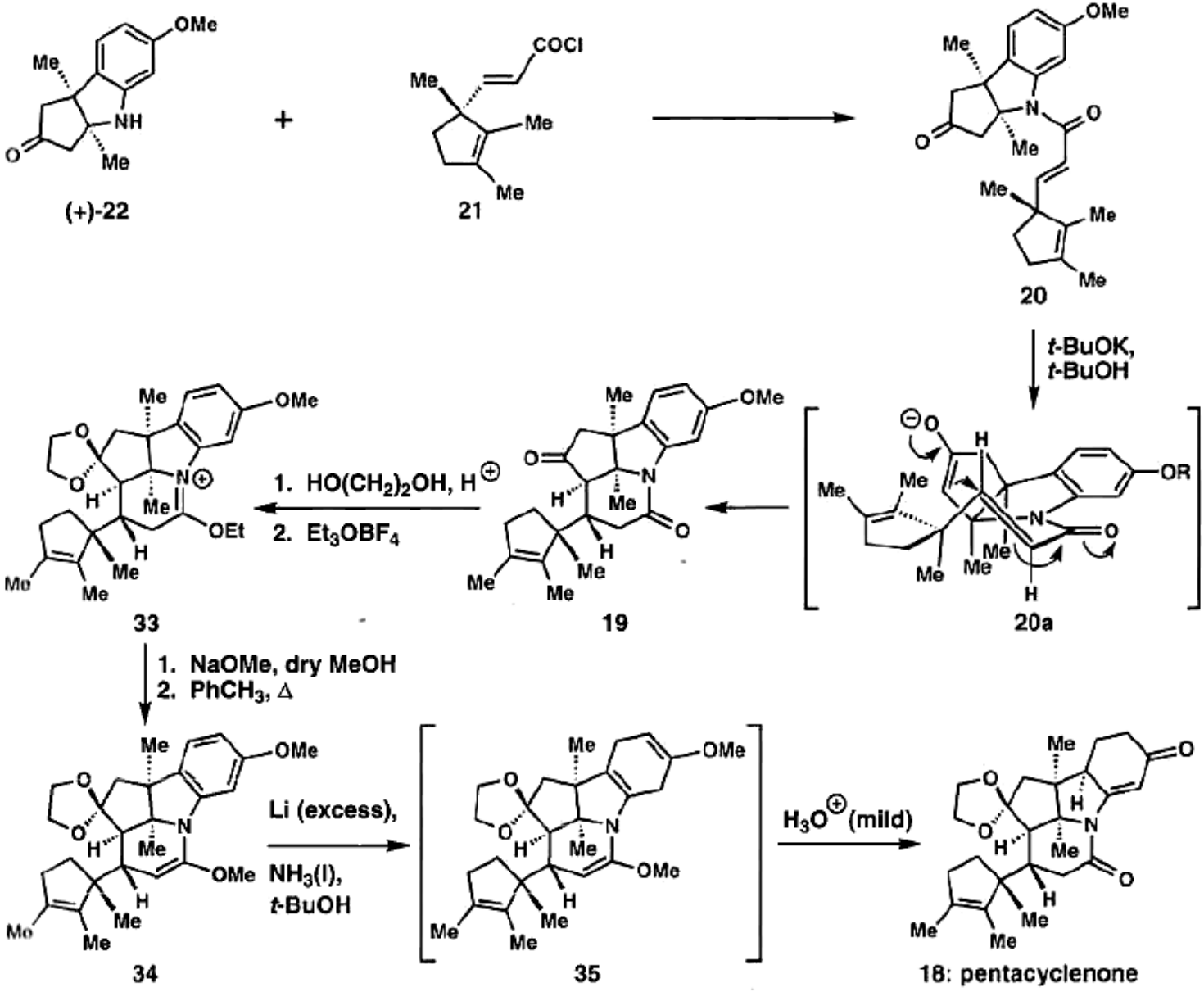


The (–)-enantiomer was used to test synthetic routes

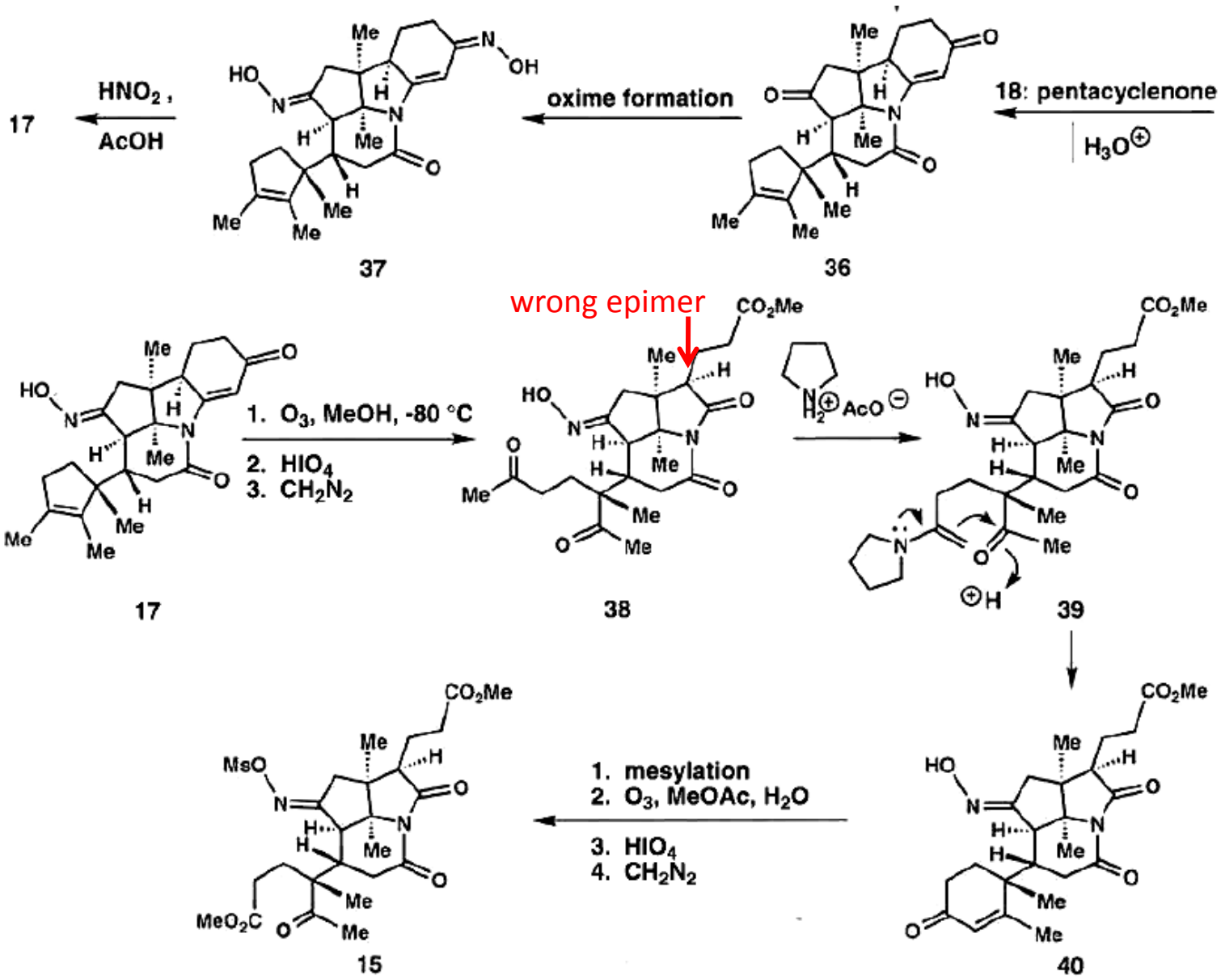
"our experience has been such that this is just about the only kind of model study which we regard as wholly reliable" –R. B. Woodward

Woodward, R.B. *Pure Appl. Chem.* **1968**, 519–520

Preparation of Pentacyclenone

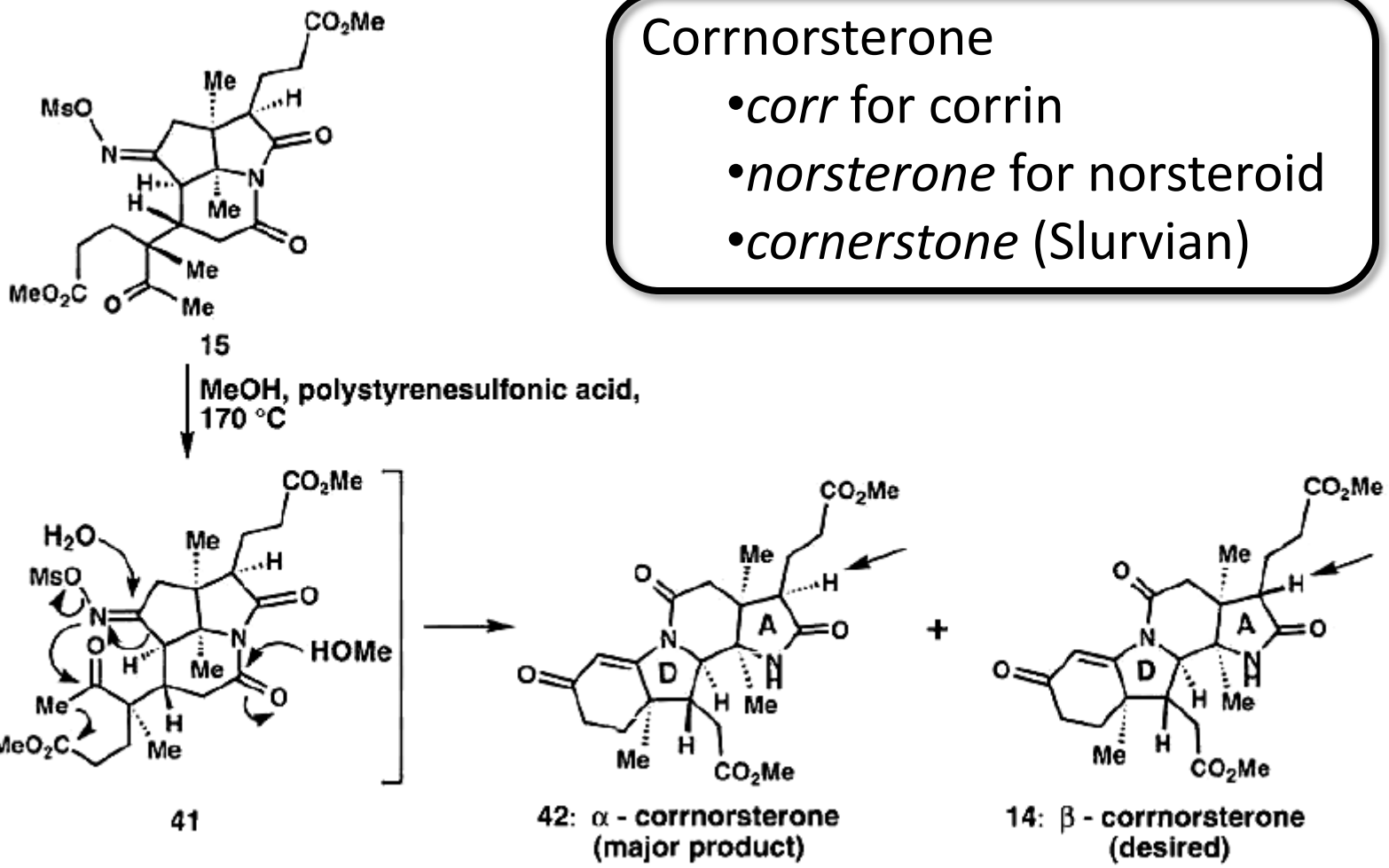


Preparation of Beckmann Precursor

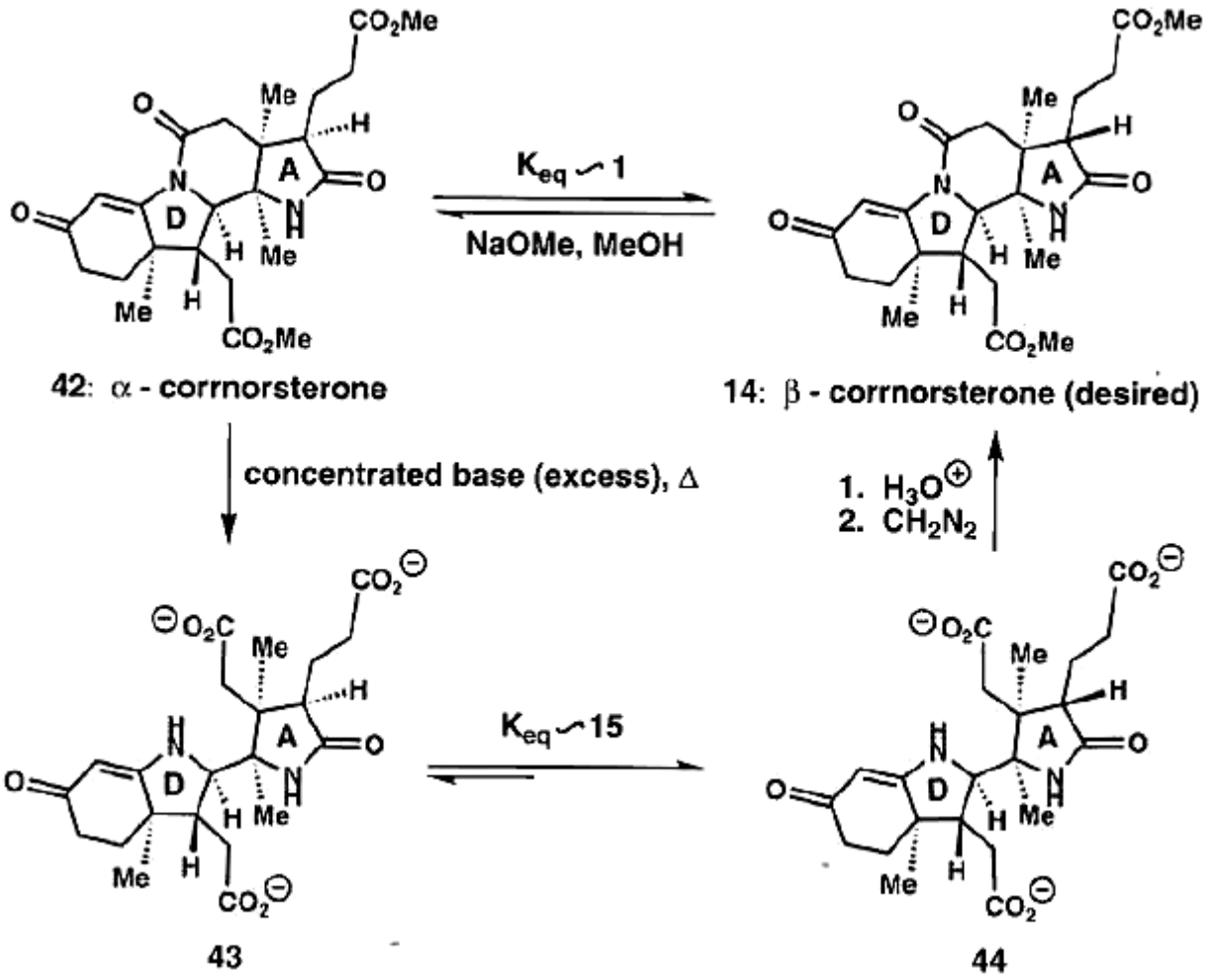


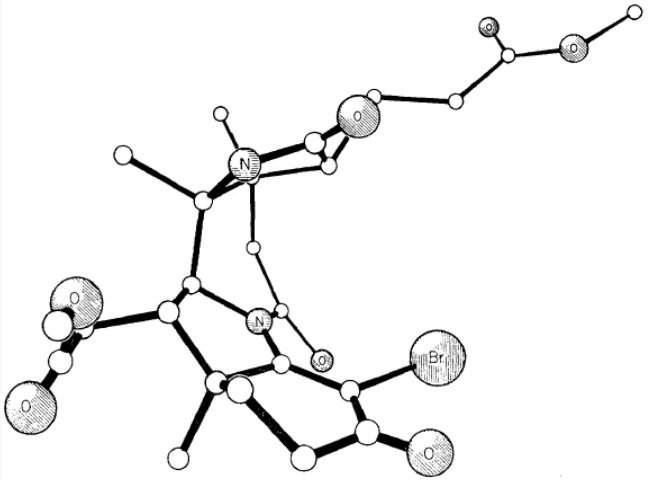
Preparation of β-Corrnorsterone

Corrnorsterone
- *corr* for corrin
- *norsterone* for norsteroid
- *cornerstone* (Slurvian)



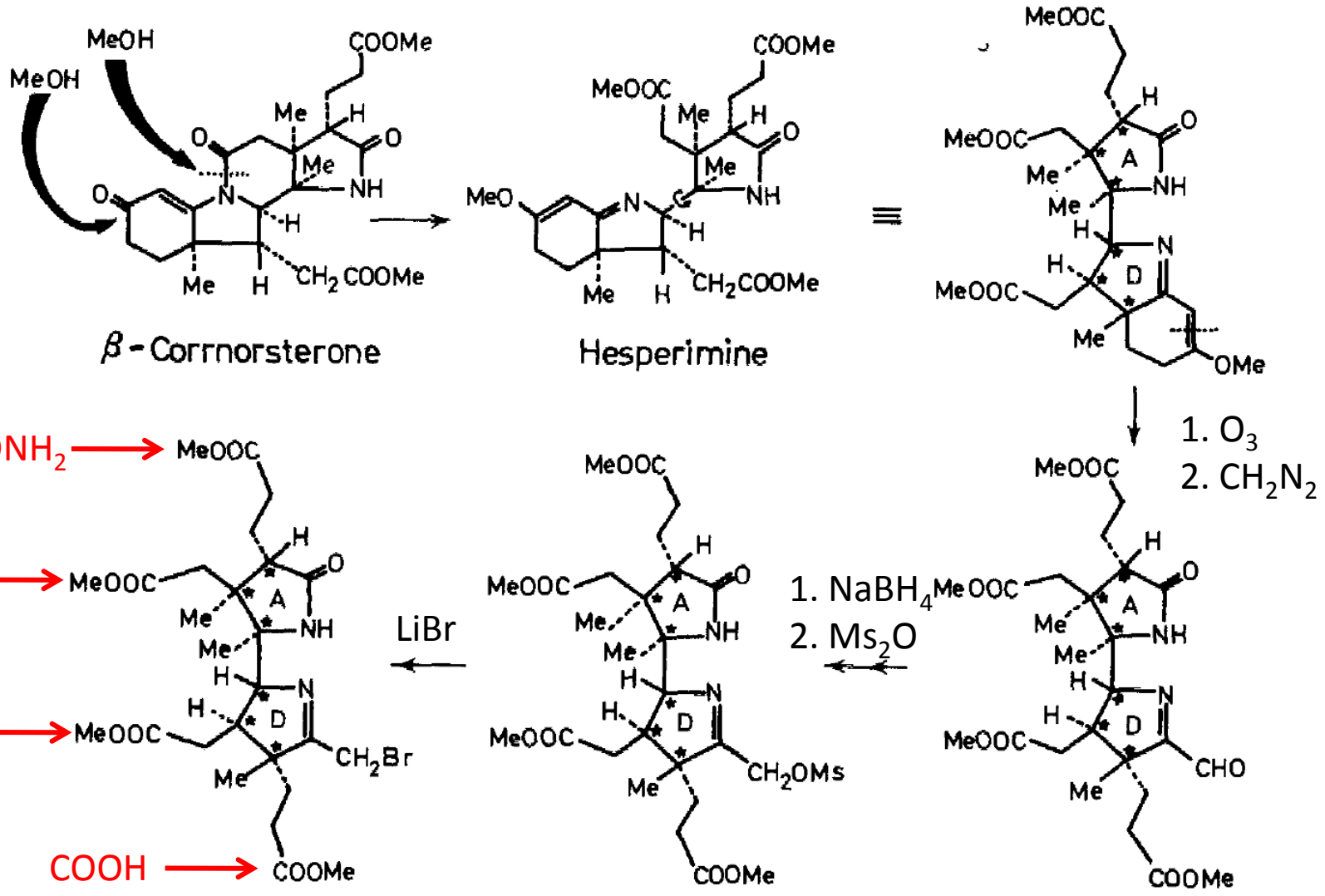
Equilibration of Corrnorsterones



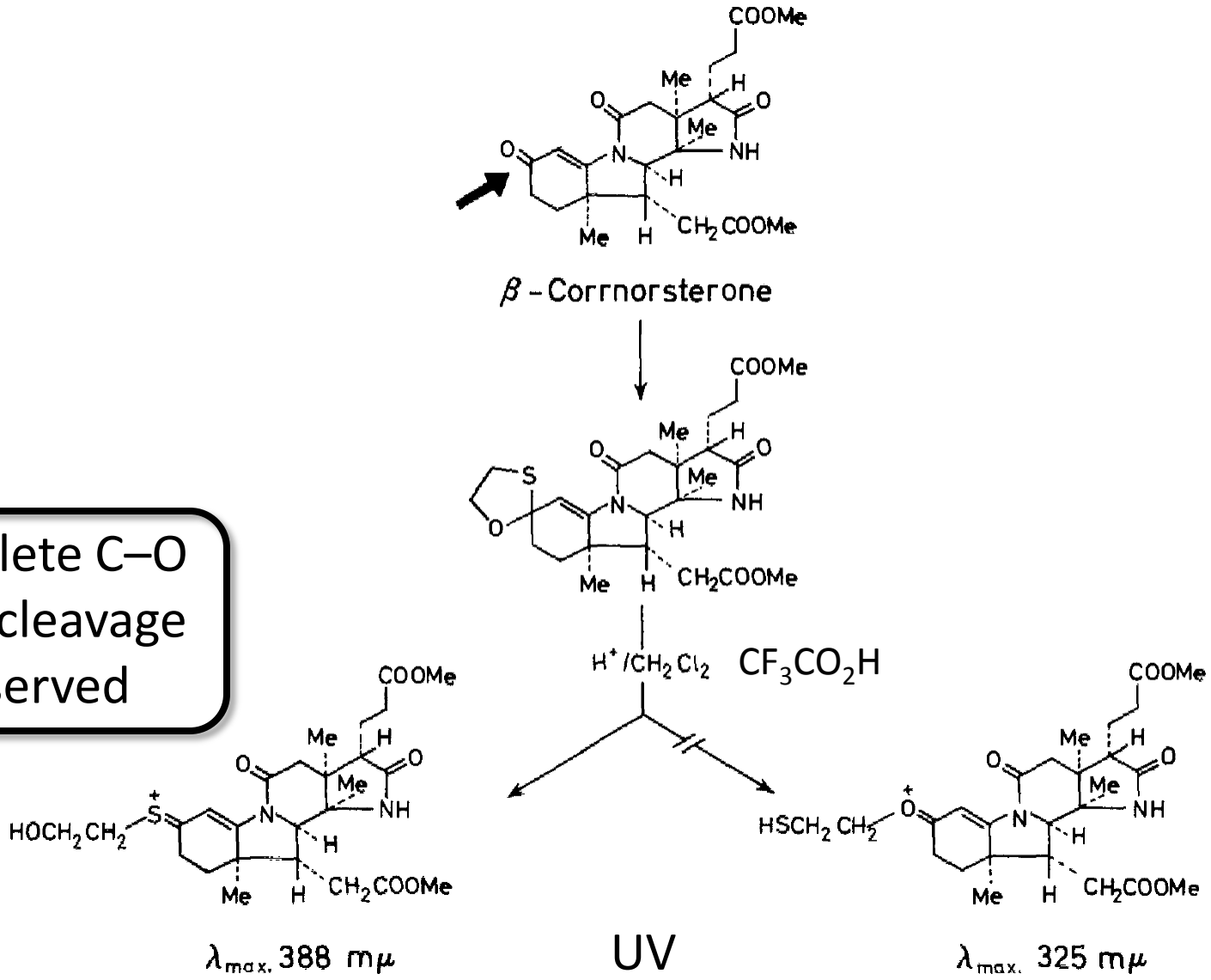


Brominated
ent-β-corrnorsterone

First Generation A-D Ring Synthesis

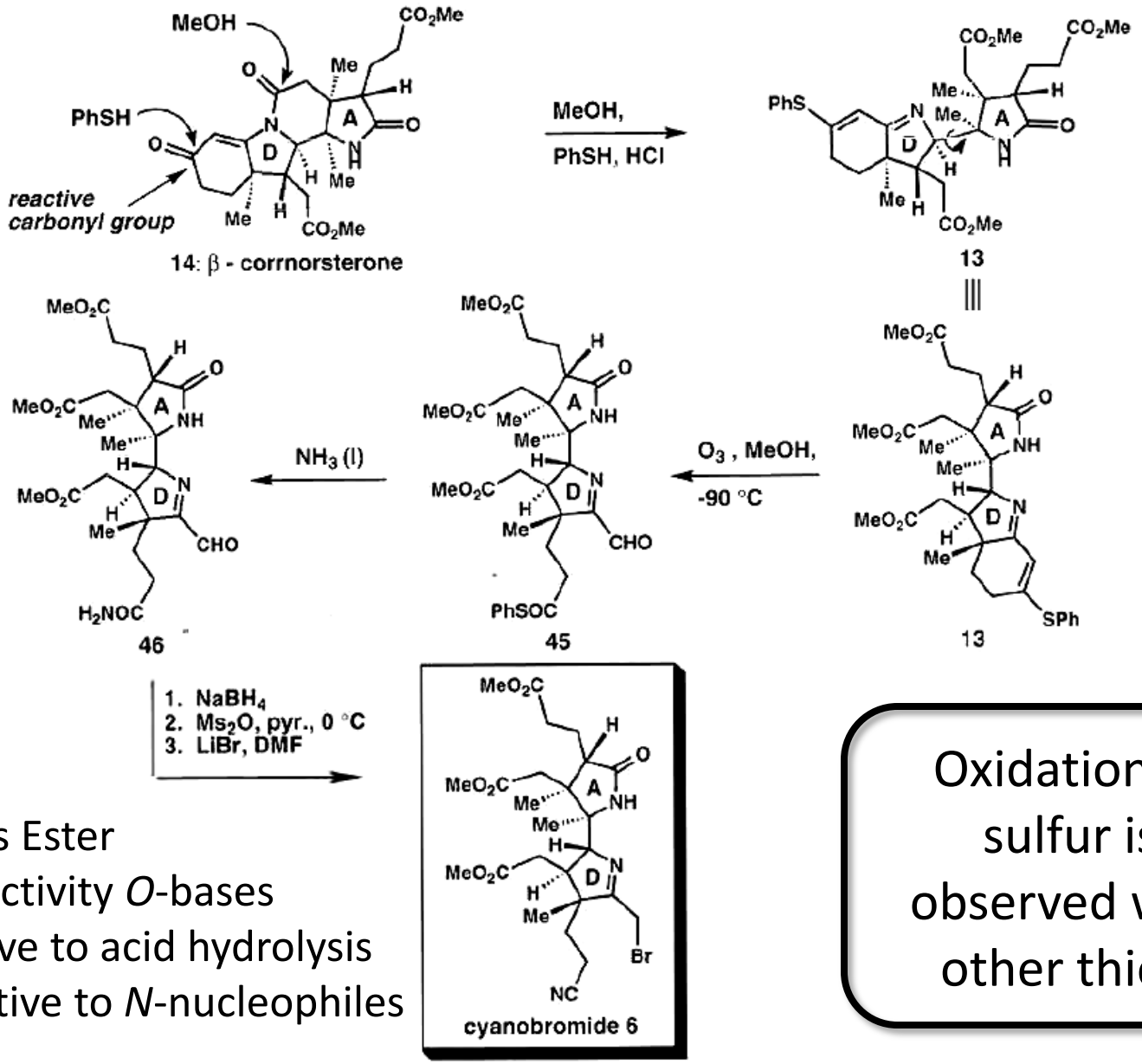


The Solution to Side-Chain Differentiation



Complete C–O bond cleavage observed

Preparation of A-D Ring Cyanobromide

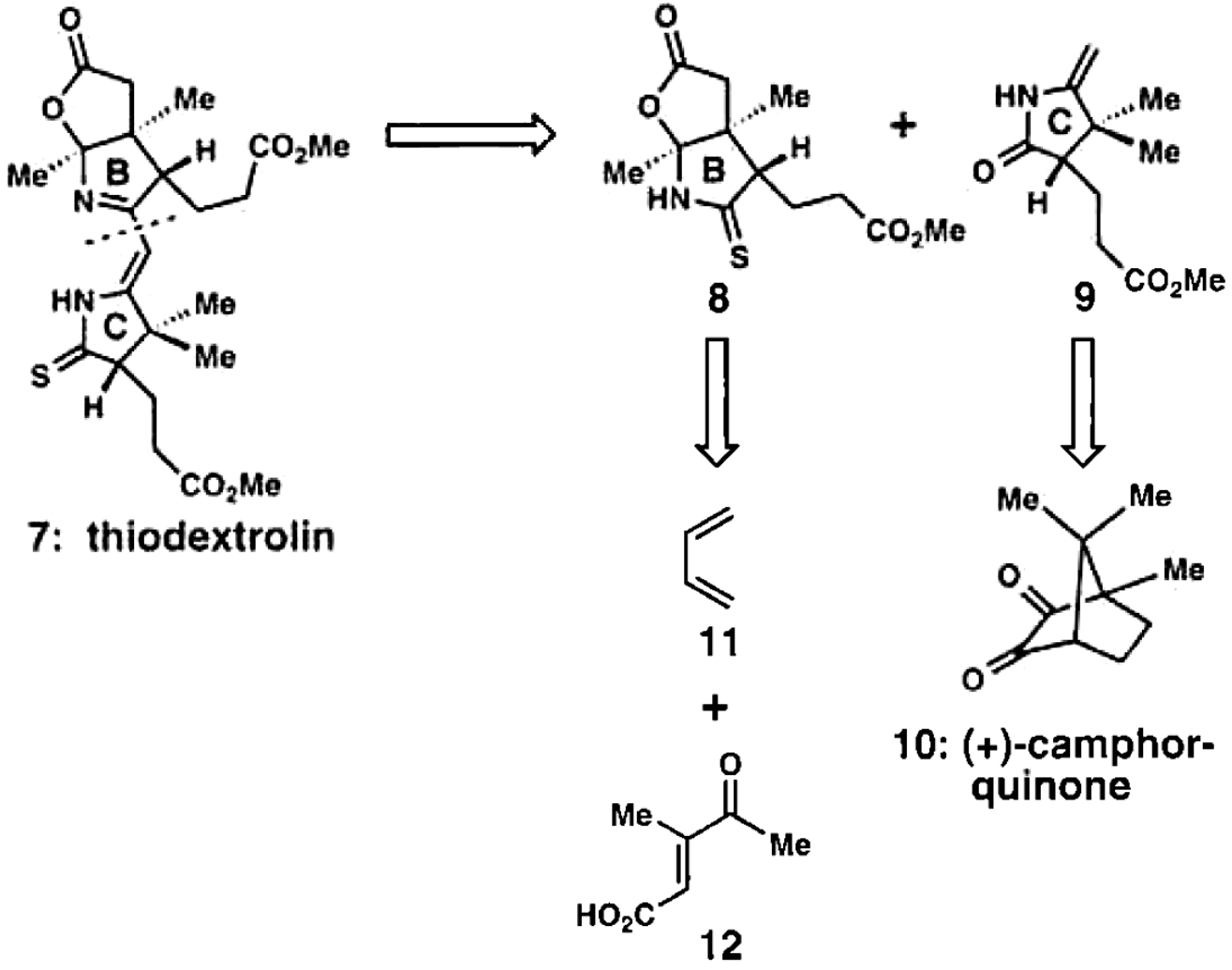


Thioester vs Ester

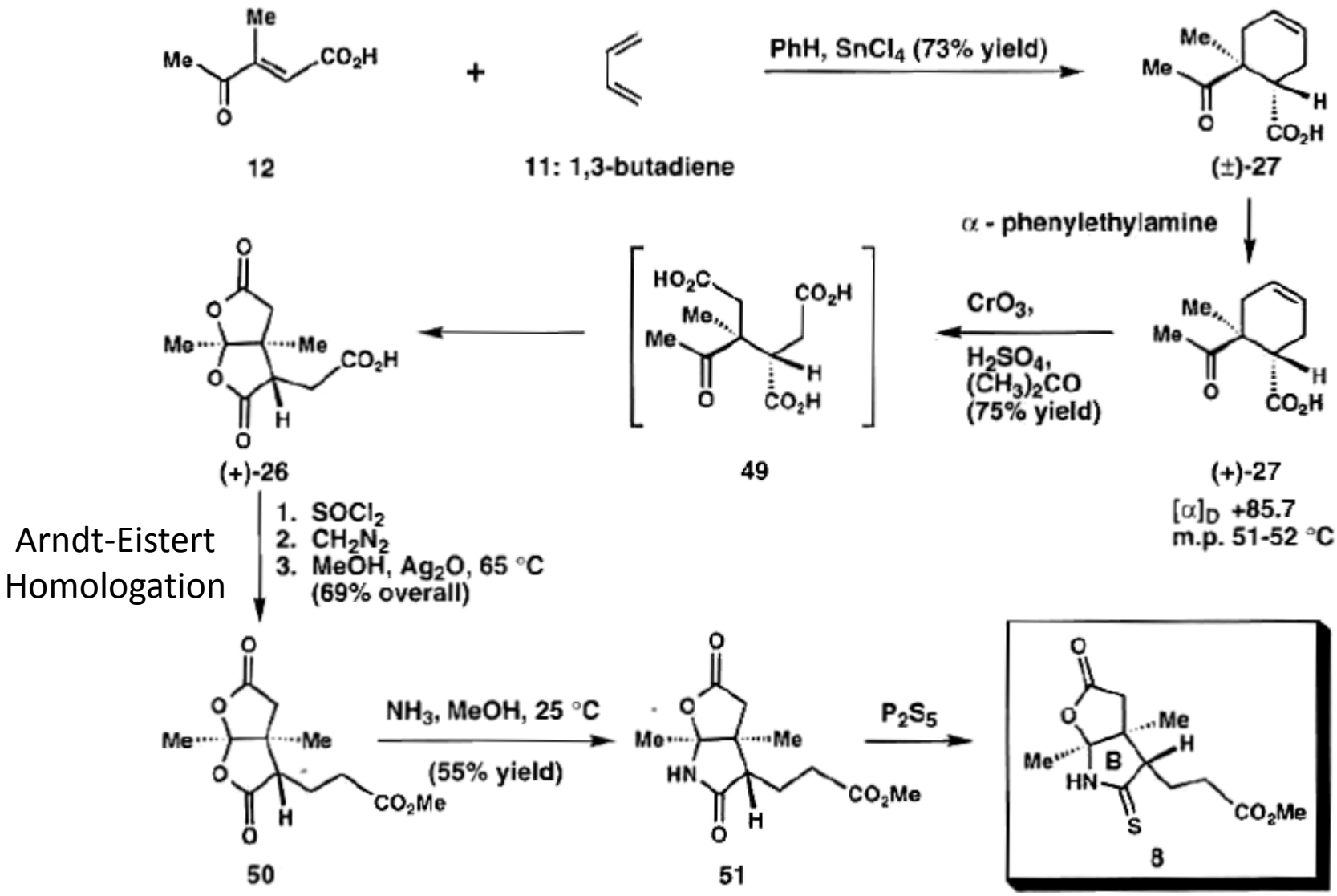
- Similar reactivity *O*-bases
- Less reactive to acid hydrolysis
- More reactive to *N*-nucleophiles

Oxidation at sulfur is observed with other thiols

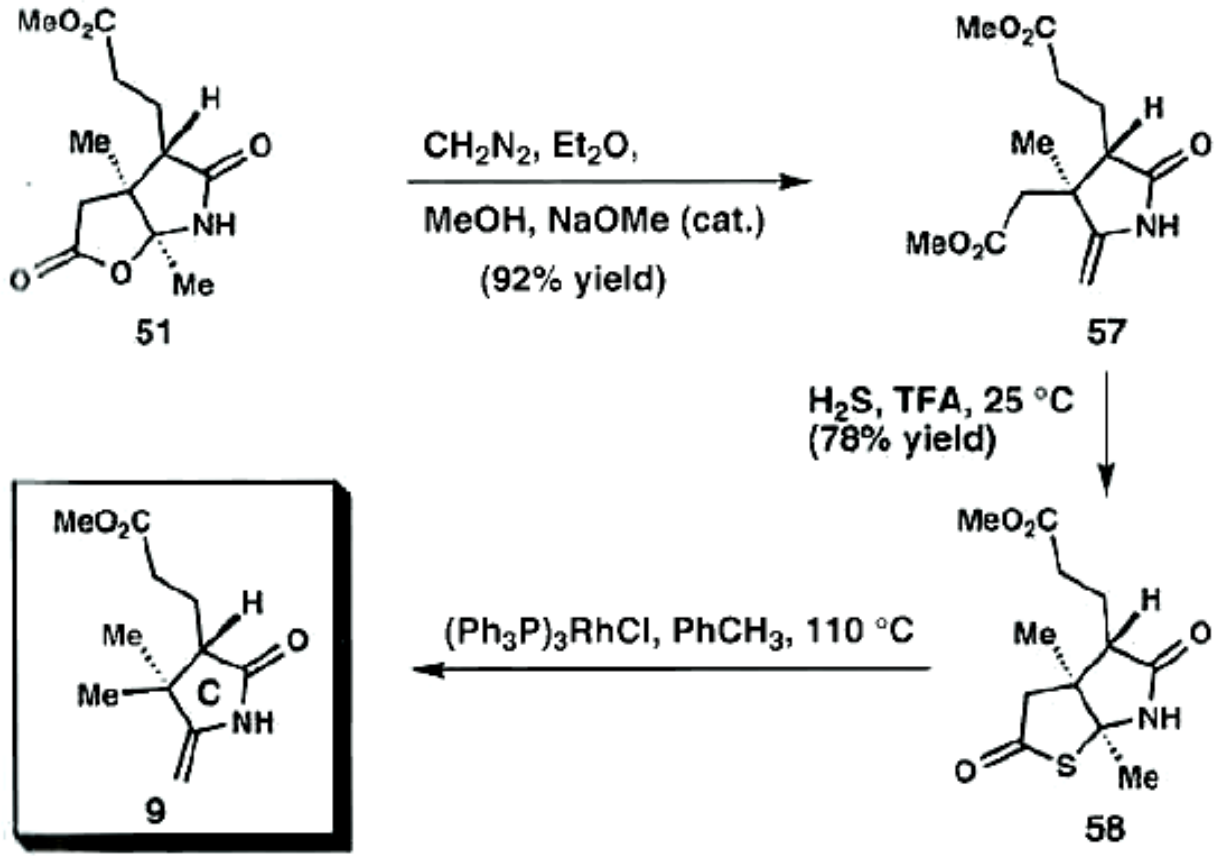
Thiodextrolin Retrosynthetic Analysis



Eschenmoser Synthesis of B-Ring

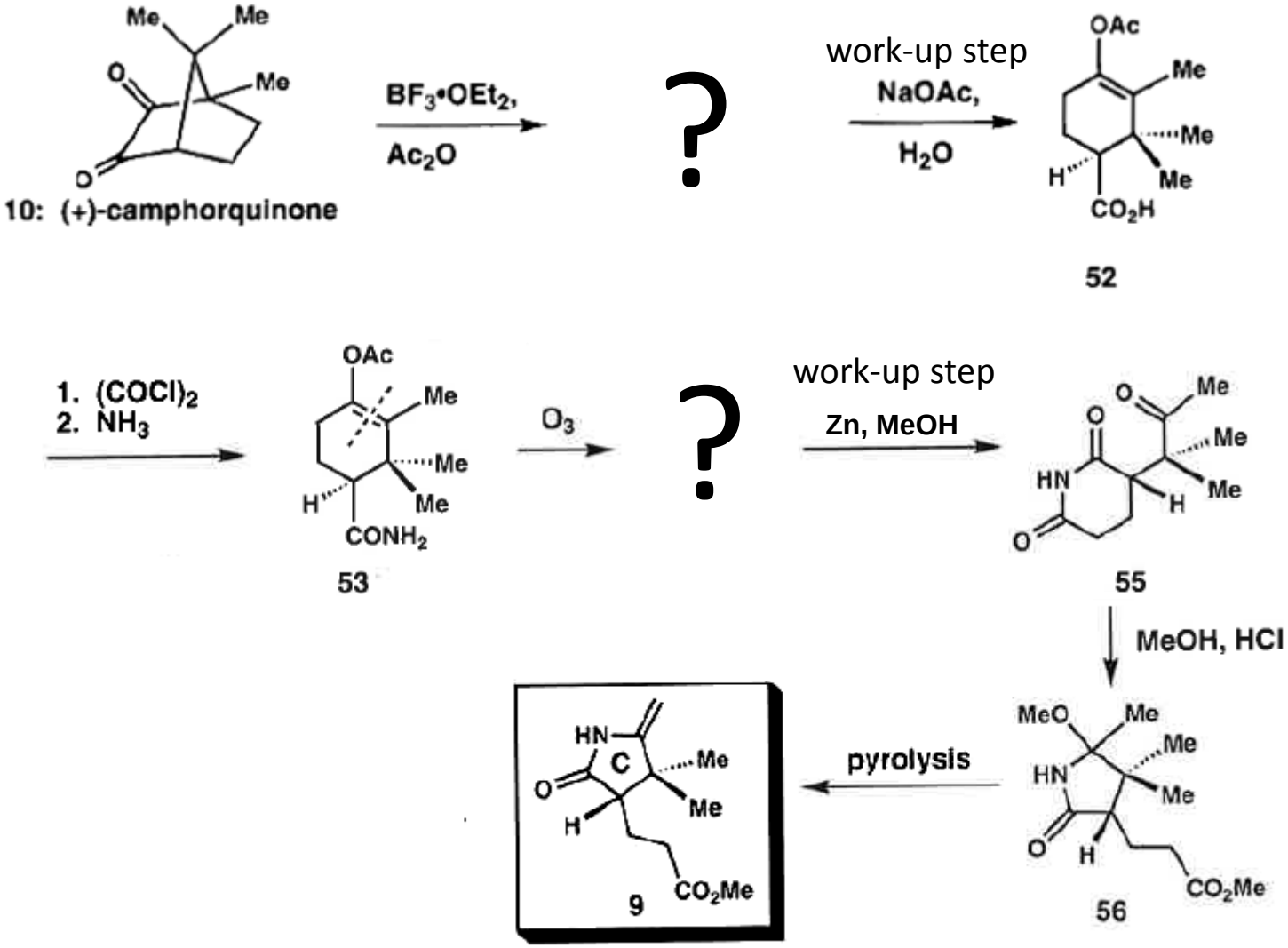


Preparation of the C-Ring



Rings B and C can be prepared from a common intermediate

Group Question



Please provide a mechanism for the formation of **52** and **55**.

Vinylogous Amidine

(a) *The condensation of enamines with iminoesters (Figure 4)*[9]

The condensation of enamines with iminoesters was successfully used in simple model systems, but failed with complex intermediates

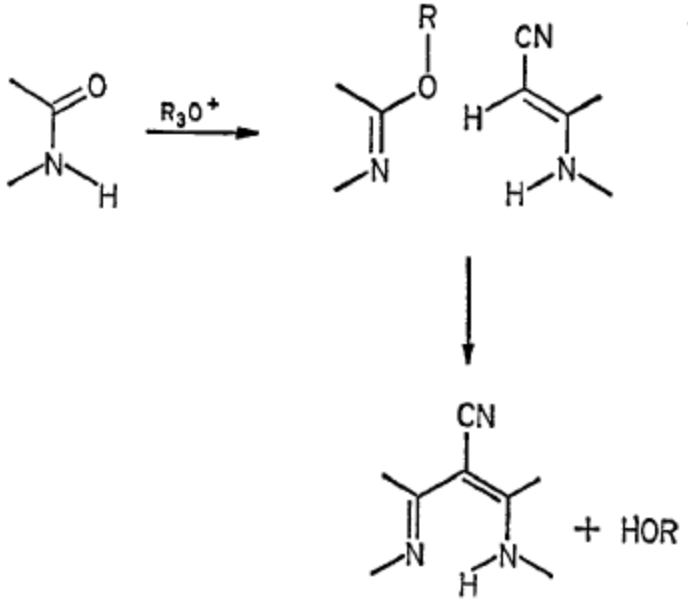
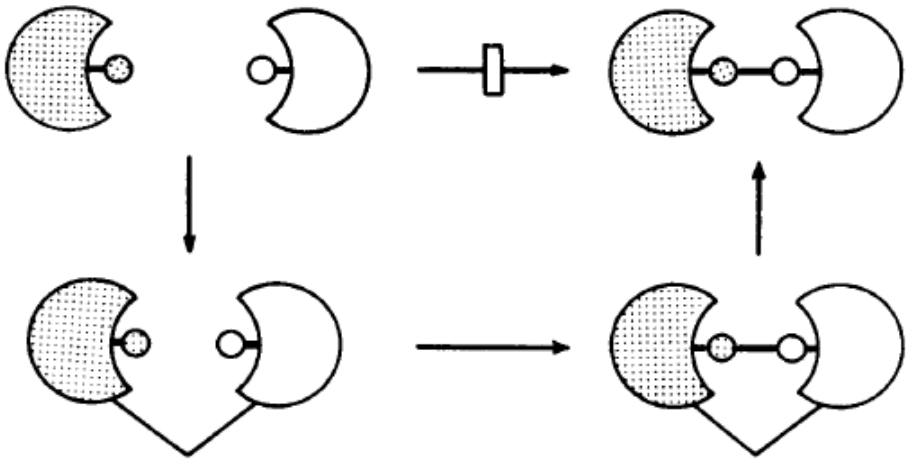


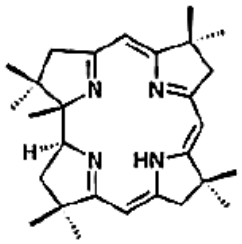
Fig. 14. "Whenever in the synthesis of complex organic molecules one is confronted with a situation where the success of an intermolecular synthetic process is thwarted by any type of kinetically controlled lack of reactivity, one should look out for opportunities of altering the structural stage in such a way that the critical synthetic step can proceed intramolecularly rather than intermolecularly."



Eschenmoser, A. *Pure Appl. Chem.* **1963**, 297–316

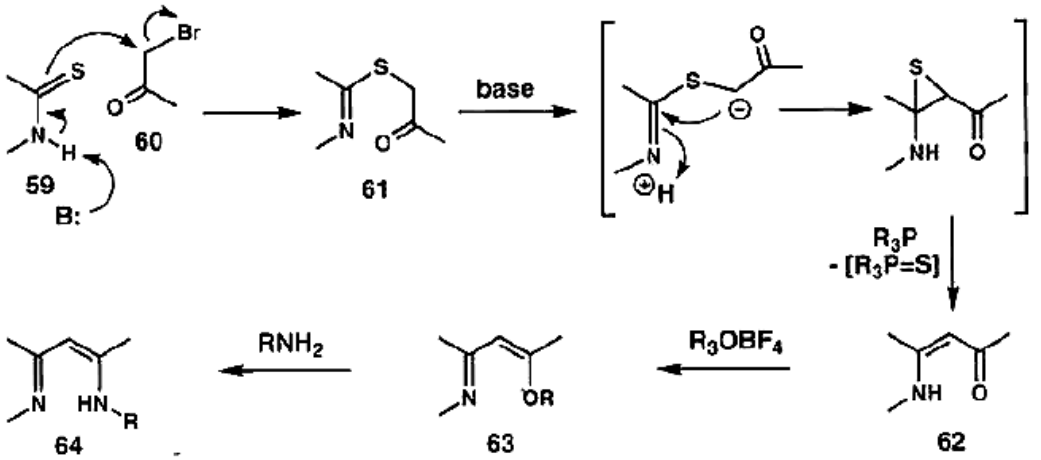
Eschenmoser, A. *Pure Appl. Chem.* **1969**, 1–23

Eschenmoser Sulfide Contraction

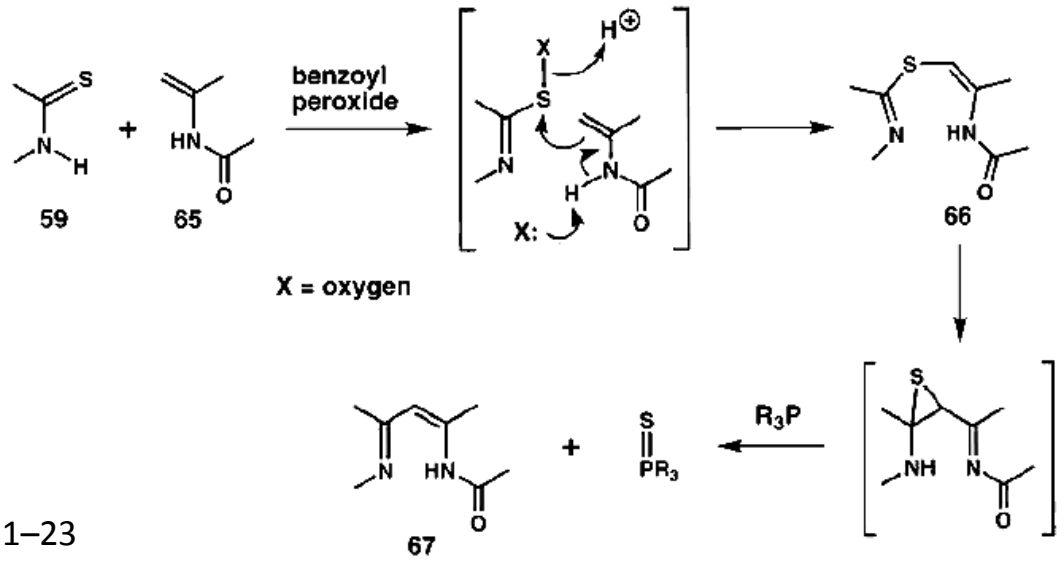


vinylogous amidine system

The sulfide contraction method via alkylative precoupling

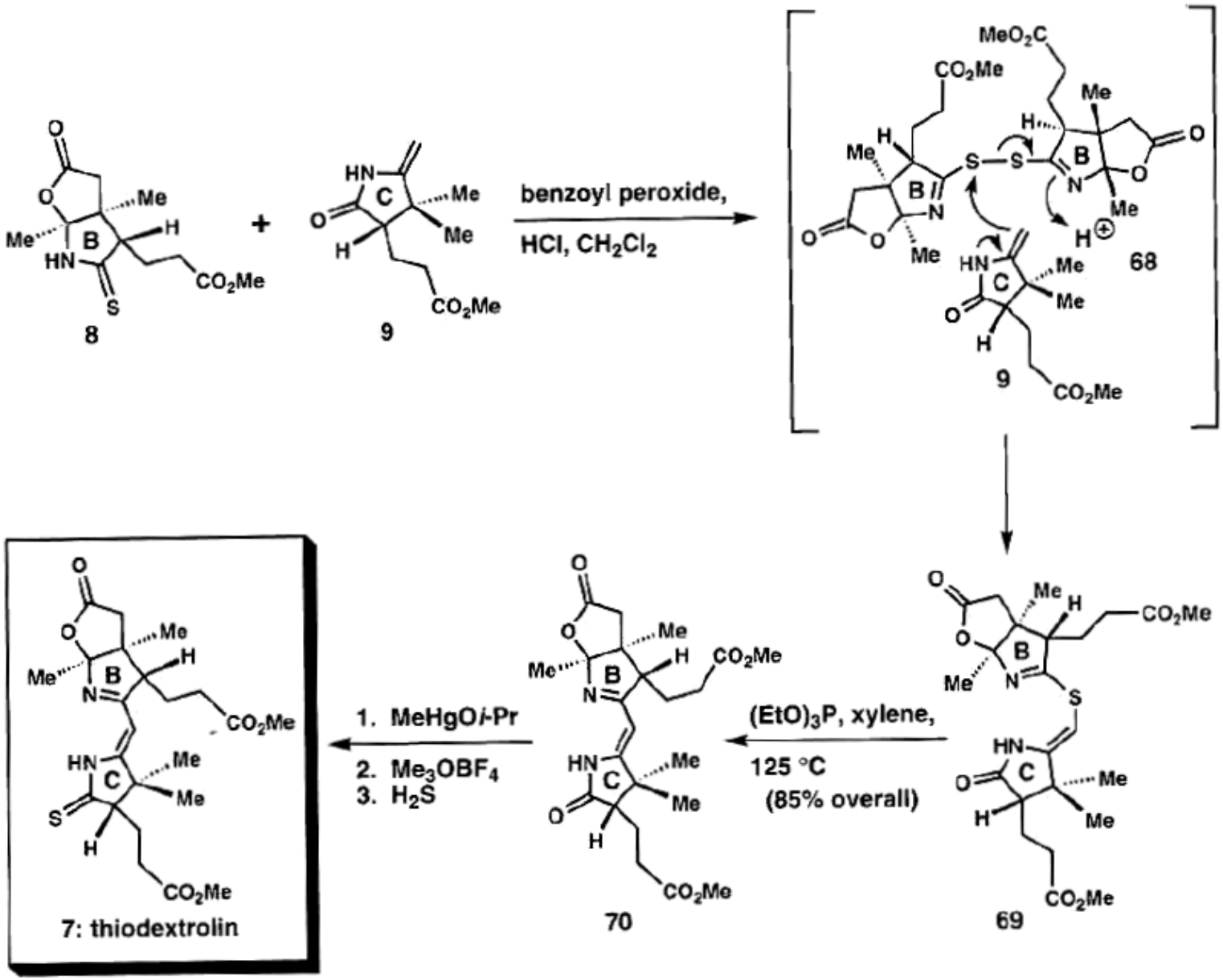


The sulfide contraction method via oxidative precoupling

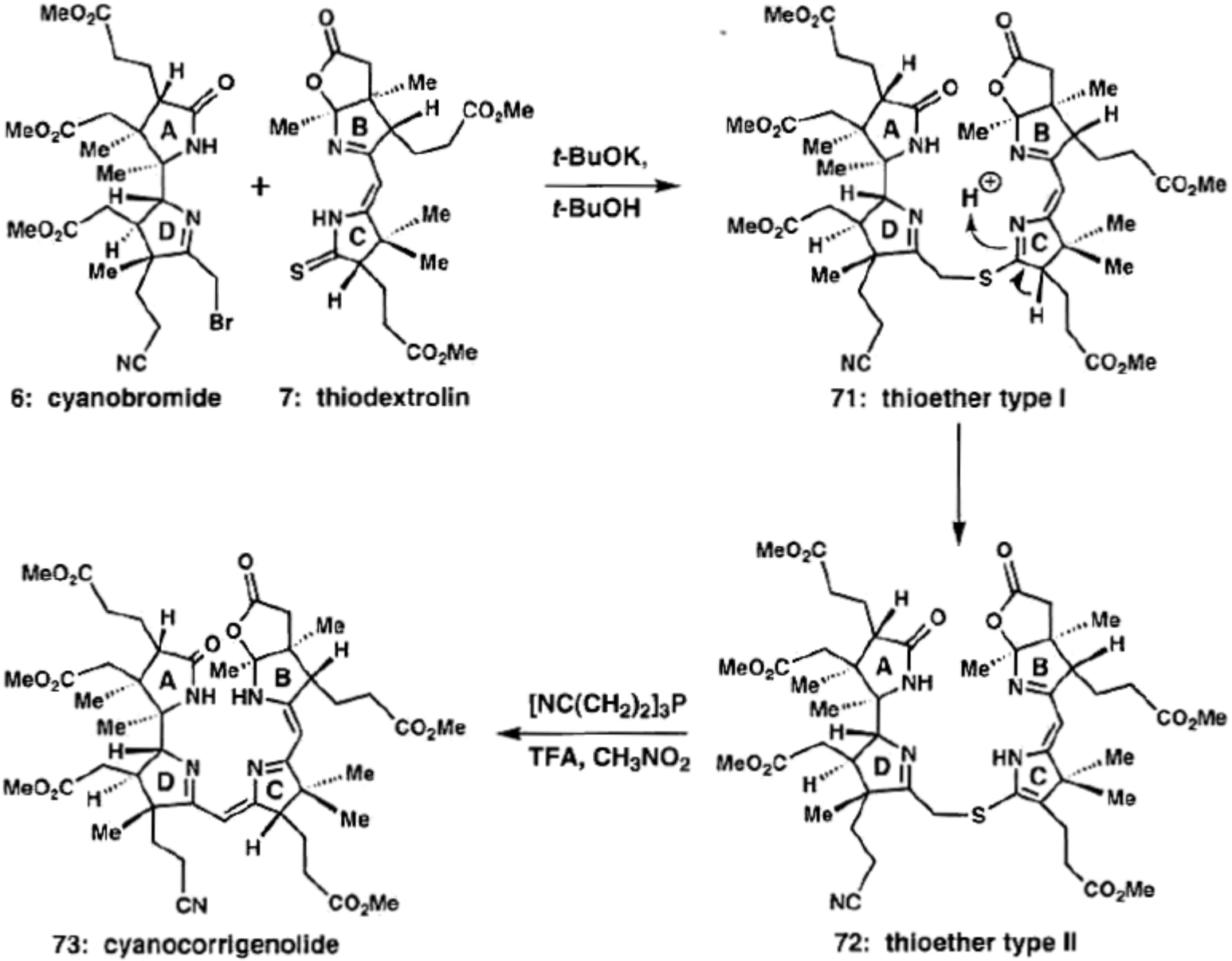


Eschenmoser, A. *Pure Appl. Chem.* **1969**, 1–23

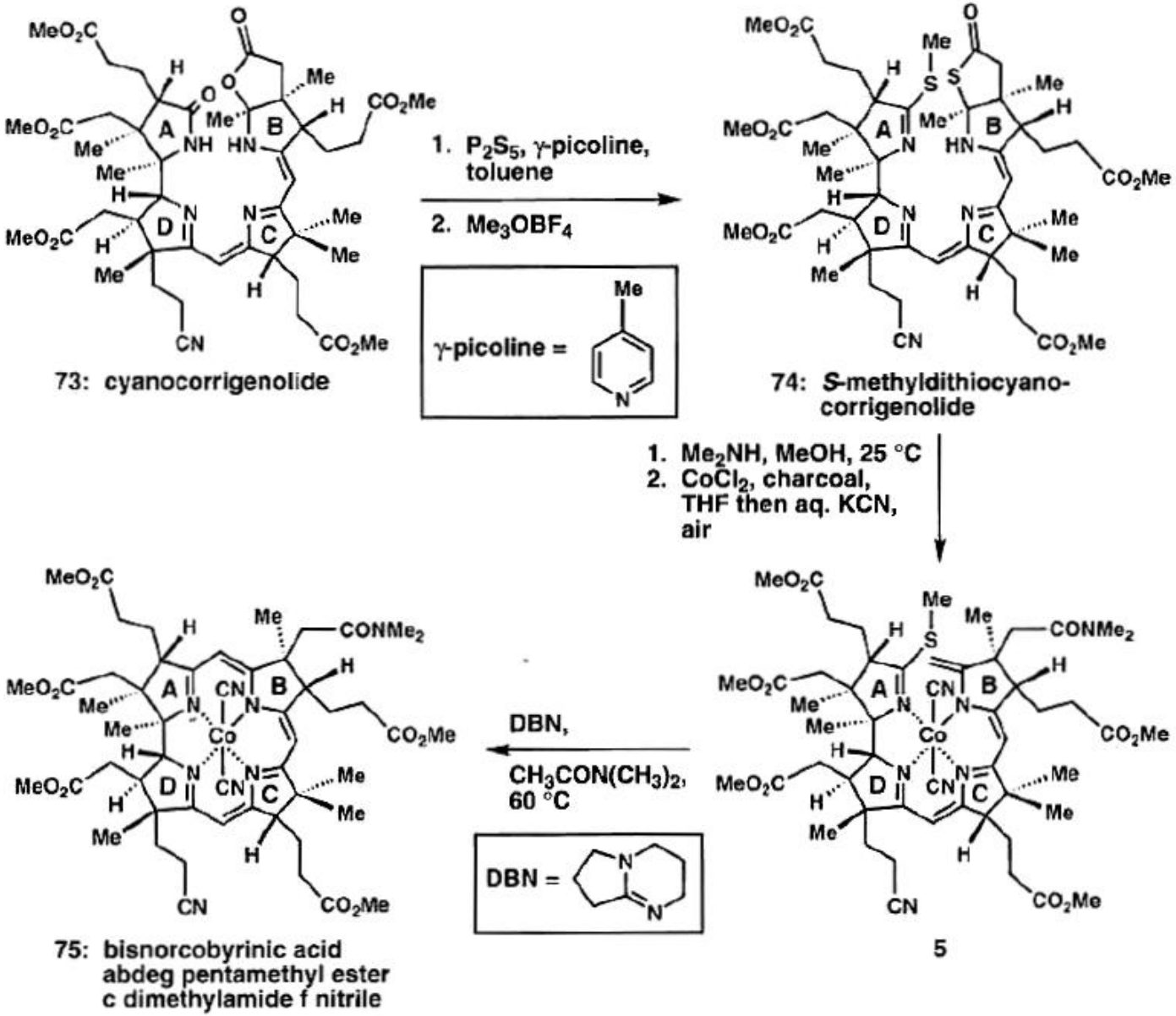
Preparation of Thiodextrolin



East Meets West



Secocorrin to Corrin



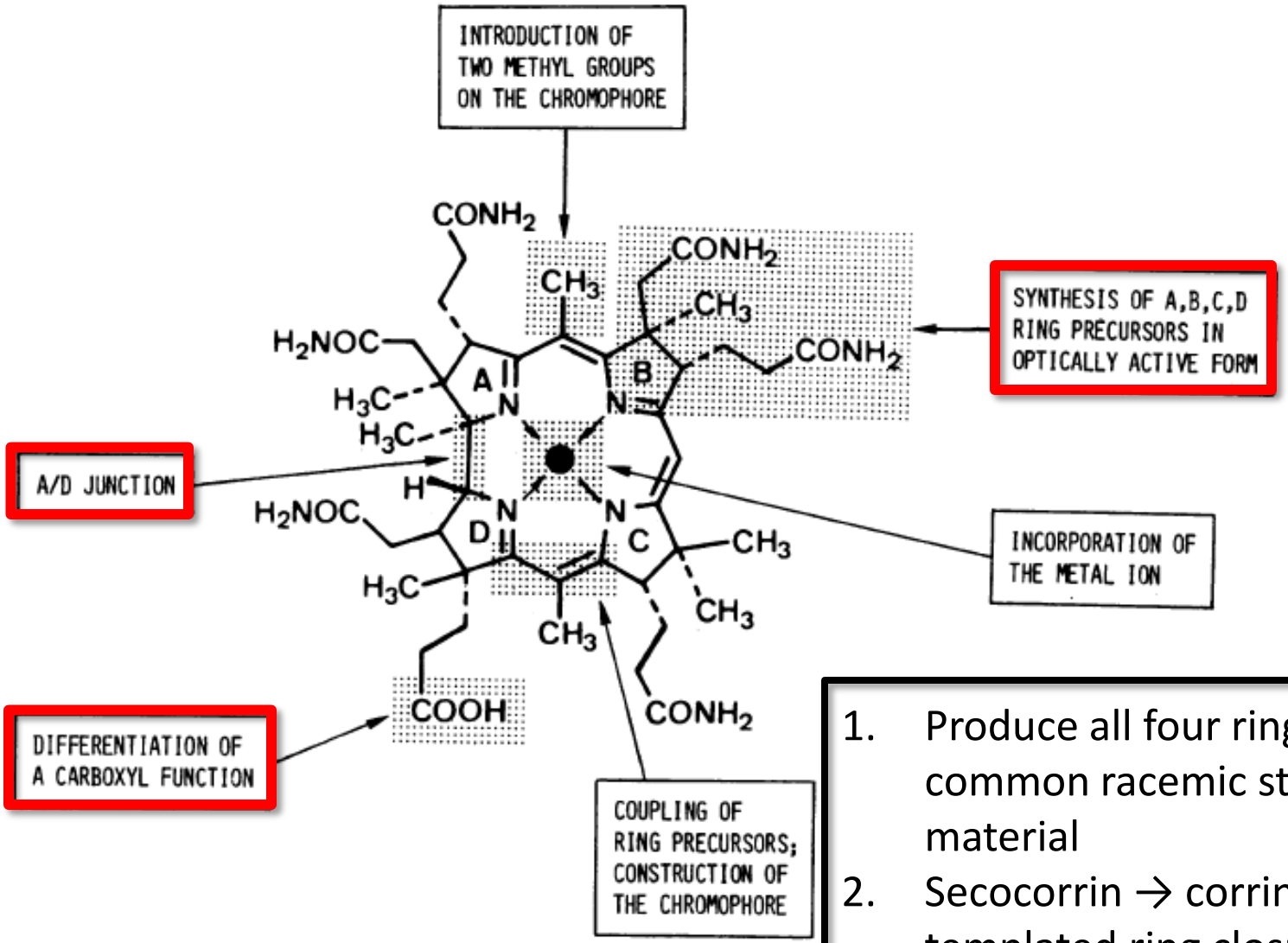
73: cyanocorrigenolide

74: *S*-methyldithiocyano-corrigenolide

75: bisnorcobyrinic acid abdeg pentamethyl ester c dimethylamide f nitrile

5

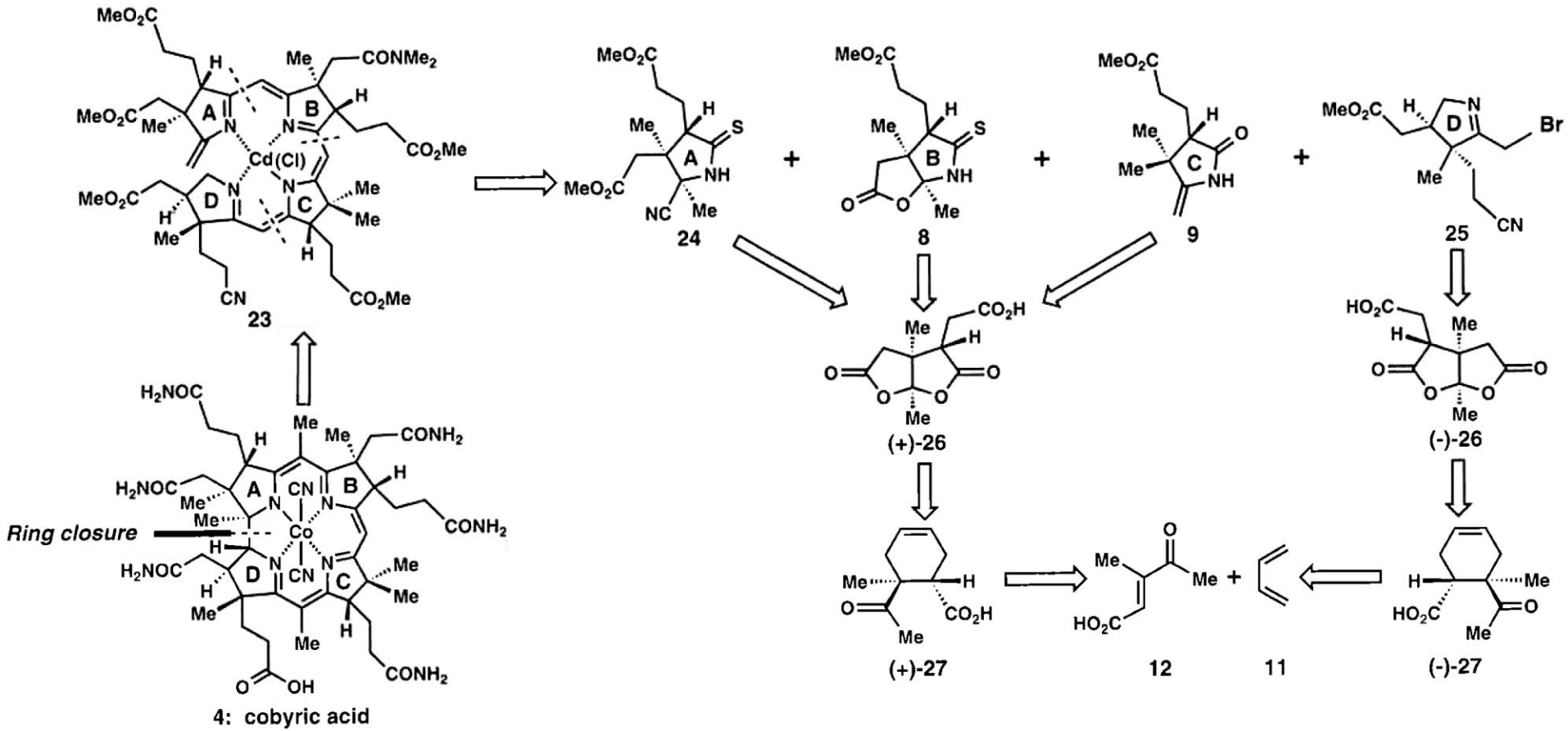
Outline of the Utopian Synthesis



1. Produce all four rings from a common racemic starting material
2. Secocorrin → corrin metal-templated ring closure

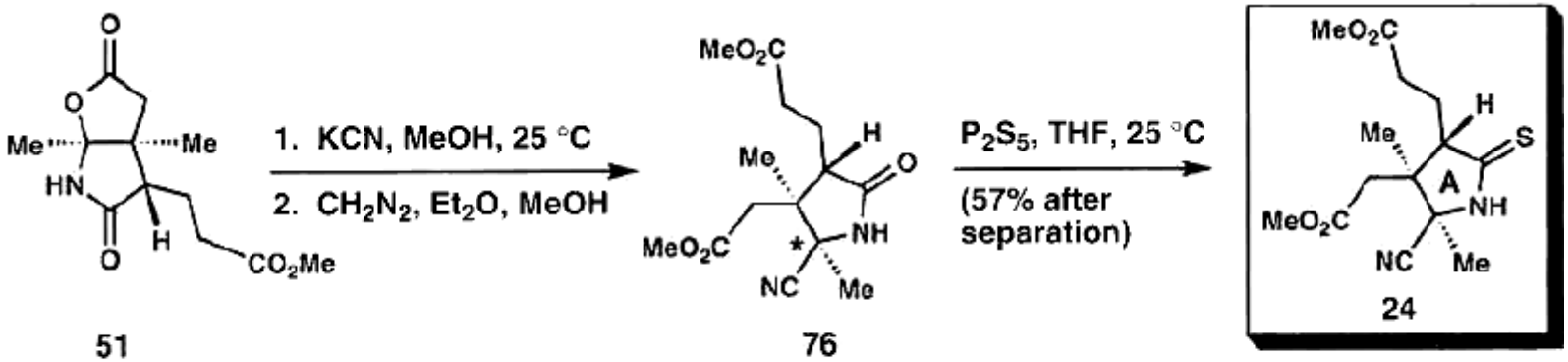
Eschenmoser, A.; et al. *Science* **1977**, 1410–1420

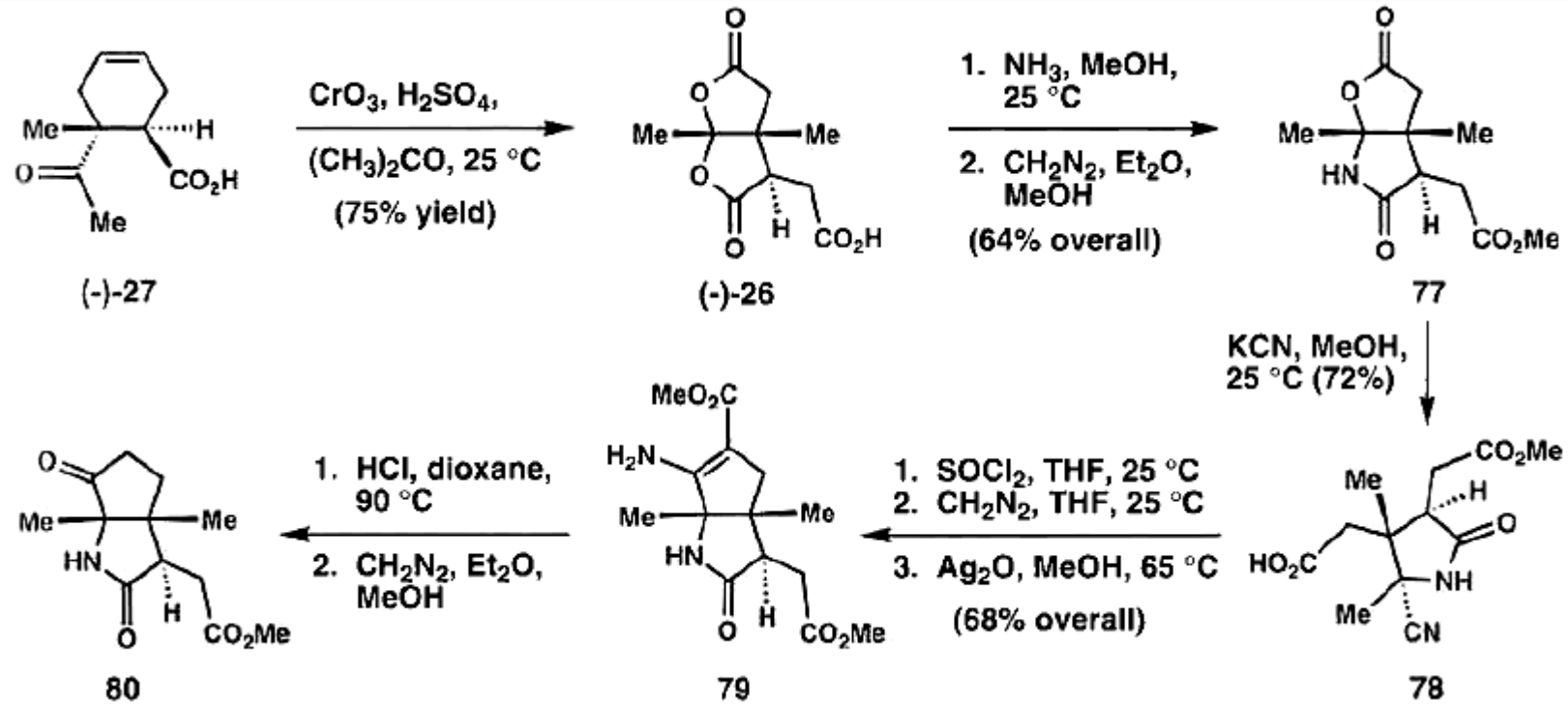
Retrosynthetic Analysis



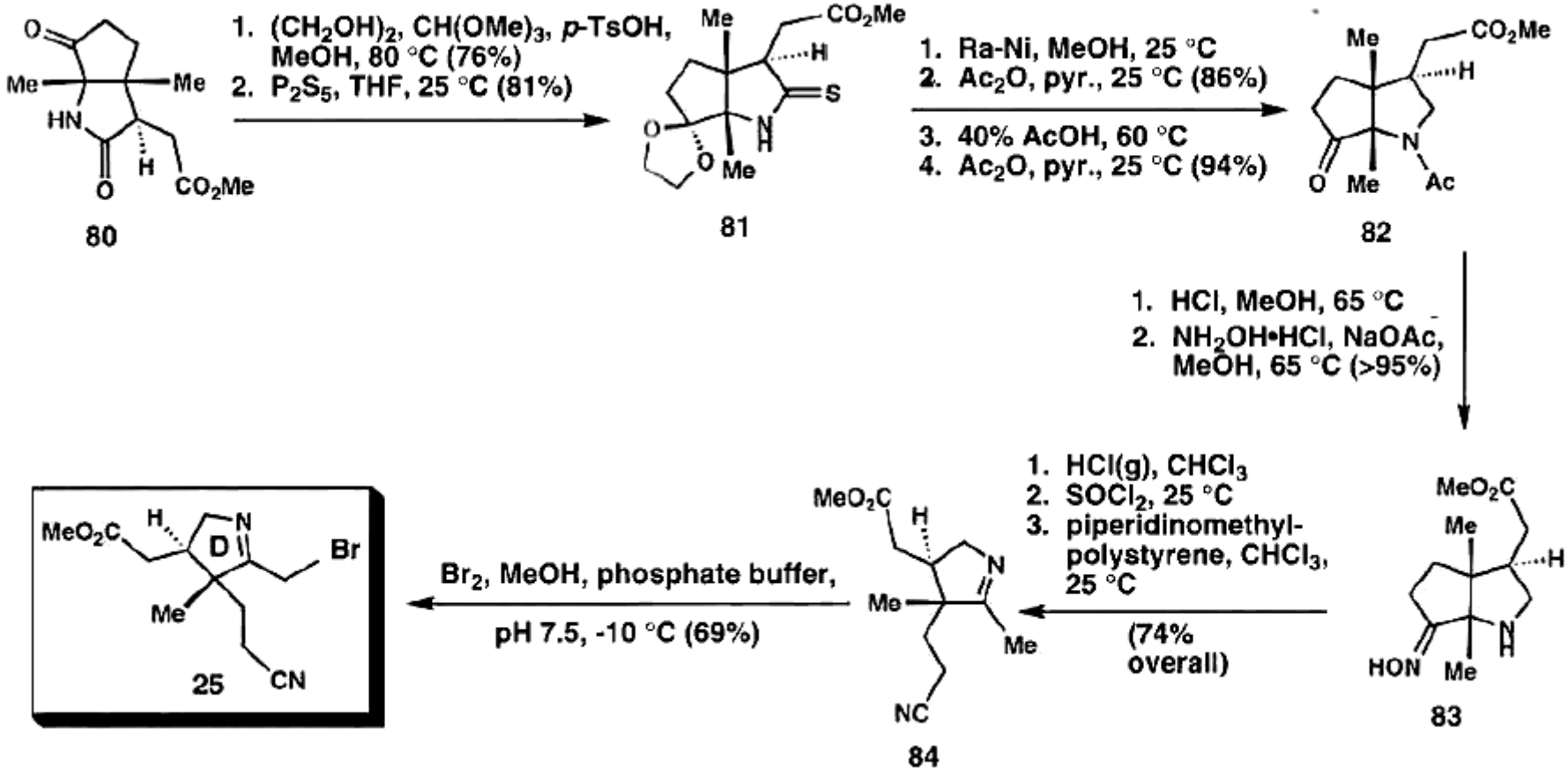
Eschenmoser, A.; et al. *Science* **1977**, 1410–1420

Synthesis of the A-Ring

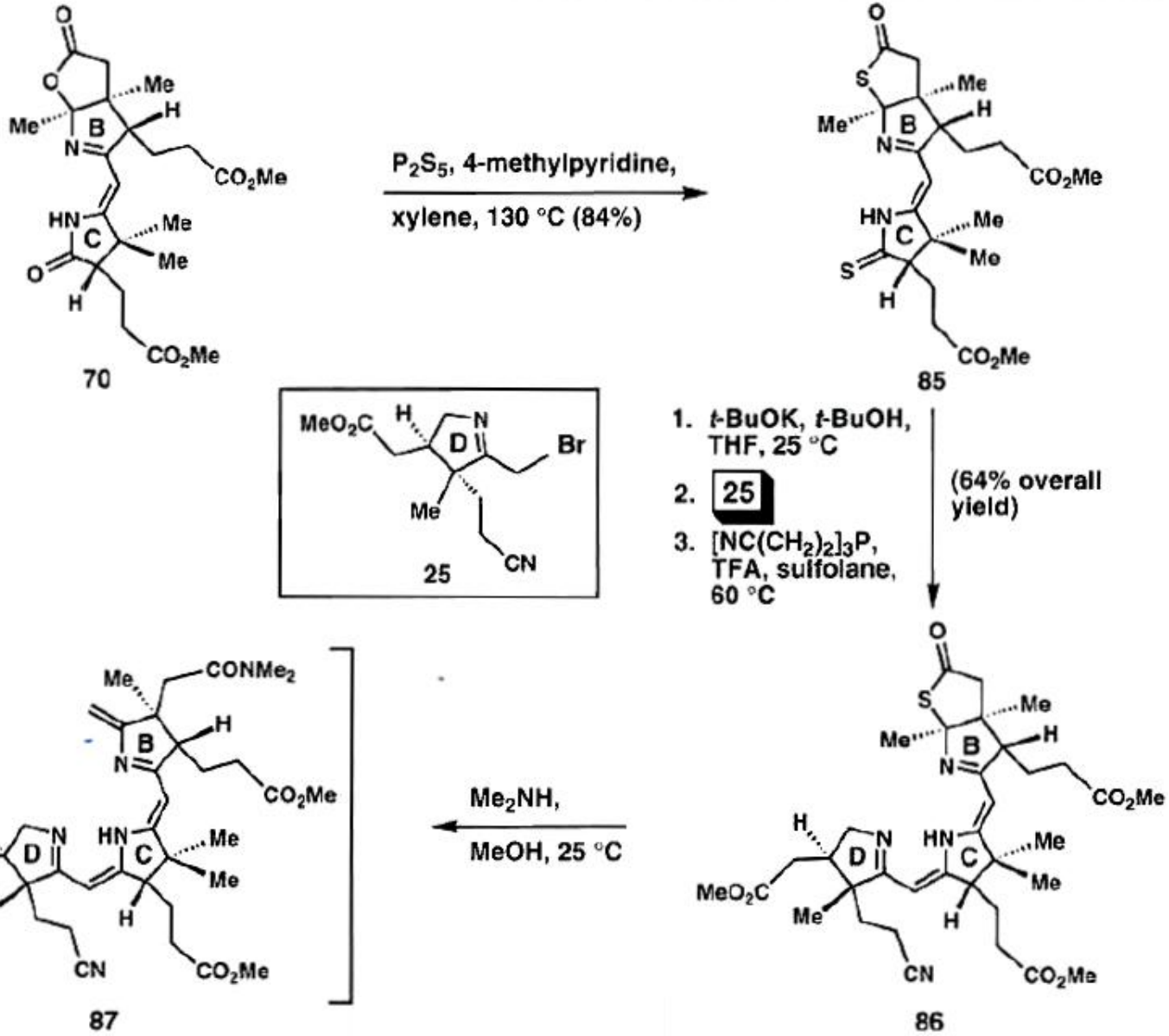




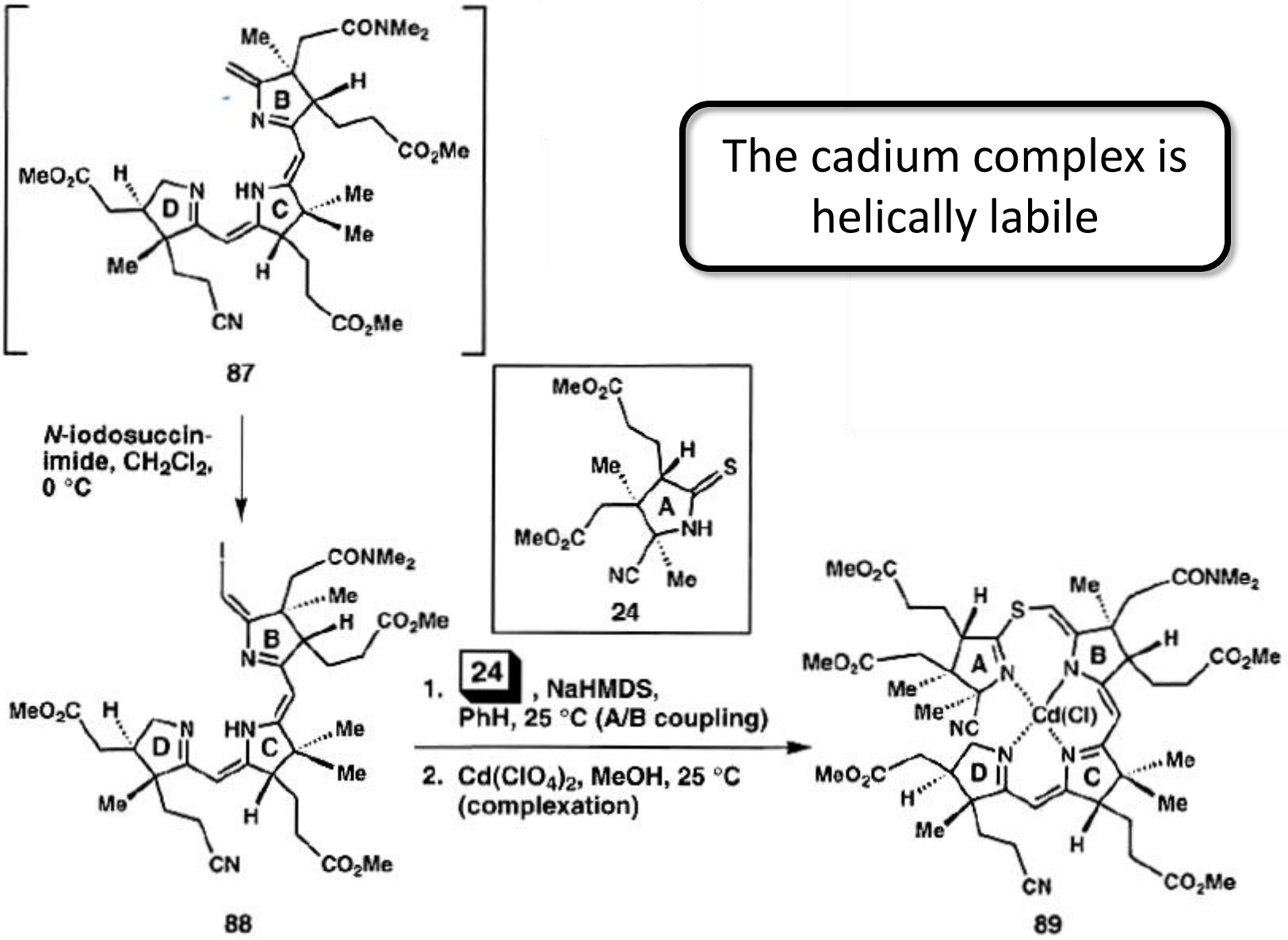
Synthesis of the D-Ring



Attachment of D-Ring

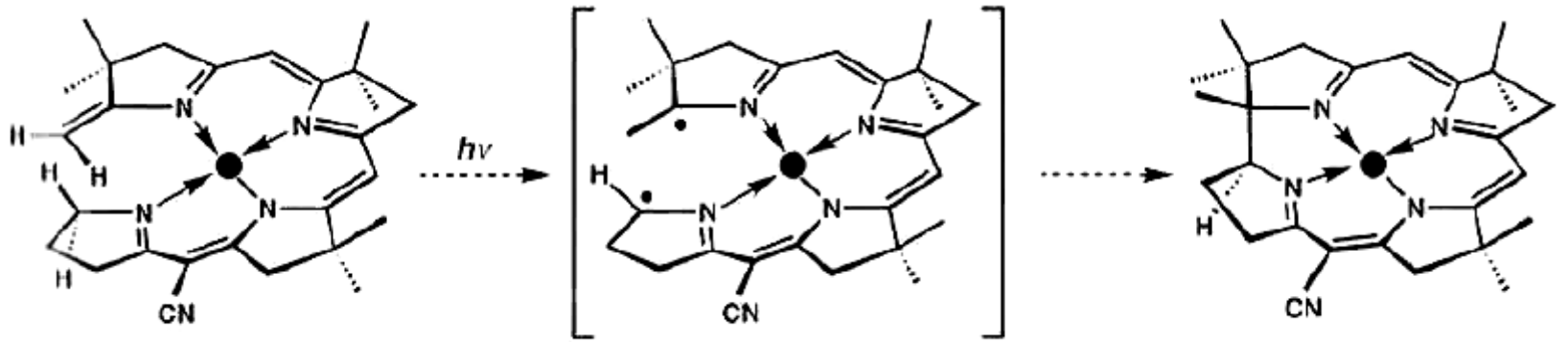


Attachment of A-Ring



The cadium complex is helically labile

Woodwood & Hoffman's Prediction



91 92 93

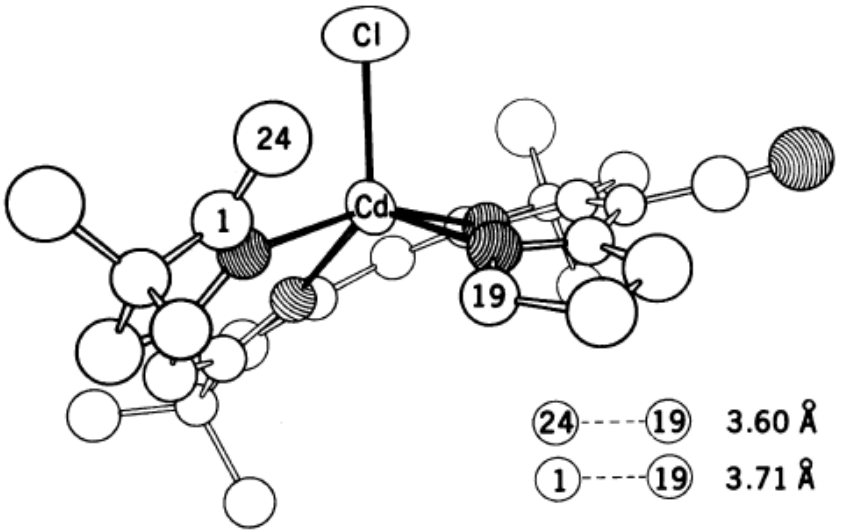
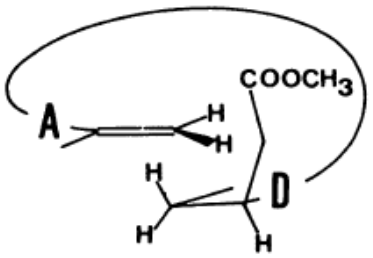
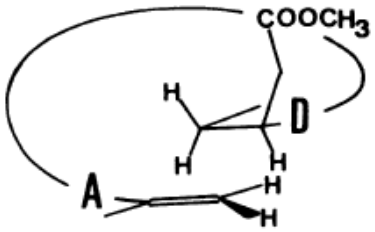
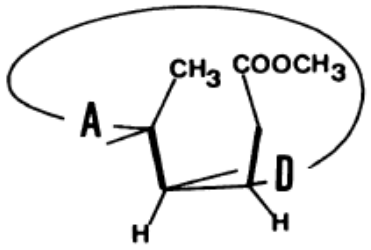


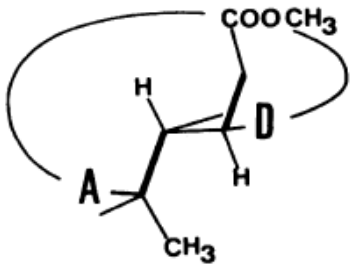
Fig. 10 (above). X-ray structure analysis of the chlorocadmium A/D-secocorrinate **11** (M is CdCl) (*20*). Fig. 11 (right). Diastereomeric reaction paths for the photochemical cycloisomerization of cobyroid A/D-secocorrin complexes.







Unnatural



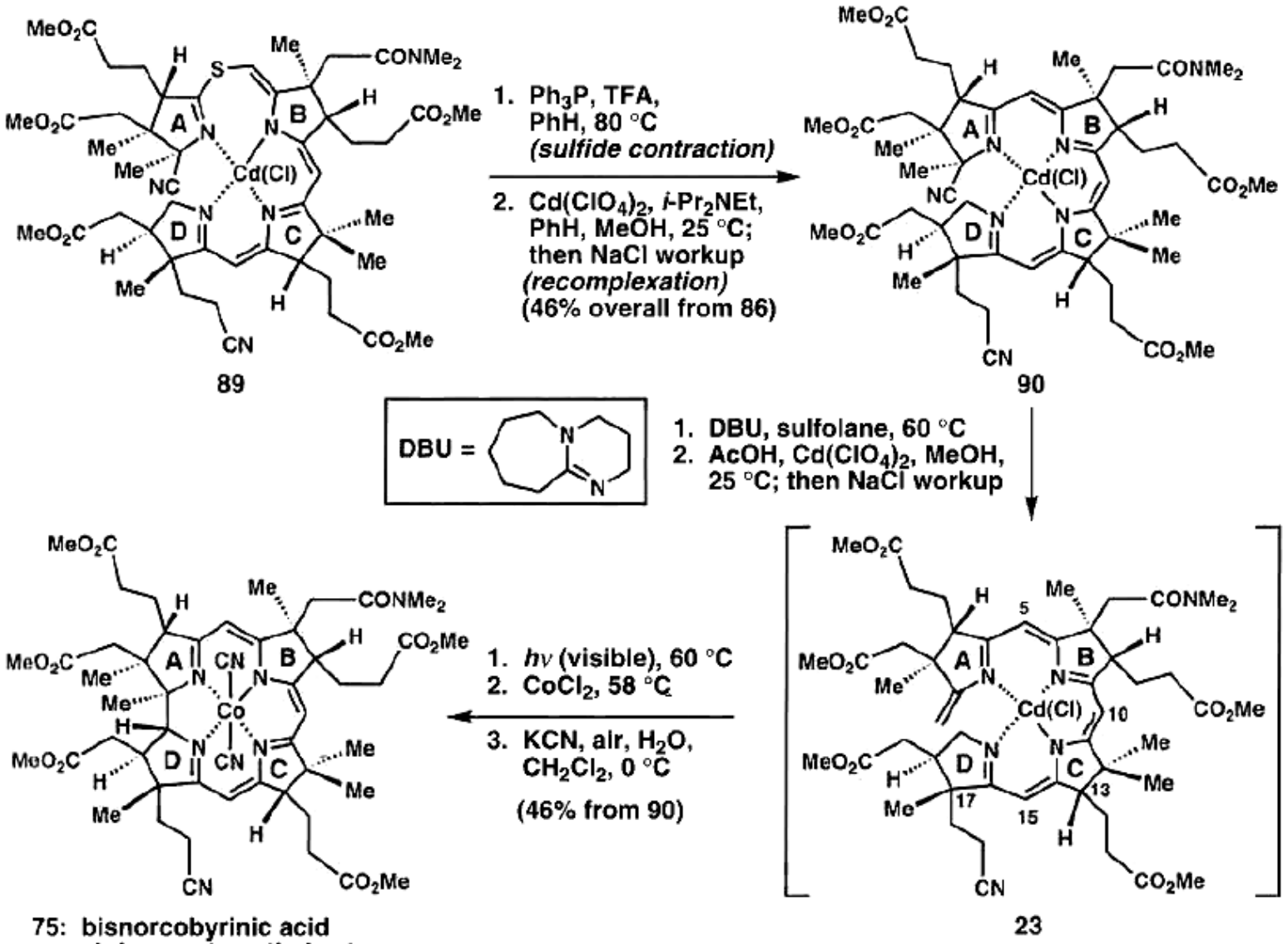
Natural

Eschenmoser, A. *Pure Appl. Chem.* **1969**, 1–23

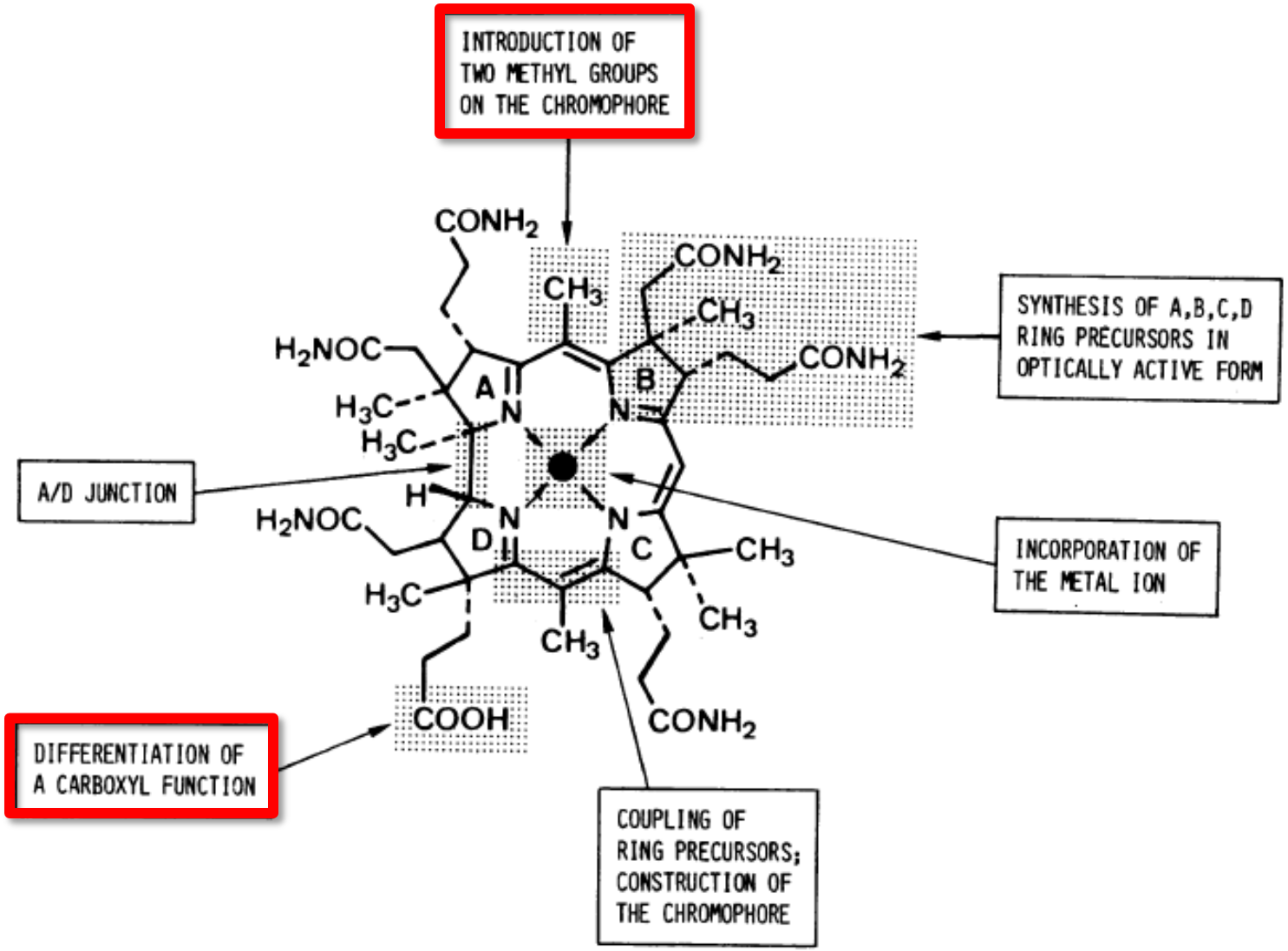
Woodward, R. B. *Angew. Chem. Int. Ed.* **1969**, 781–853

Eschenmoser, A.; et al. *Science* **1977**, 1410–1420

Secocorrin → Corrin

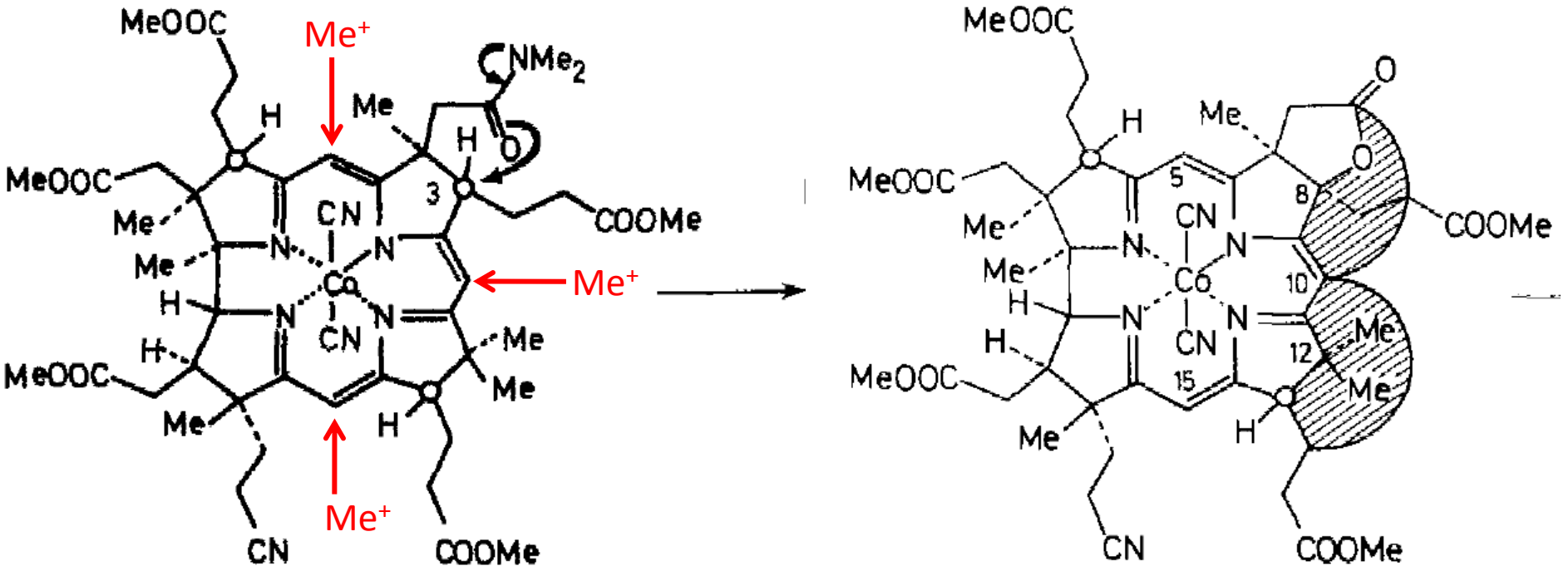


Remaining Challenges

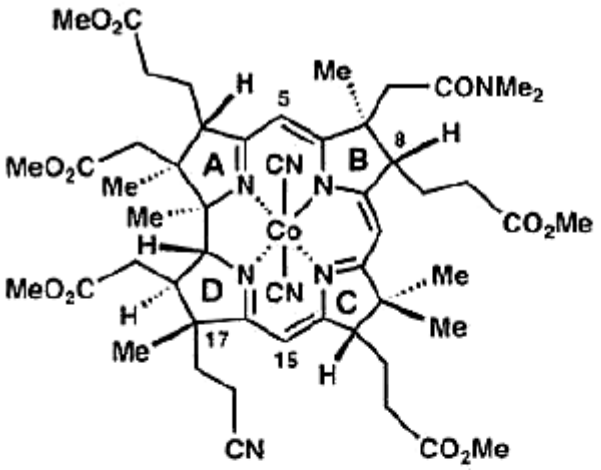


Eschenmoser, A.; et al. *Science* **1977**, 1410–1420

Selective Methylation

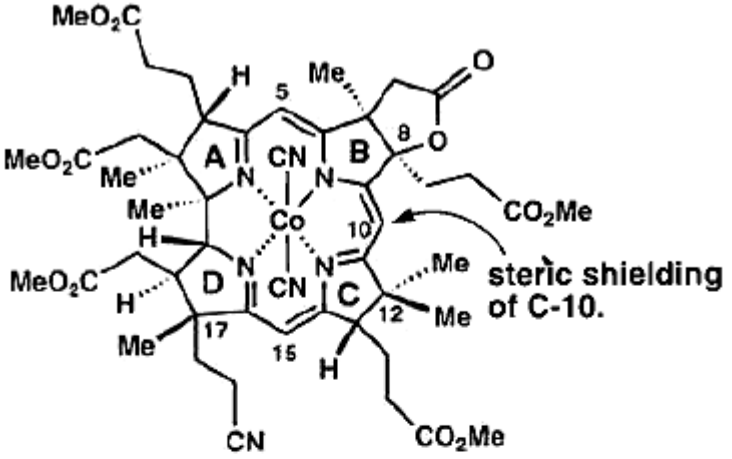


Application of Selective Methylation



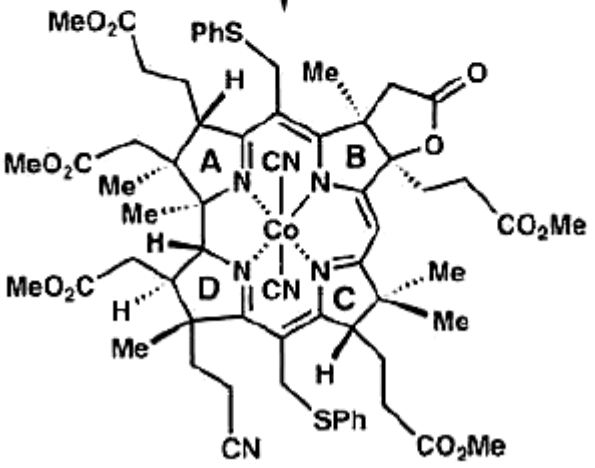
75: bisnorcobyrinic acid abdeg pentamethyl ester c dimethylamide f nitrile

I_2, AcOH



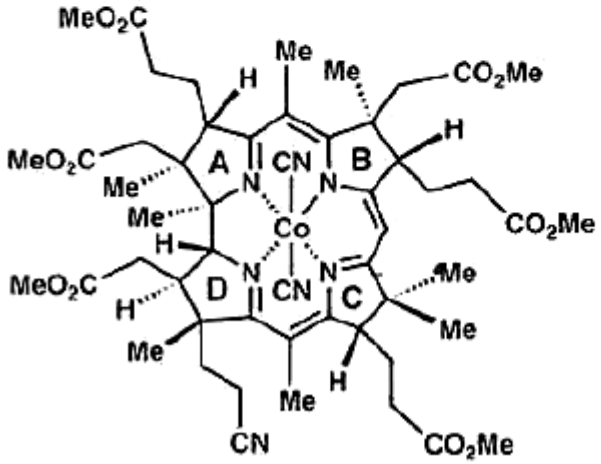
94

1. $ClCH_2OCH_2Ph$ sulfolane, 75 °C
2. PhSH



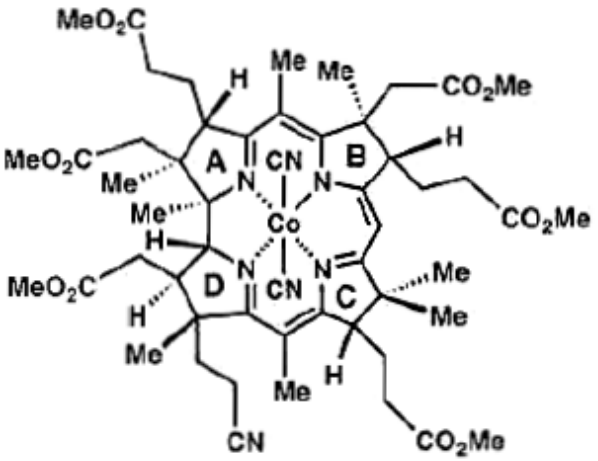
95

1. Raney Ni
2. CH_2N_2



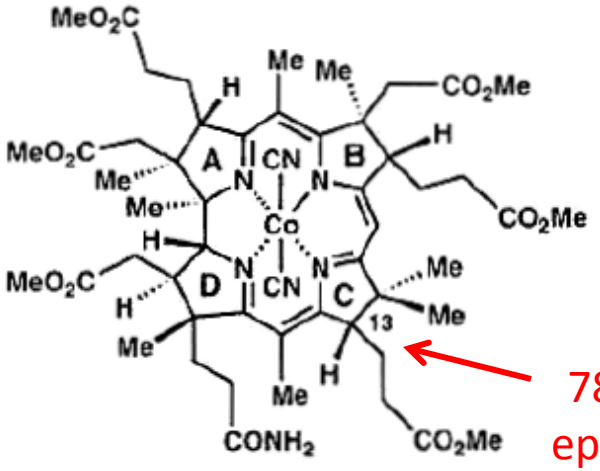
96: cobyrinic acid abcdeg hexamethylester f nitrile

End-Game



96: cobyrinic acid abcdeg hexamethylester f nitrile

conc. H_2SO_4

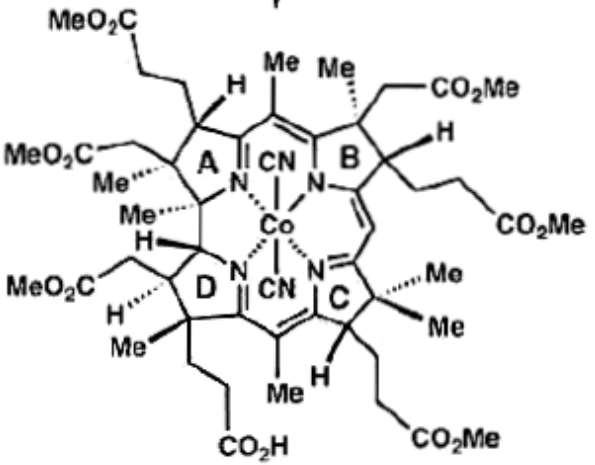


97: cobyrinic acid abcdeg hexamethylester f amide

78:28 epi/nat

N_2O_4, CCl_4, NaOAc

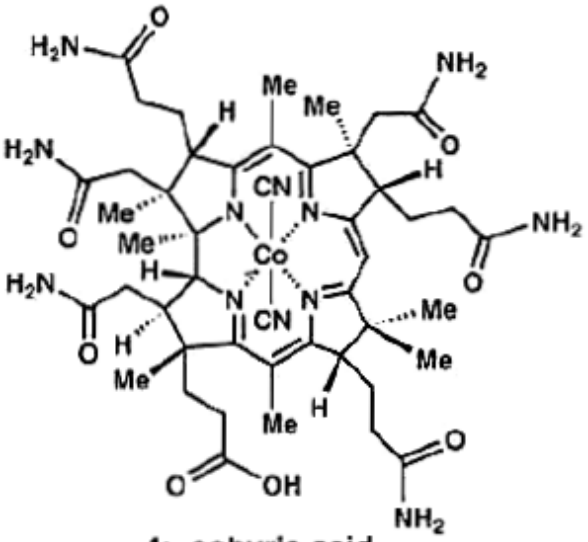
70–80%



98: cobyrinic acid abcdeg hexamethylester f acid

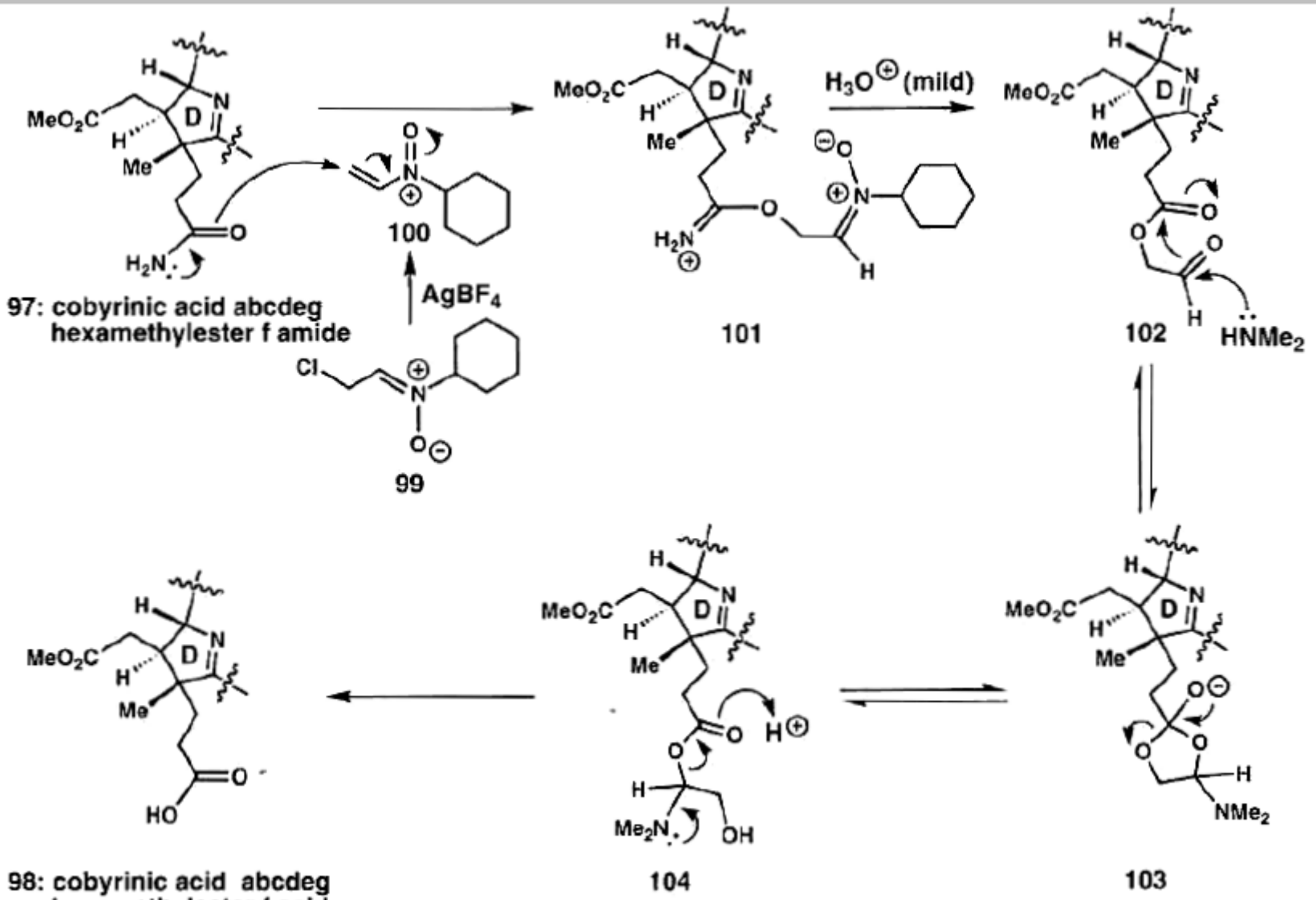
NH_3 (l), $HO(CH_2)_2OH$,

NH_4Cl, 75 °C



4: cobyric acid

Eschenmoser's Amide Solution



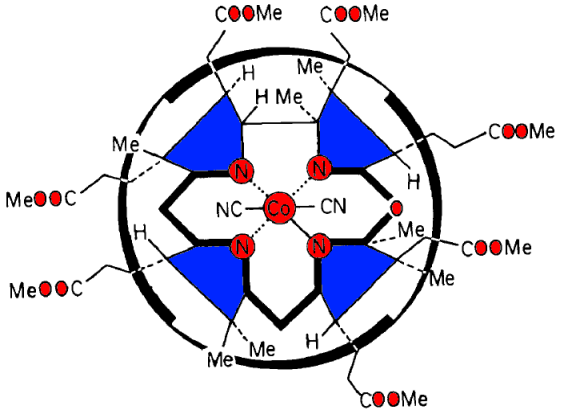
"a diabolically clever scheme" –R. B. Woodward

Eschenmoser, A.; et al. *Science* **1977**, 1410–1420

Woodward, R.B. *Pure Appl. Chem.* **1973**, 145–177

Conclusions

- The asymmetric total synthesis of Vitamin B_{12} stands as one of the most significant achievements in organic chemistry.
  - Produced chemical understanding in the form of:
    - Synthetic Strategy & Methods
    - Physical Organic Chemistry
      - The Woodward-Hoffman Rules
    - Corrin Chemistry
    - Diastereoselective Synthesis
  - Remains unrivaled even after almost 40 years



For additional analysis and references:
Nicolaou, K.C.; Sorensen, E. J. Vitamin B_{12}. *Classics in Total Synthesis*, VCH: New York, 2003; 100–136
For additional references on the chemistry of corrins:
Eschenmoser, A. *Pure Appl. Chem.* **1963**, 297–316
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