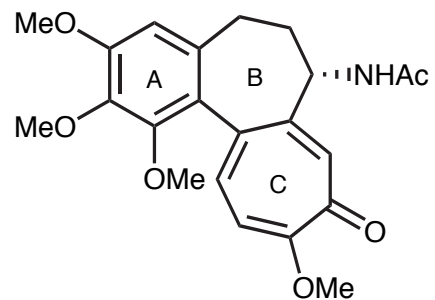


# Colchicine

An Evans Group Afternoon Seminar

Forrest Michael



Active component of the meadow saffron or autumn crocus *Colchicum autumnale*

## Leading References

Chemistry and Biological Activity:

Brossi "The Alkaloids" v.23, p.1

Brossi "The Alkaloids" v.41, p.125

History and Biology:

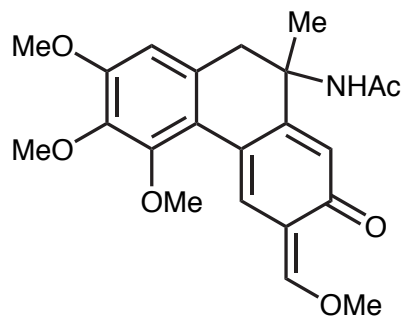
Eigsti "Colchicine in agriculture, medicine, biology, and chemistry"

Most Recent Synthesis:

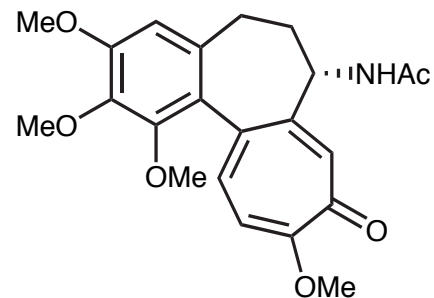
Banwell, *Pure and Appl. Chem.*, **1996**, 539

## A Brief History of Colchicine

- Use of the autumn crocus or meadow saffron *Colchicum autumnale* for both medicinal and nefarious purposes has been known since the time of ancient Greece
- The plant is named after the region of Colchis, located along the Eastern tip of the Black sea
- The infamous sorceress Medea may have used it in her black arts, and landowners of the region probably grew it for its toxic properties
- Described in Dioscorides' *De materia medica* (1st c. AD)-"But being eaten, it killeth by choking like to ye [mushrooms]... But there help them which eat these,...cows milk being drunk"
- A related species (*Colchicum parnassicum*), which contains a smaller amount of colchicine, was described as such: "The root of this is a remedy for ye toothache...But ye leaves being sodden in wine and smeared on do dissolve Oedemata (swellings) and tumors"
- Also known as "mort a chien" (death to dogs)
- Earliest documented use as medicine was in the treatment of gout as early as 560 AD
- Colchicine was first isolated in pure form in 1820
- First structure proposed by Windaus in 1924 on the basis of degradation studies
- Correct structure proposed by Dewar in 1945



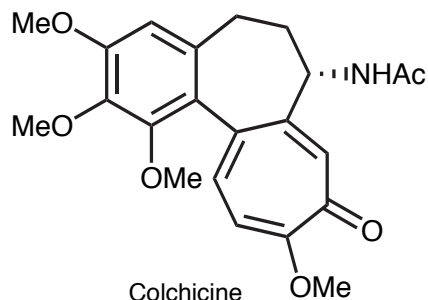
Windaus, 1924



Dewar, 1945

Brossi "The Alkaloids" v.23, p.1  
Brossi "The Alkaloids" v.41, p.125  
Eigsti "Colchicine in Agriculture, Medicine, Biology, and Chemistry"  
Dioscorides "De Materia Medica"

## Biological Activity



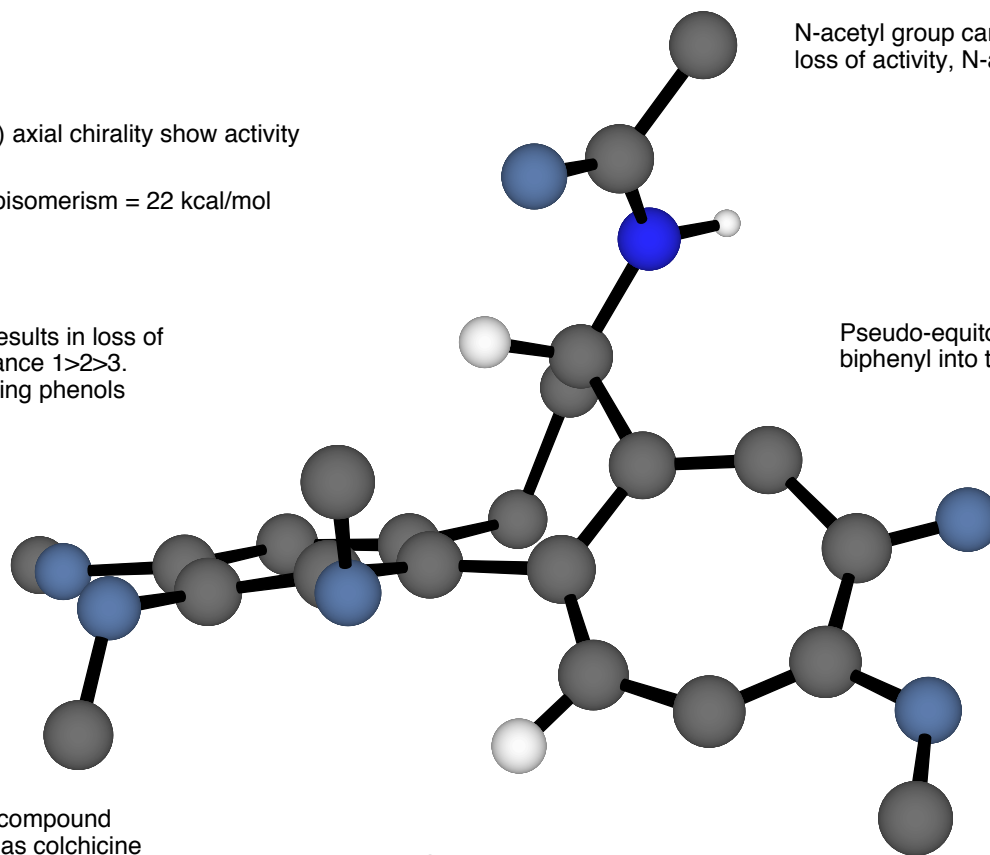
- In 1889, it was discovered that colchicine caused "a veritable explosion of mitosis". However, it was noticed that a majority of the dividing cells stopped at metaphase
- This useful property has been used to create and study polyploidy in plants
- Colchicine inhibits the formation of the microtubules necessary for chromosome transport during metaphase
- It forms a 1:1 complex with tubulin, which binds to the end of the forming microtubule and inhibits further polymerization
- This binding is slow and essentially irreversible and likely involves changes in conformation of both the protein and colchicine
- It has been calculated that the A/C dihedral angle in bound colchicine is nearly 0°
- Its use in the treatment of gout, familial Mediterranean fever, and certain liver disorders is directly related to its tubulin binding activity
- Although analogs have been tested for anti-cancer activity with some success, the potent toxicity (lethal dose ~10mg) prohibits its use as a drug
- For all analogs, anti-gout activity, tubulin binding affinity, and *in vivo* toxicity of analogs closely parallel one another
- In addition to its medicinal uses, colchicine is an important substance for biological research

# Structure-Activity Relationship

Only compounds with (aS) axial chirality show activity

Activation energy for atropisomerism = 22 kcal/mol

Demethylation of A-ring results in loss of activity in order of importance 1>2>3. Esterification of the resulting phenols restores activity.



N-acetyl group can be replaced with almost acyl group without loss of activity, N-alkyl versions are slightly less active

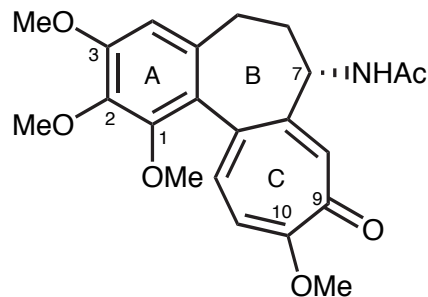
Pseudo-equatorial NHAc group gears the biphenyl into the (aS)-atropidiastereomeric form

Iso (C-9/10 reversed) compounds have no activity at all

The 2,3-methylenedioxy compound (cornigerine) is as active as colchicine

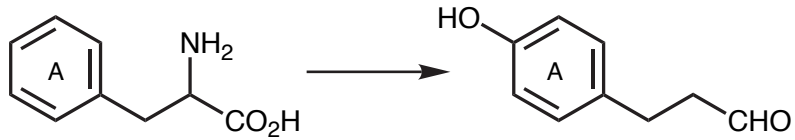
In the 10-position activity decreases in the series  $\text{SMe} > \text{NR}_2 > \text{OMe} > \text{OH} > \text{H}$ . An Et substituent in this position is also active

Contraction of the troponone ring to a phenyl ring results in a slight decrease in activity

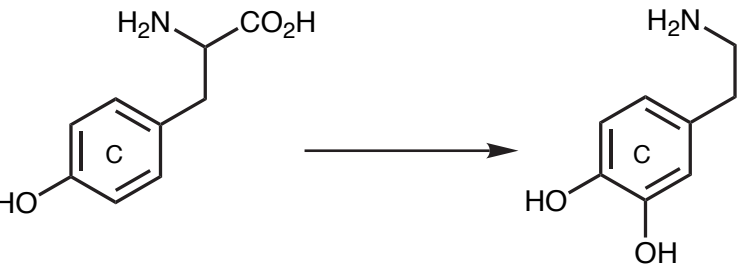


Brossi "The Alkaloids" v.23, p.1  
Brossi "The Alkaloids" v.41, p.125

# Biosynthesis of Colchicine

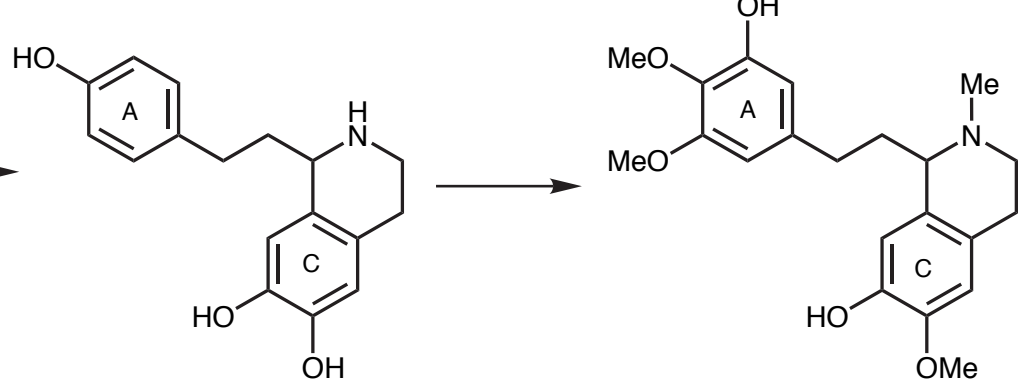


Phenylalanine



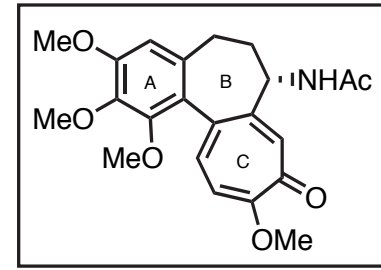
Tyrosine

Dopamine



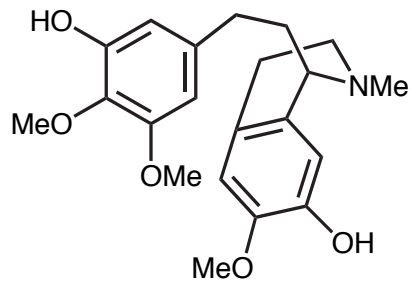
Autumnaline

- Deamination of phenylalanine to cinnamic acid followed by reduction to the saturated aldehyde occurs before oxidation of the aromatic ring



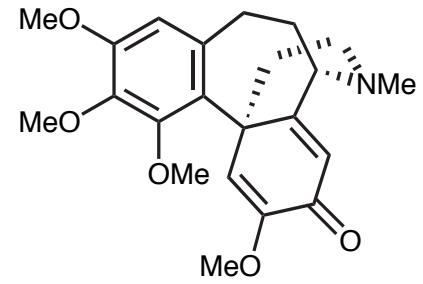
Brossi "The Alkaloids" v.23, p.1  
 Brossi "The Alkaloids" v.41, p.125  
 Herbert *Tetrahedron*, 1990, 7119

# Biosynthesis of Colchicine

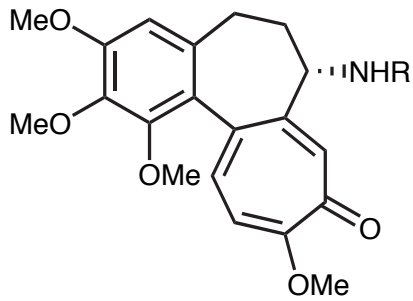


Autumnaline

Cytochrome P-450

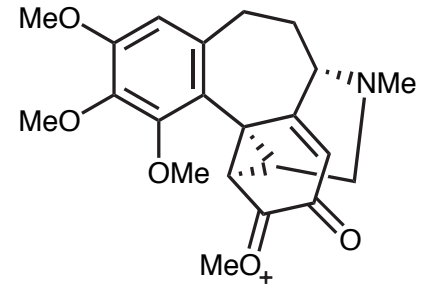


O-Methylandrocymbine



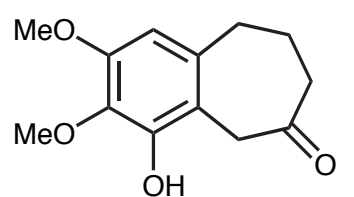
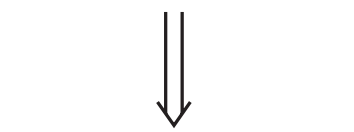
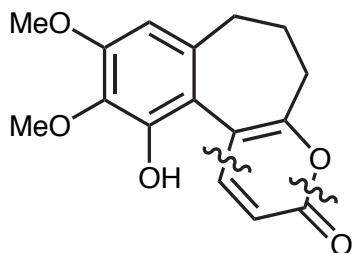
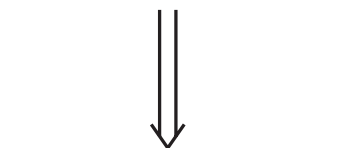
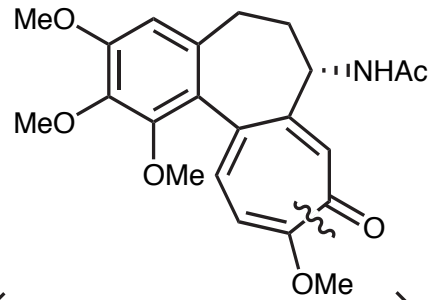
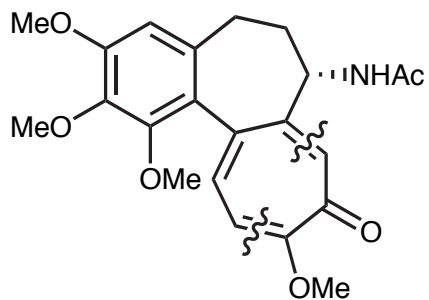
Demecolcine R = Me

Colchicine R = Ac

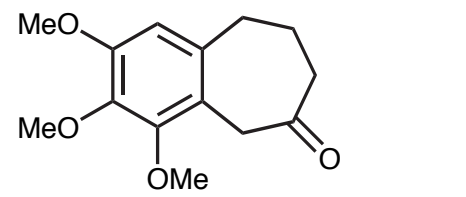
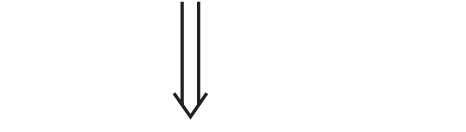
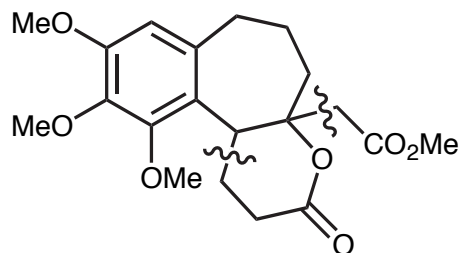


Brossi "The Alkaloids" v.23, p.1  
 Brossi "The Alkaloids" v.41, p.125  
 Zenk *Tetrahedron Lett.*, **1996**, 8161

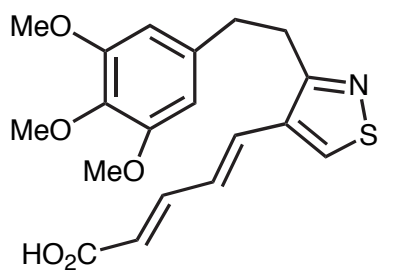
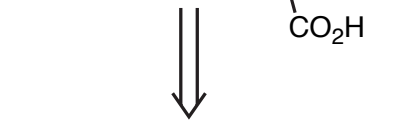
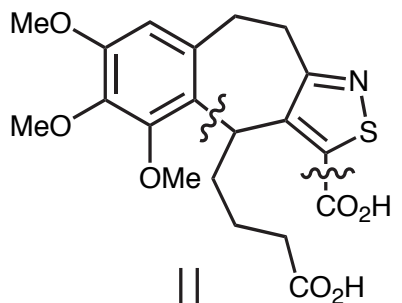
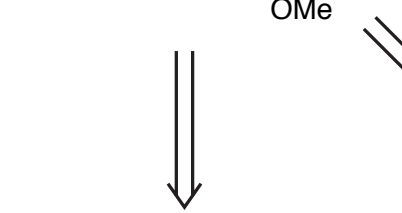
Retrosynthetic Analyses of Colchicine-A->AB->ABC\*->ABC



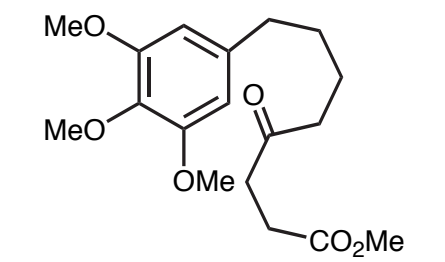
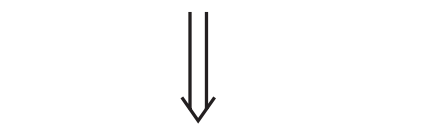
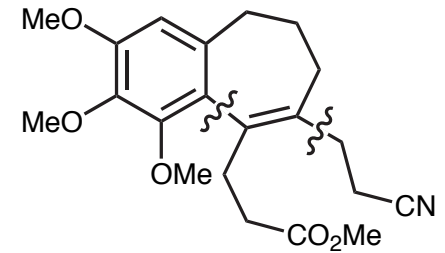
Eschenmoser, Boger



van Tamelen

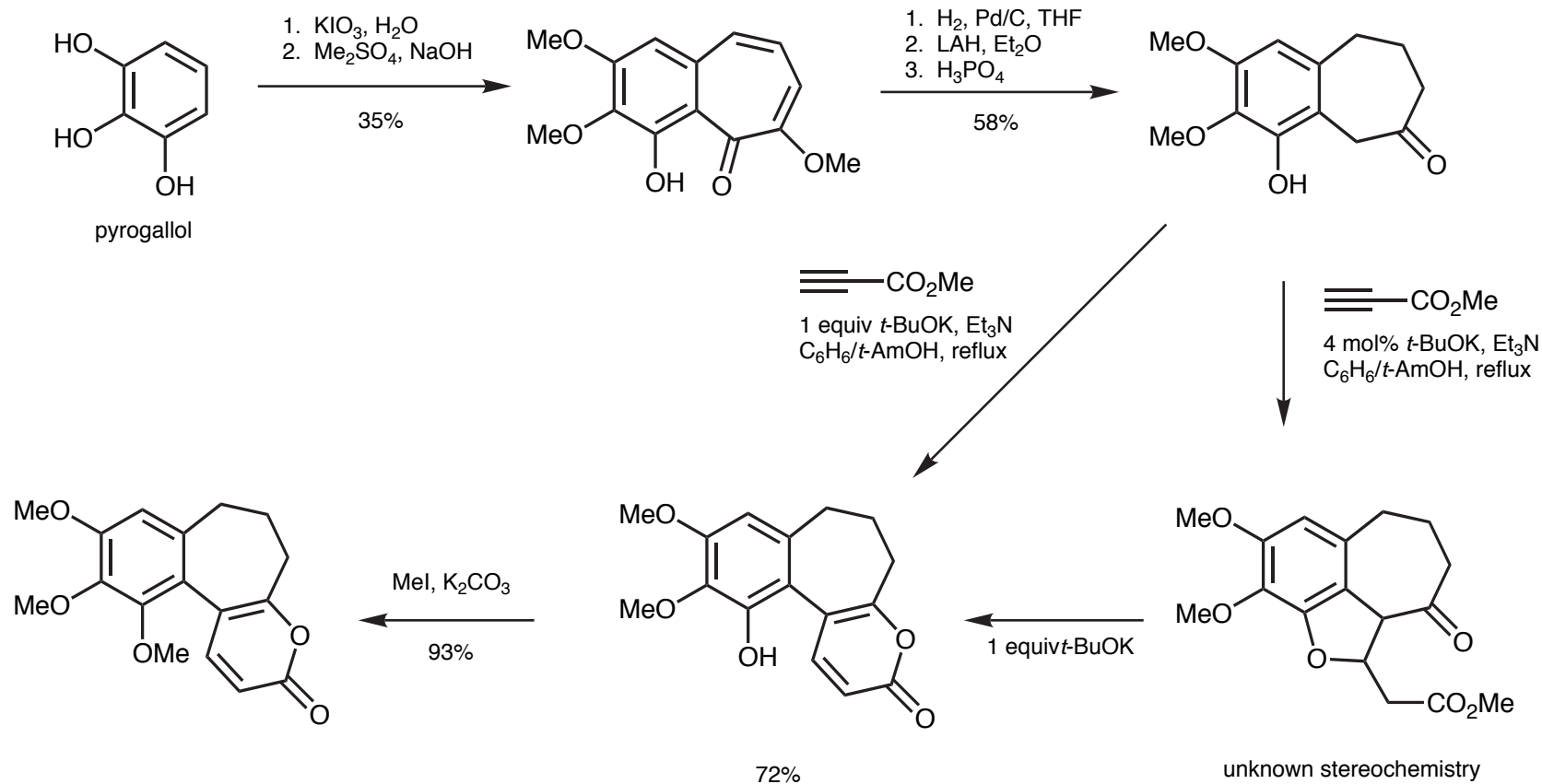
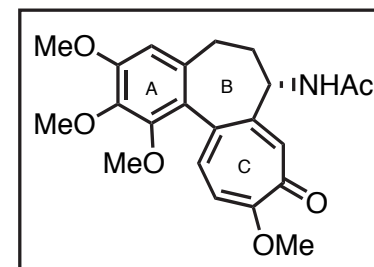


Woodward



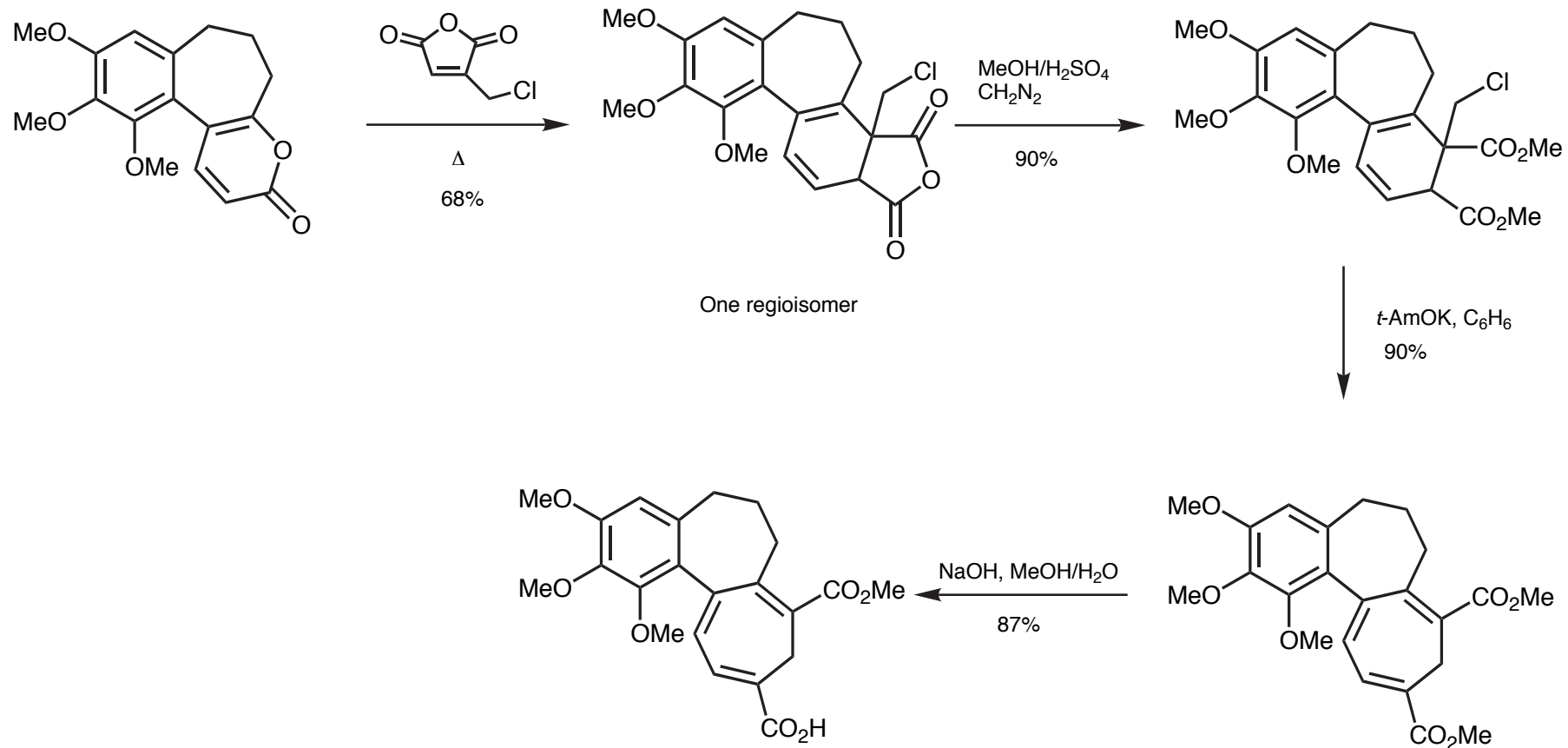
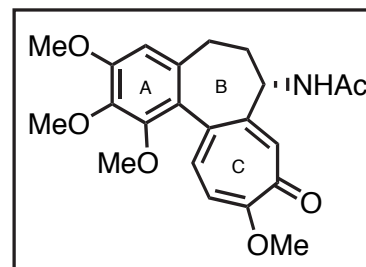
Martel

# Eschenmoser Synthesis-Formation of the B ring



A. Eschenmoser *Helv. Chim. Acta* 1961, 540

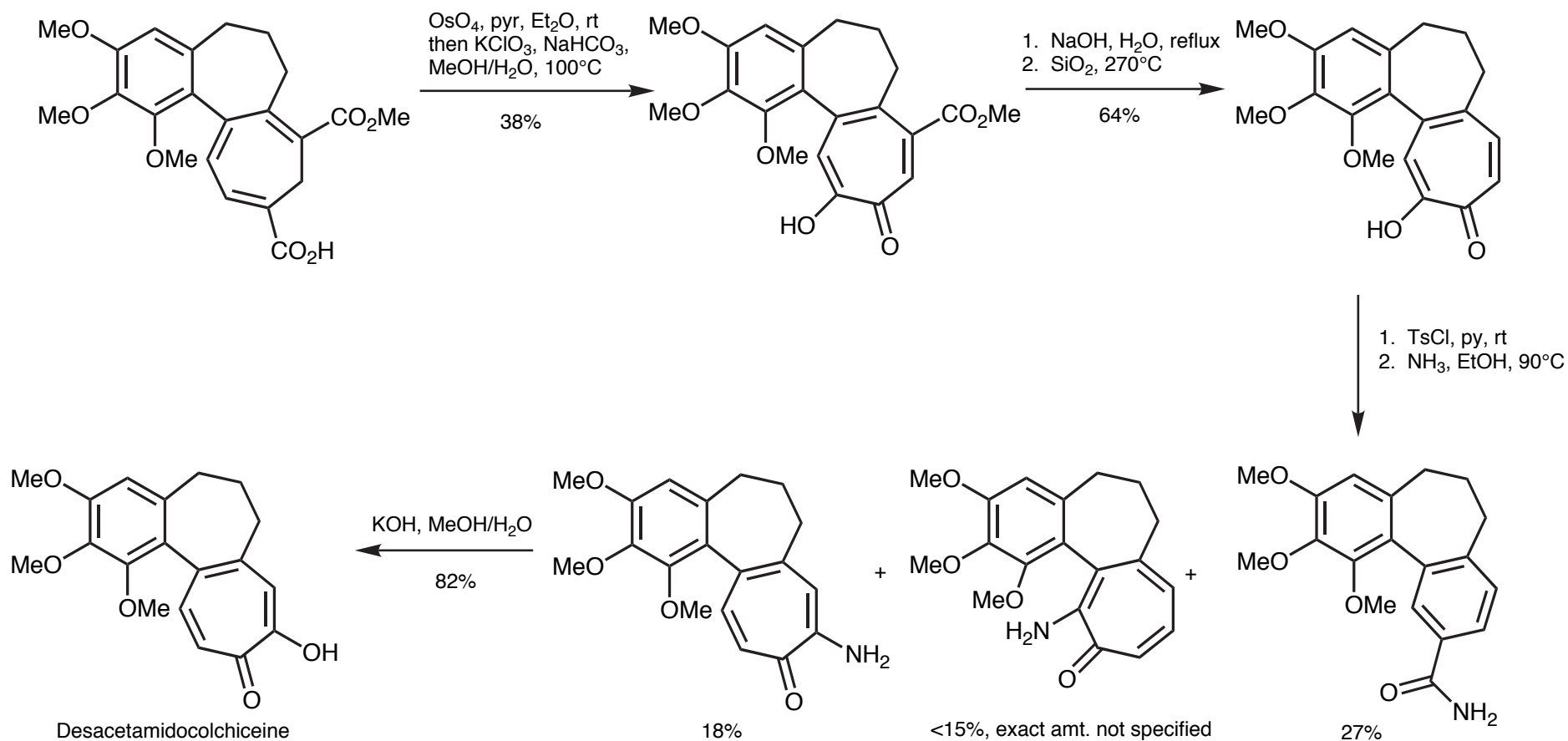
Eschenmoser Synthesis-Elaboration of the C ring (Clint Eastwood)



- Reaction of the  $\alpha$ -pyrone with methyl propiolate gave a 1:1 mixture of regioisomers
- Norcaradiene form preferred when carboxylates are tied back as the anhydride
- No trace of other cycloheptatriene isomers resulting from  $\epsilon$ -attack observed

A. Eschenmoser *Helv. Chim. Acta* **1961**, 540

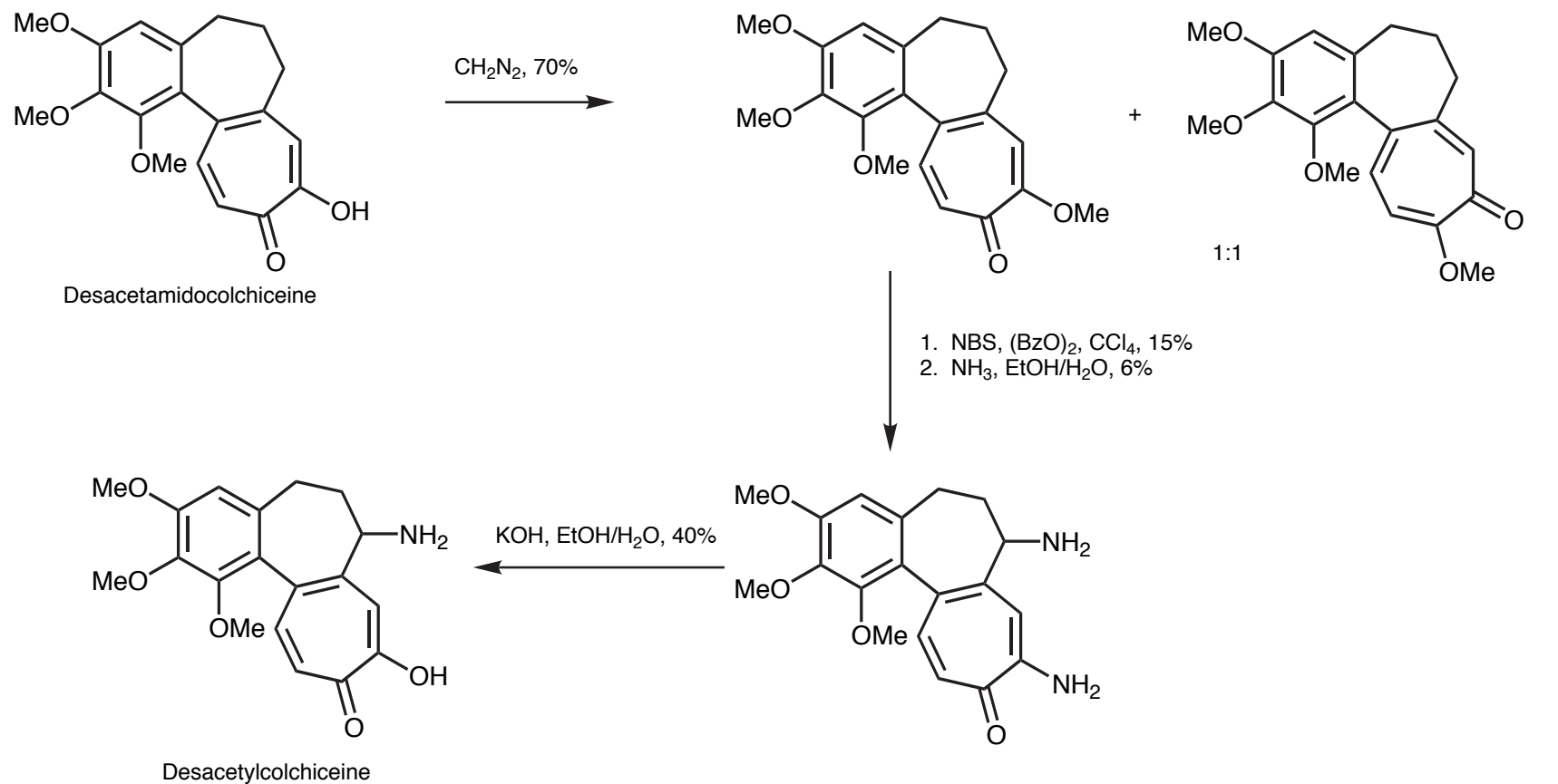
## Eschenmoser Synthesis-Tropolonization (Lee Van Cleef)



- $\text{KClO}_3$  not necessary for decarboxylation, but improves the yield somewhat
- Significant losses occurred during the isolation of the tropolone (spectroscopic yield 54%)

A. Eschenmoser *Helv. Chim. Acta* **1961**, 540

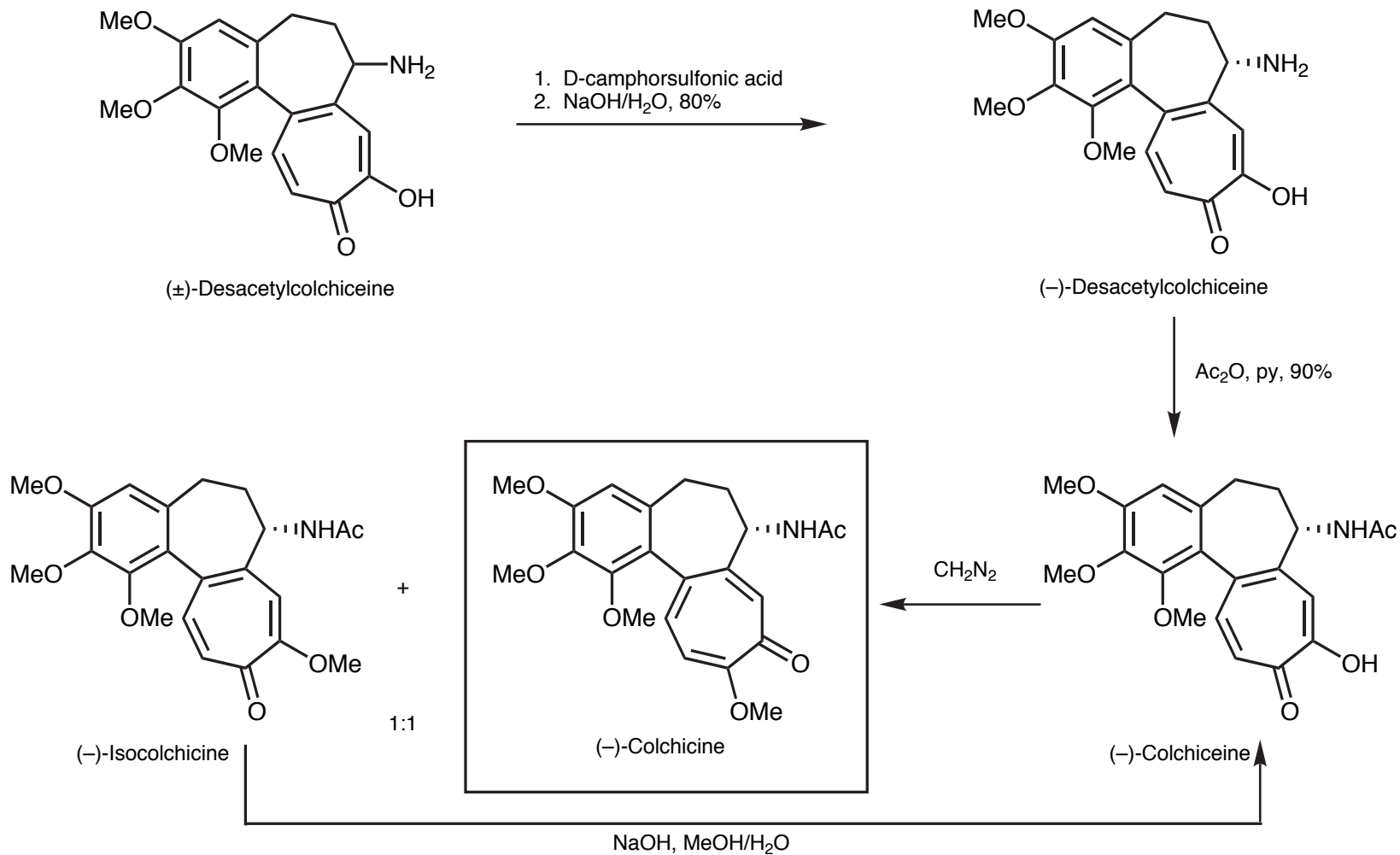
# Eschenmoser Synthesis-Amination (The Ugly)



- Attempted bromination of the other tropolone isomer gave no desired product
- The major product from ammonolysis was elimination (50%)

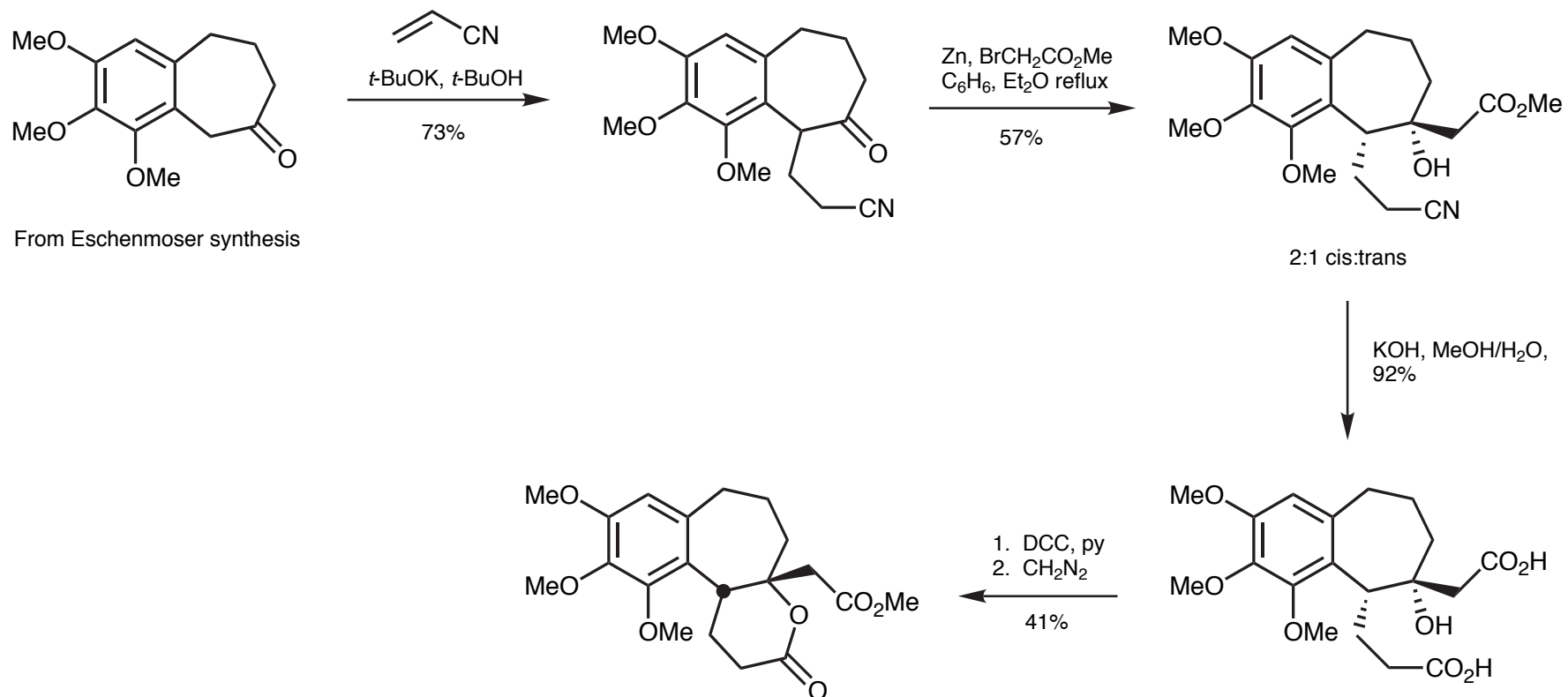
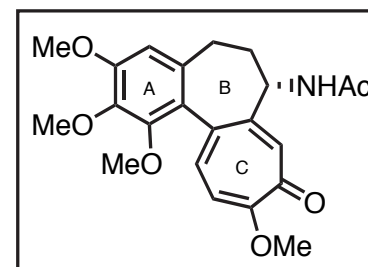
A. Eschenmoser *Helv. Chim. Acta* **1961**, 540

## Resolution, Acetylation, and Methylation



• (+)-Desacetylcolchicine could be isolated from the mother liquor and crystallized to enantiomeric purity

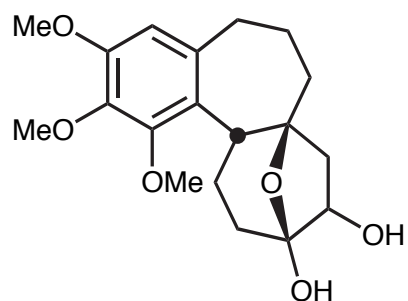
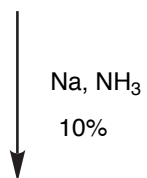
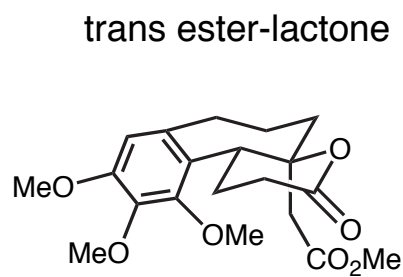
## van Tamelen Synthesis-C-ring Formation



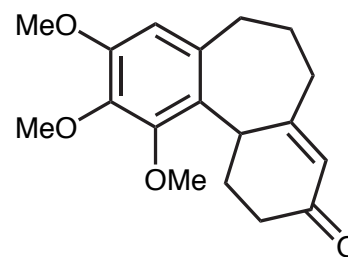
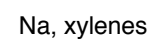
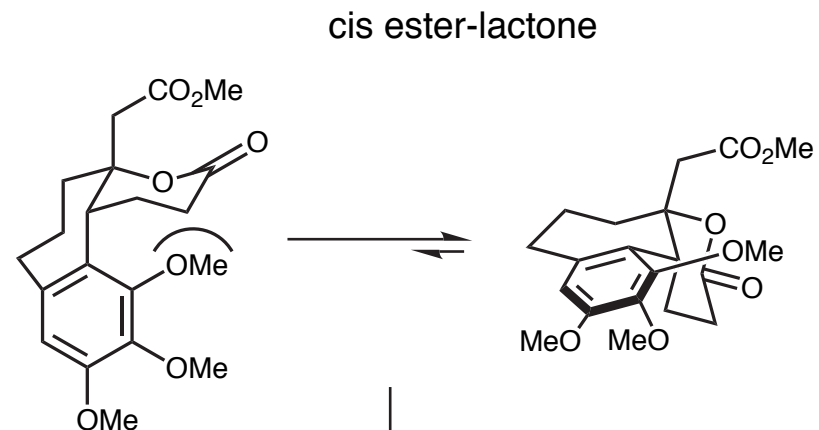
- Attempted reaction of several other electrophiles with starting ketone failed due to steric hindrance from ortho methoxy group
- Diastereomers from the Reformatsky reaction were separated and carried through the sequence separately

E. E. van Tamelen *Tetrahedron* **1961**, 8

## van Tamelen Synthesis-Acyloin Condensation



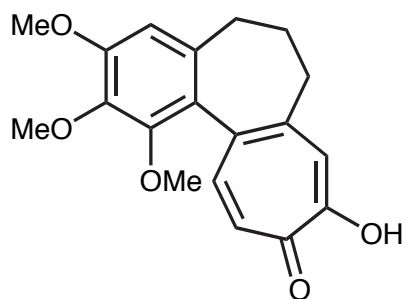
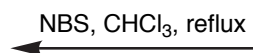
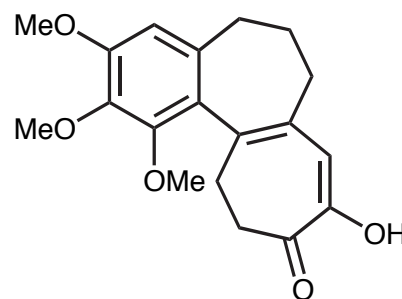
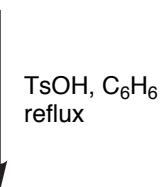
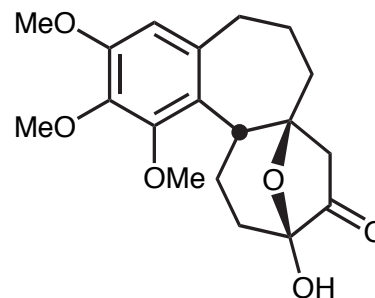
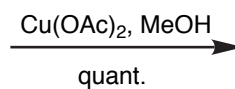
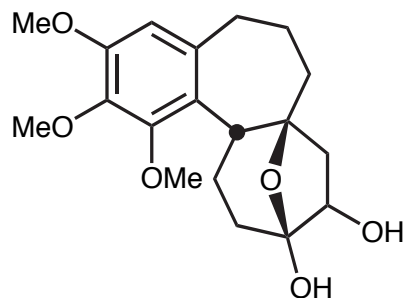
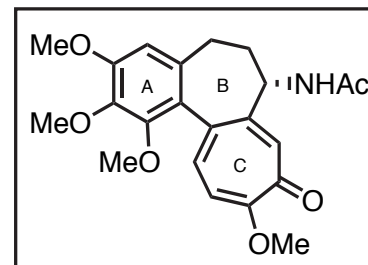
- isolated as a 9:1 mixture of diastereomers at C-9
- Na in xylenes yielded no recognizable products



- Na in NH<sub>3</sub> yielded no recognizable products

E. E. van Tamelen *Tetrahedron* **1961**, 8

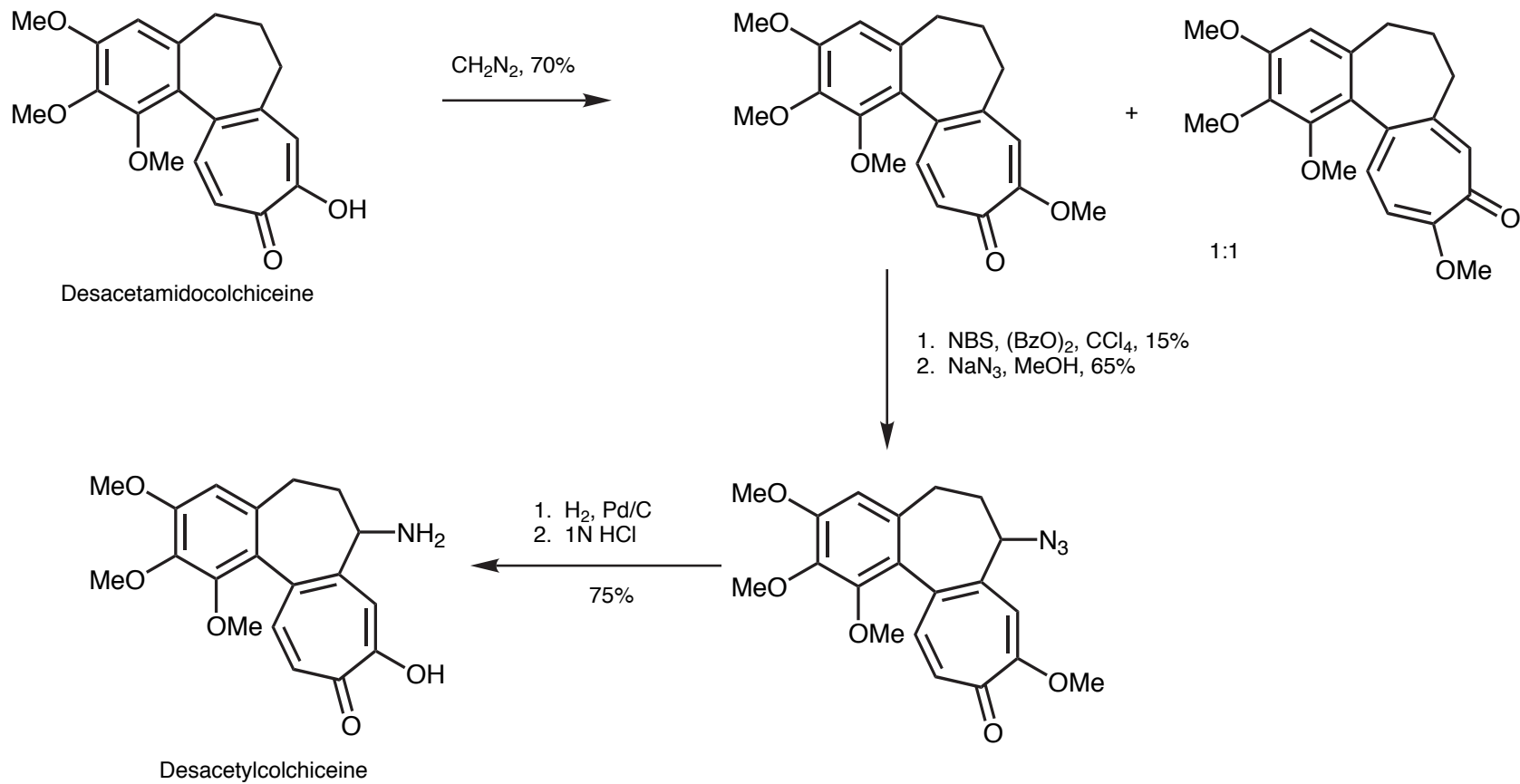
# van Tamelen Synthesis-Completion



desacetamidocolchicine  
40%

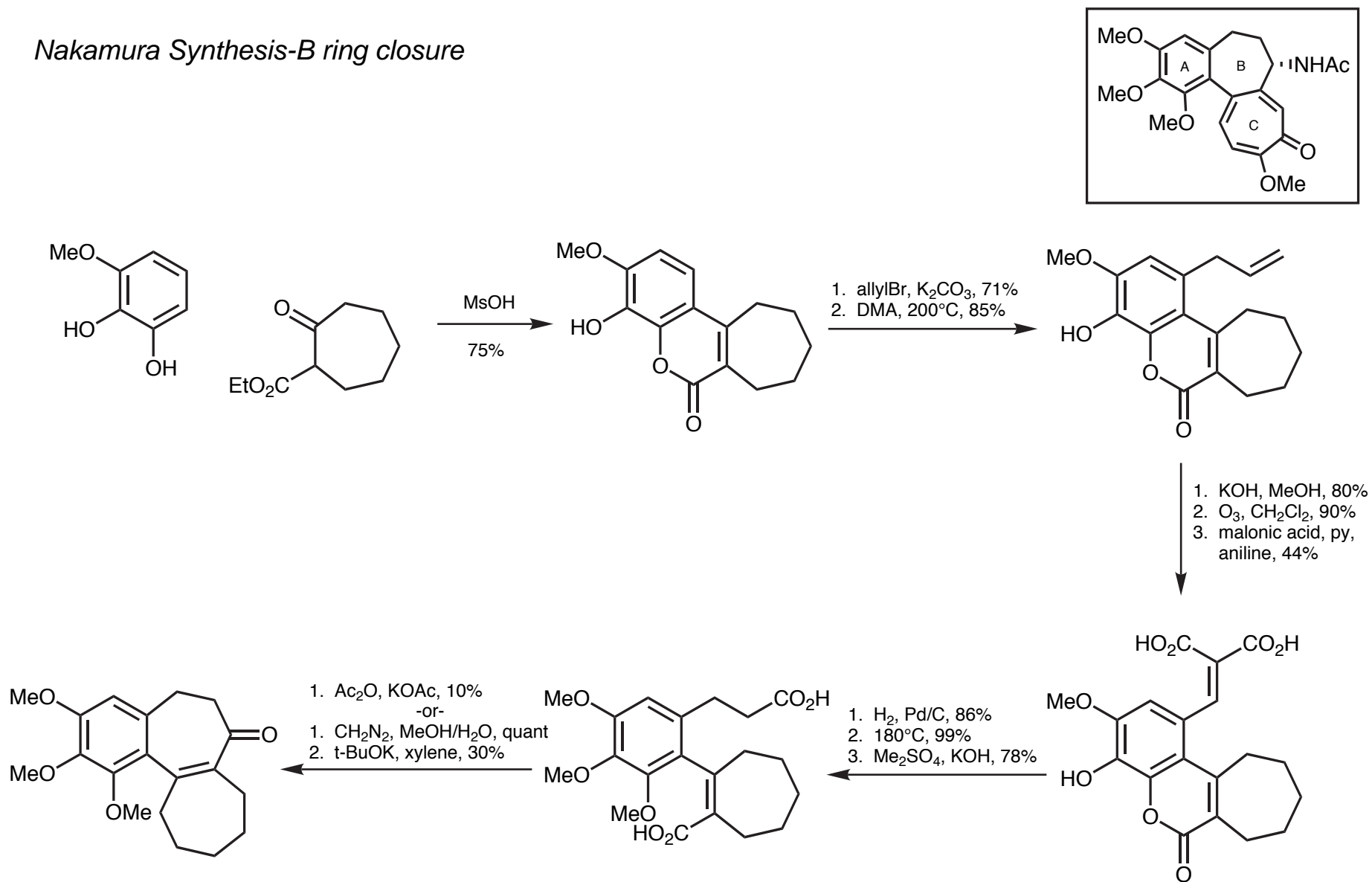
E. E. van Tamelen *Tetrahedron* **1961**, 8

van Tamelen Synthesis-The Not-Quite-So-Ugly



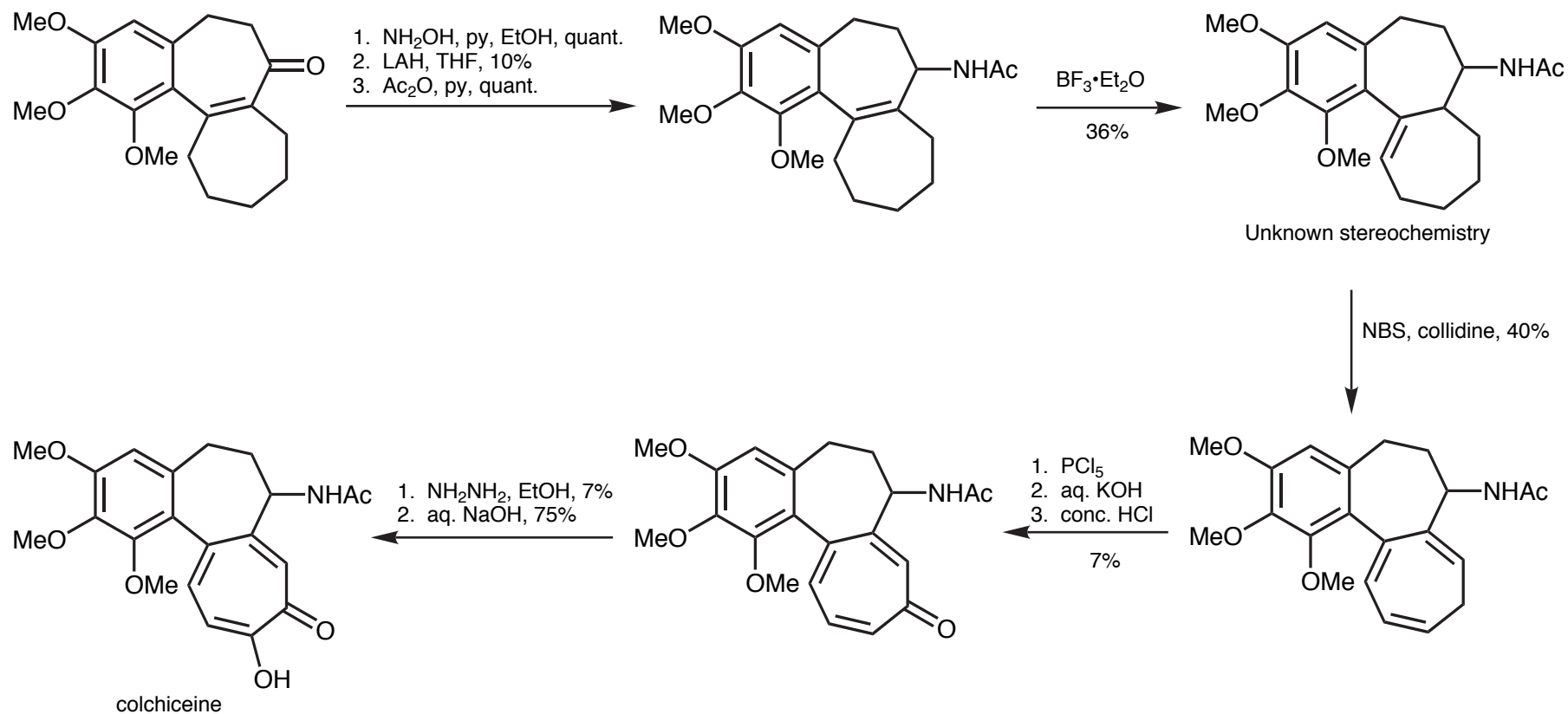
• Attempted bromination of the other troponone isomer gave no desired product

Nakamura Synthesis-B ring closure



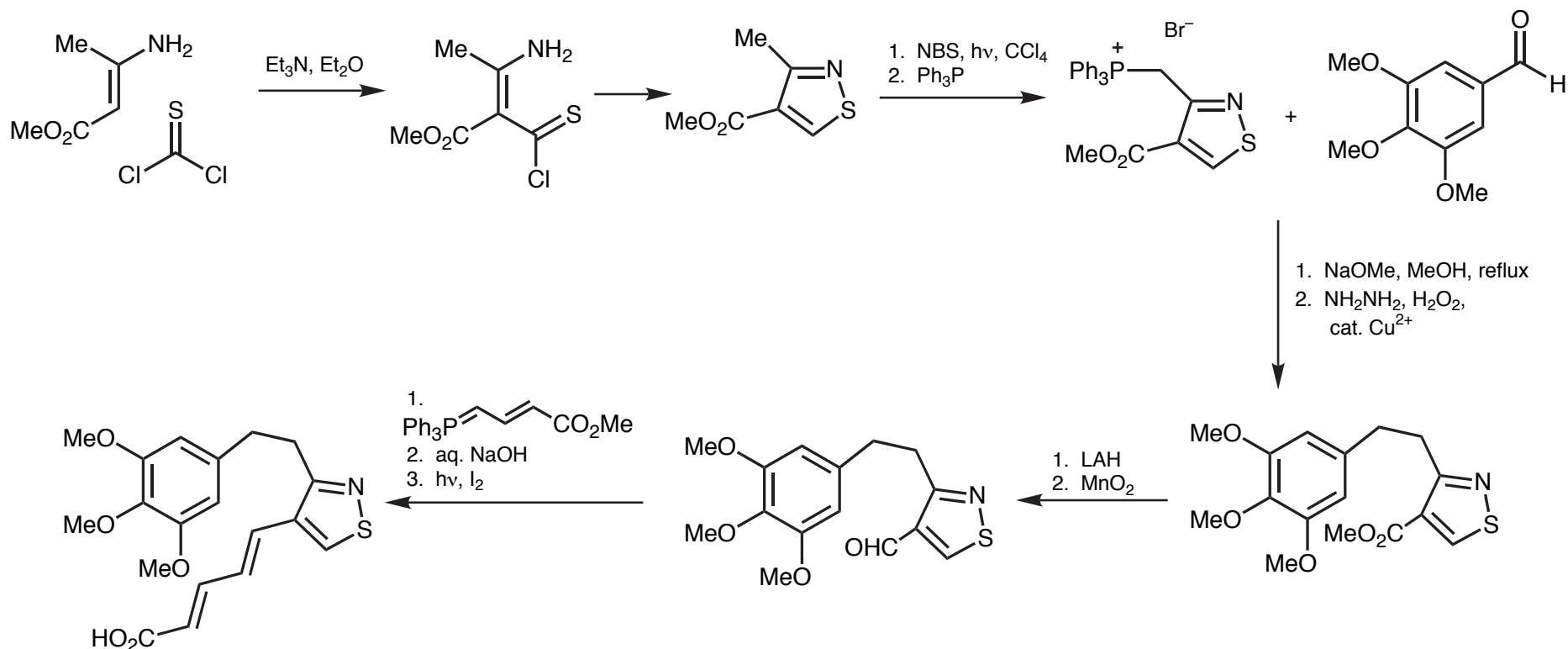
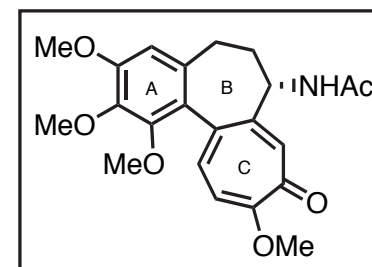
Nakamura *Chem. Pharm. Bull.* **1962**, 291

## Nakamura Synthesis-Tropolonization



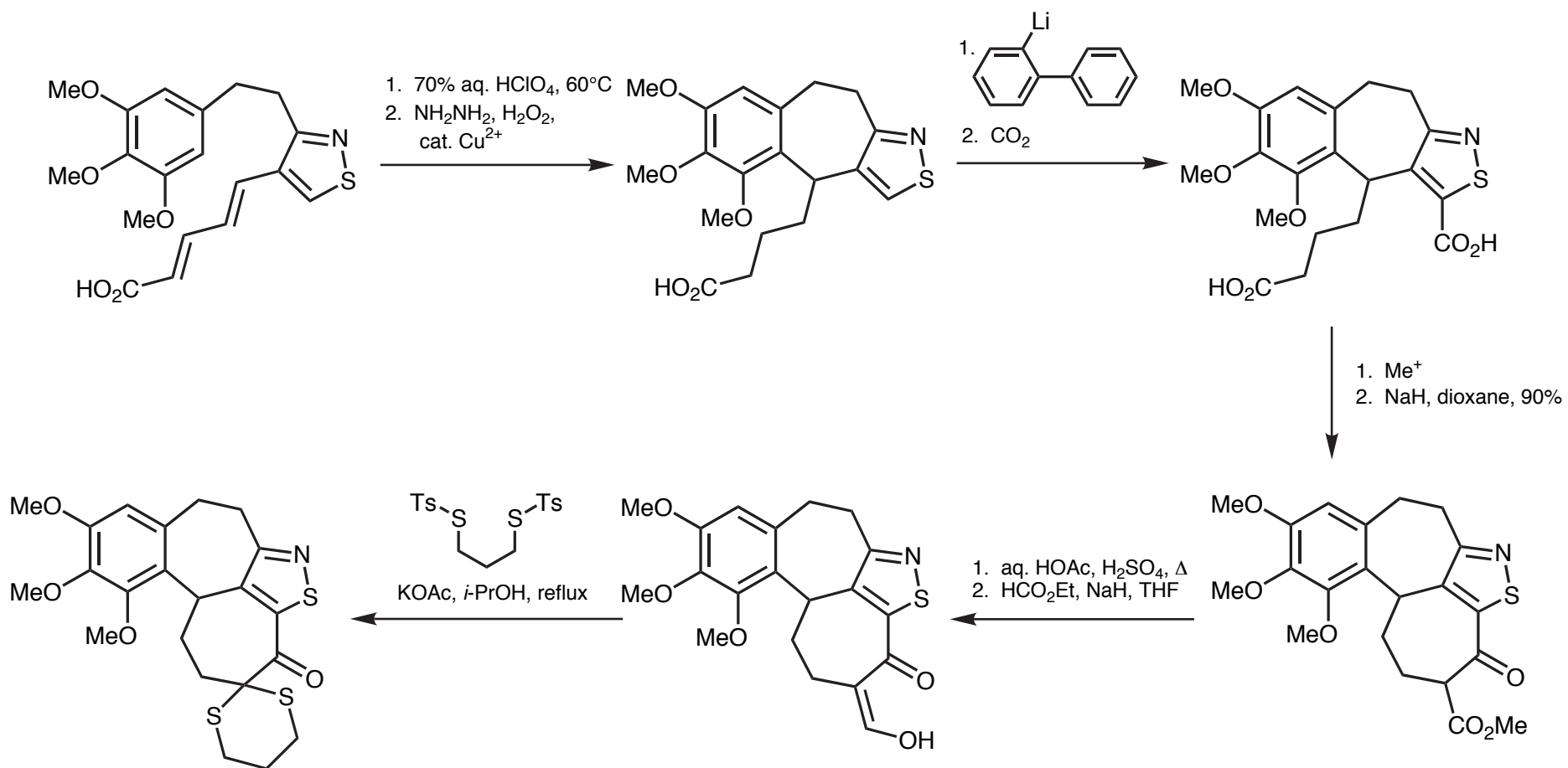
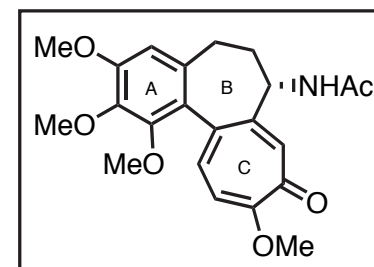
- Yield of LAH reduction before recrystallization was about 40%
- Resolution of free amine with tartaric acid or camphorsulfonic acid failed
- The major product from the bromination reaction was a bromodiene that could not be converted to the desired triene

## Woodward Synthesis- Isothiazole Formation and Elaboration

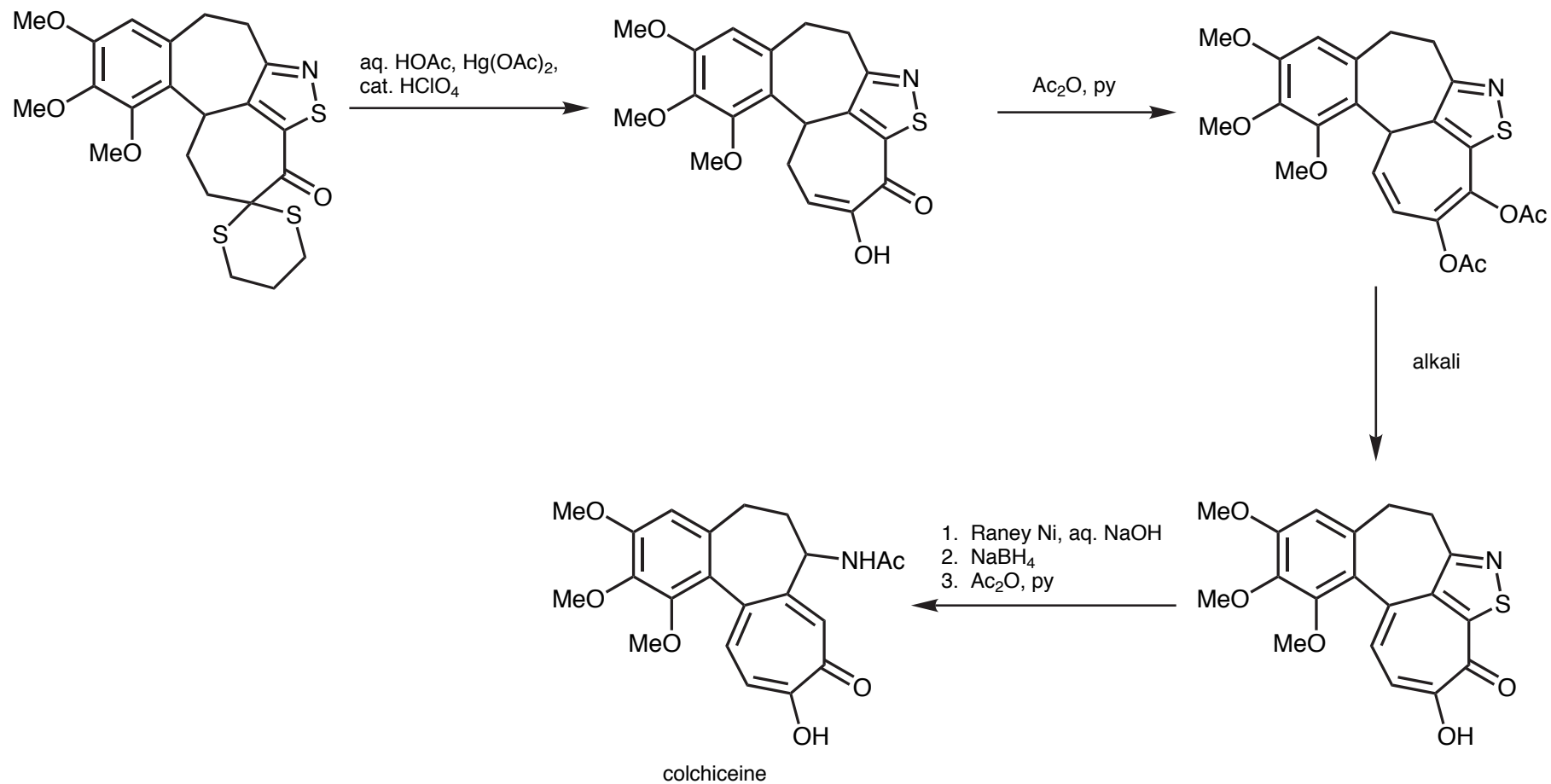


- "One aspect of our plan to base a synthesis of colchicine upon a simple isothiazole intermediate might well have given us pause. A forceful reminder of the fantastic multiformity of organic chemistry is provided by the fact that although literally millions of different organic molecules were known at the time our plan was laid down, no simple isothiazole of any kind had been prepared!"
- The mixture of geometrical isomers originally formed in the olefination was transformed to the all-*trans* arrangement with  $\text{hv}$ ,  $\text{I}_2$  procedure

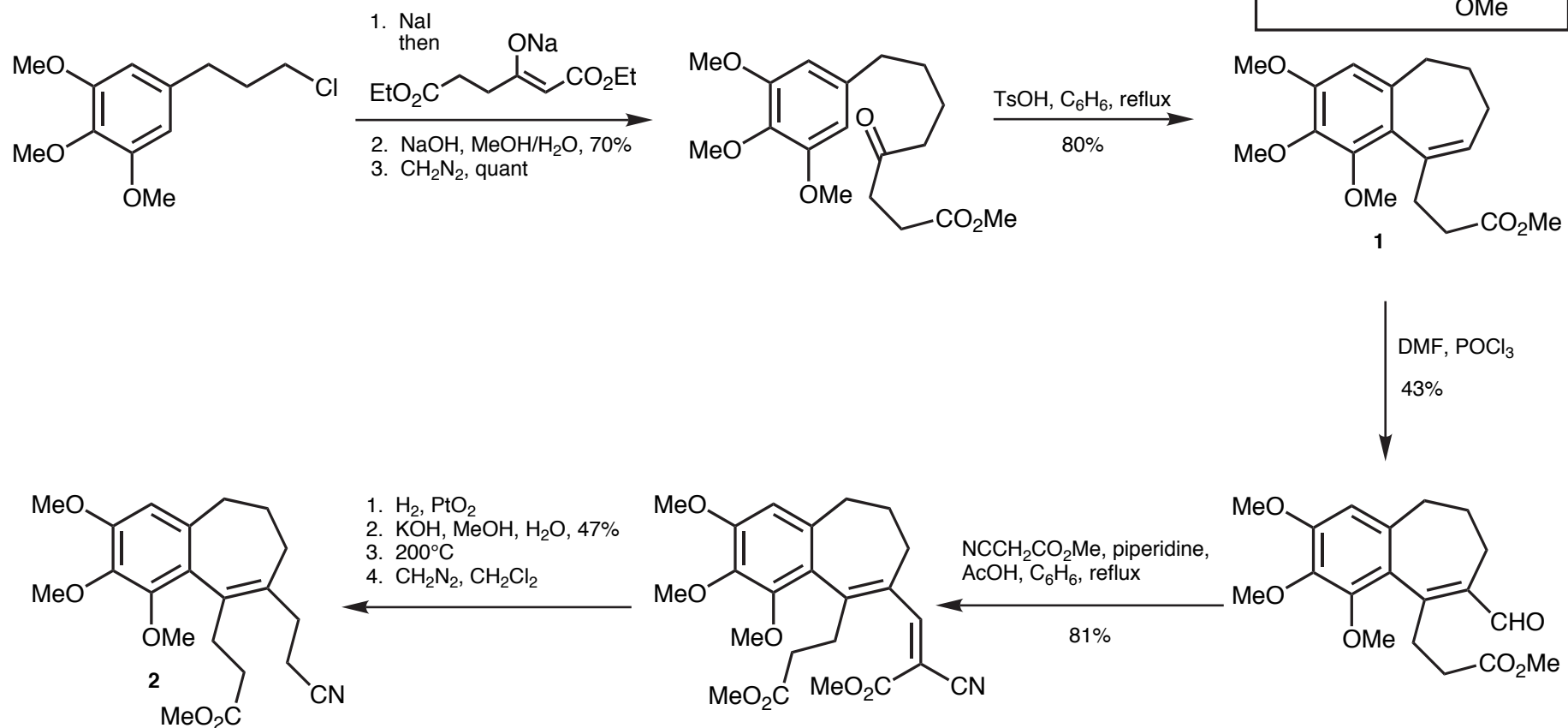
# Woodward Synthesis-B and C-ring Formation



## Woodward Synthesis-Tropolonization



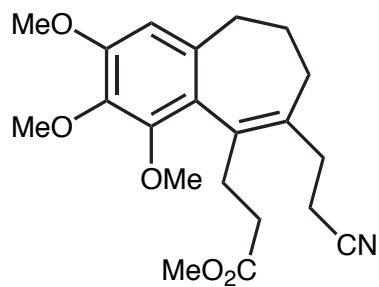
## Martel Synthesis-B-ring Closure



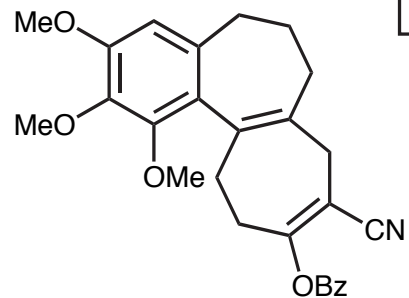
- If not rigorously dried by azeotropic removal of water, the acid-catalyzed cyclization did not stop at **1**, but cyclized further to give the tricyclic ketone product of Friedel-Crafts type acylation
- "The yields given in this series of reaction [sic] [from **1** to **2**] are those obtained in the first trials but we have indications suggesting that all the steps can be adjusted to proceed nearly quantitatively."
- The conversion of **1** to **2** could also be achieved via an alternate route in 7 steps and 5% overall yield

Martel *J. Org. Chem.* **1965**, 1752

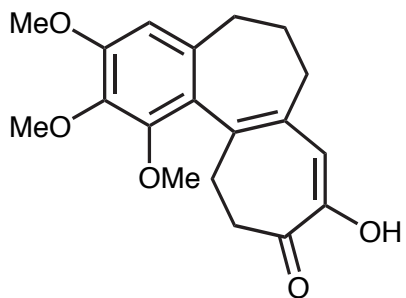
## Martel Synthesis-C-ring Formation



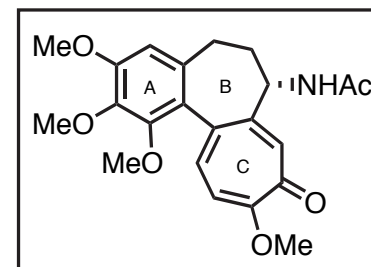
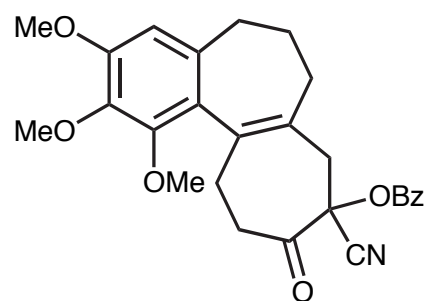
K, toluene, reflux  
then BzCl, py, 17%



1. KOH, MeOH/H<sub>2</sub>O, 90%  
2. Na, C<sub>6</sub>H<sub>6</sub>, reflux  
then (BzO)<sub>2</sub>, rt, 76%



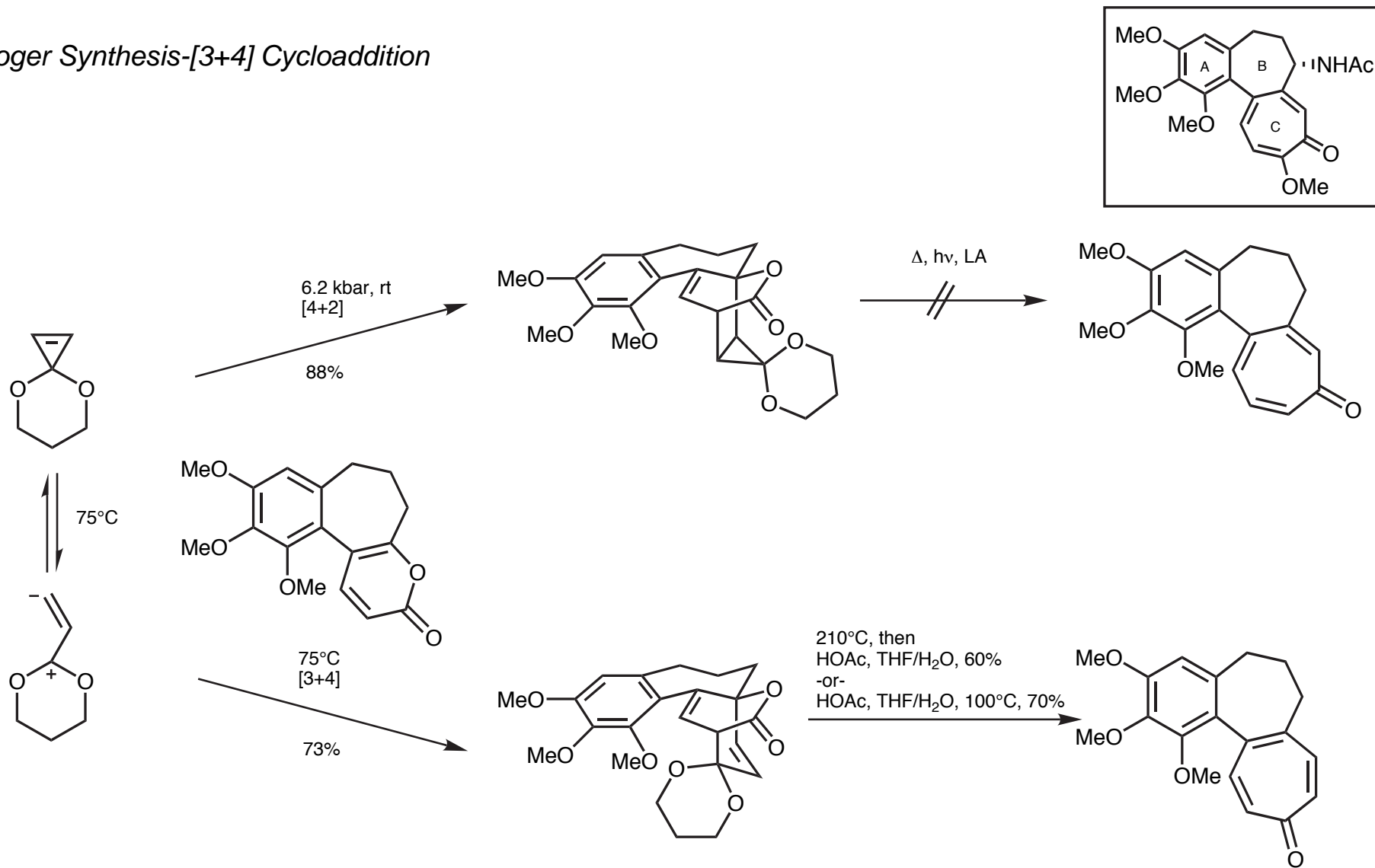
aq. NaHCO<sub>3</sub>, EtOH, 70%



• The final compound has already been converted to desacetamidocolchicine in 40% yield in the synthesis by van Tamelen

Martel *J. Org. Chem.* **1965**, 1752

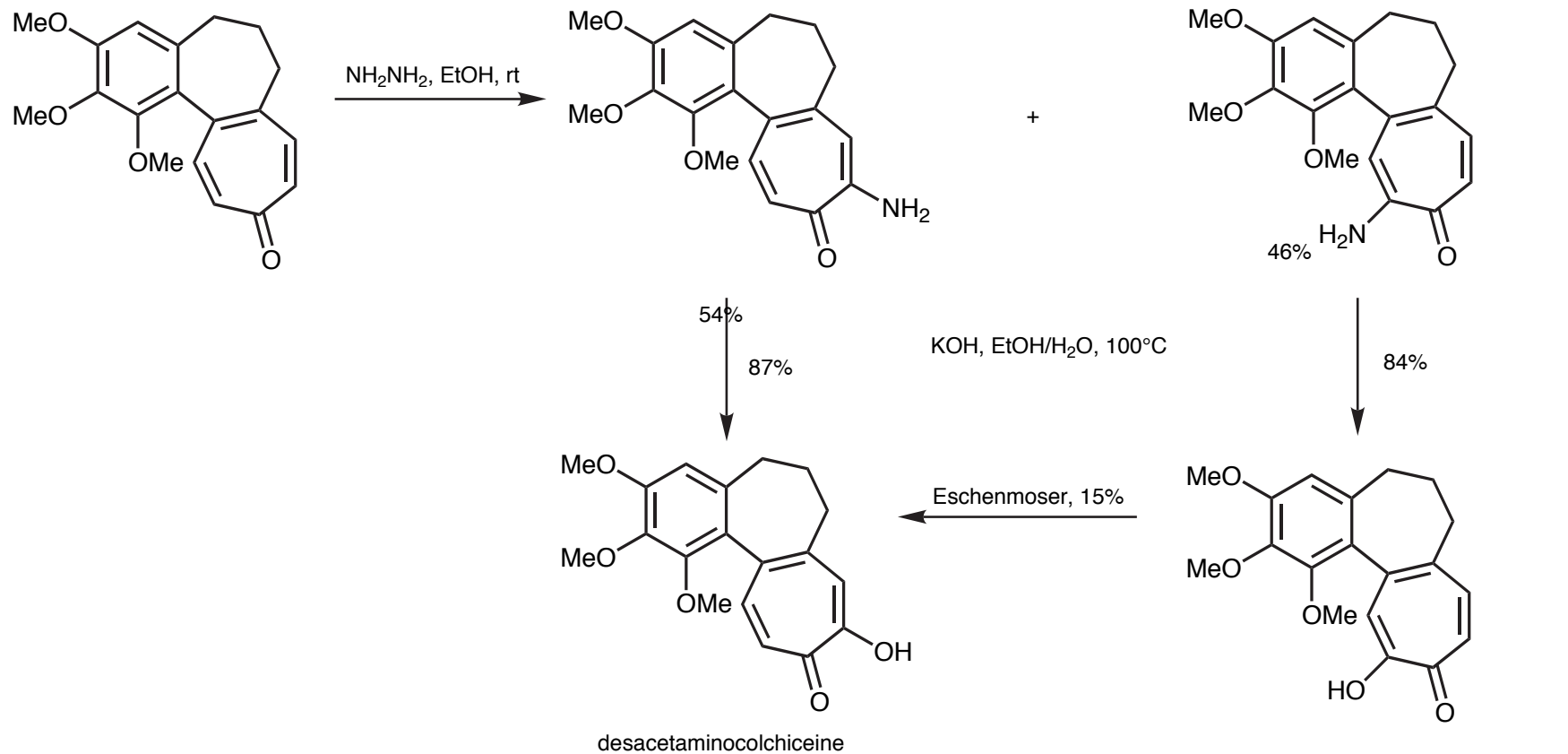
## Boger Synthesis-[3+4] Cycloaddition



- The pyrone used in the cycloaddition is an intermediate on Eschenmoser's route to colchicine
- Steric hinderance disfavors the [4+2] cycloaddition at higher temperatures

Boger *J. Am. Chem. Soc.* **1986**, 6713

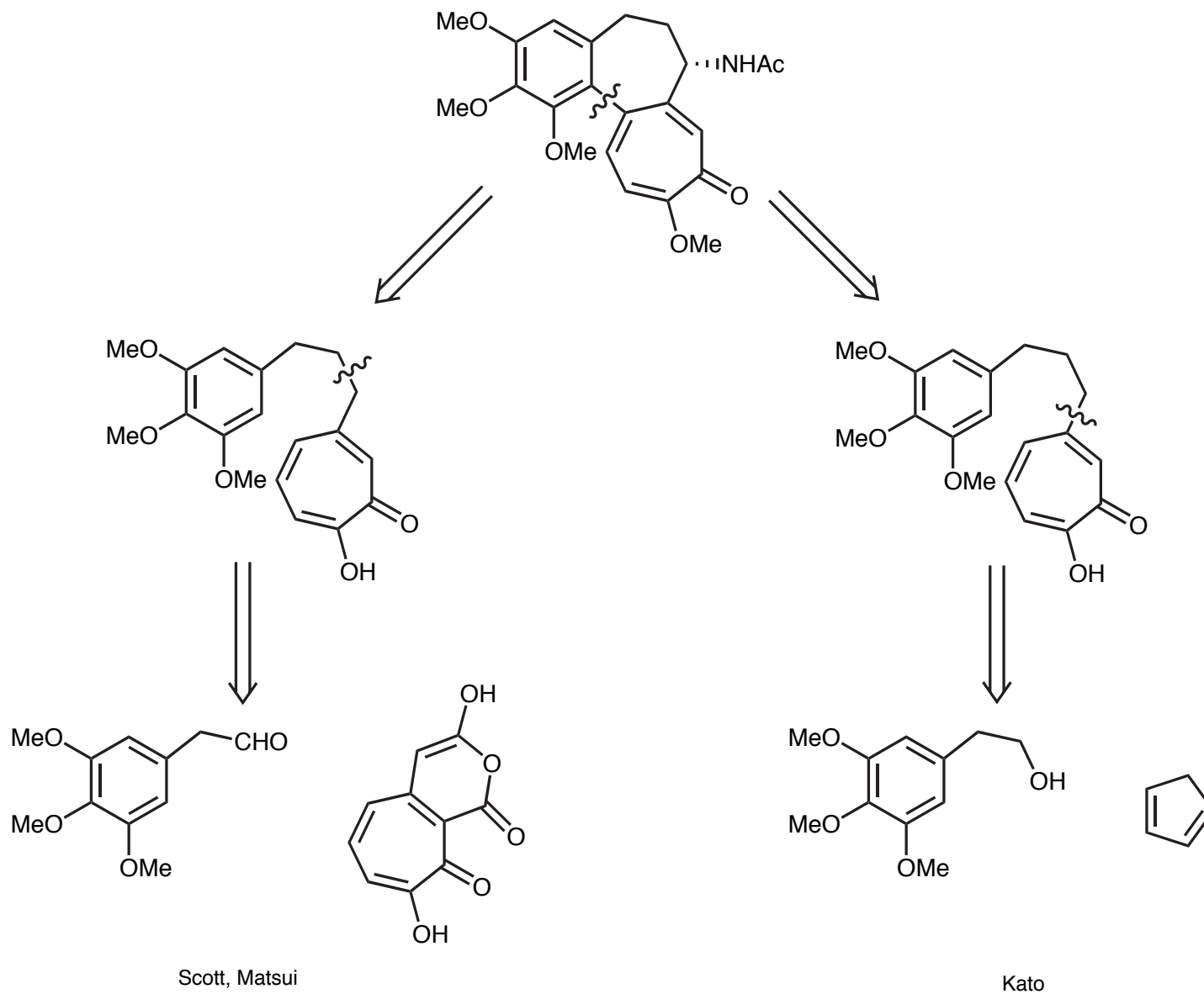
## Boger Synthesis-Completion



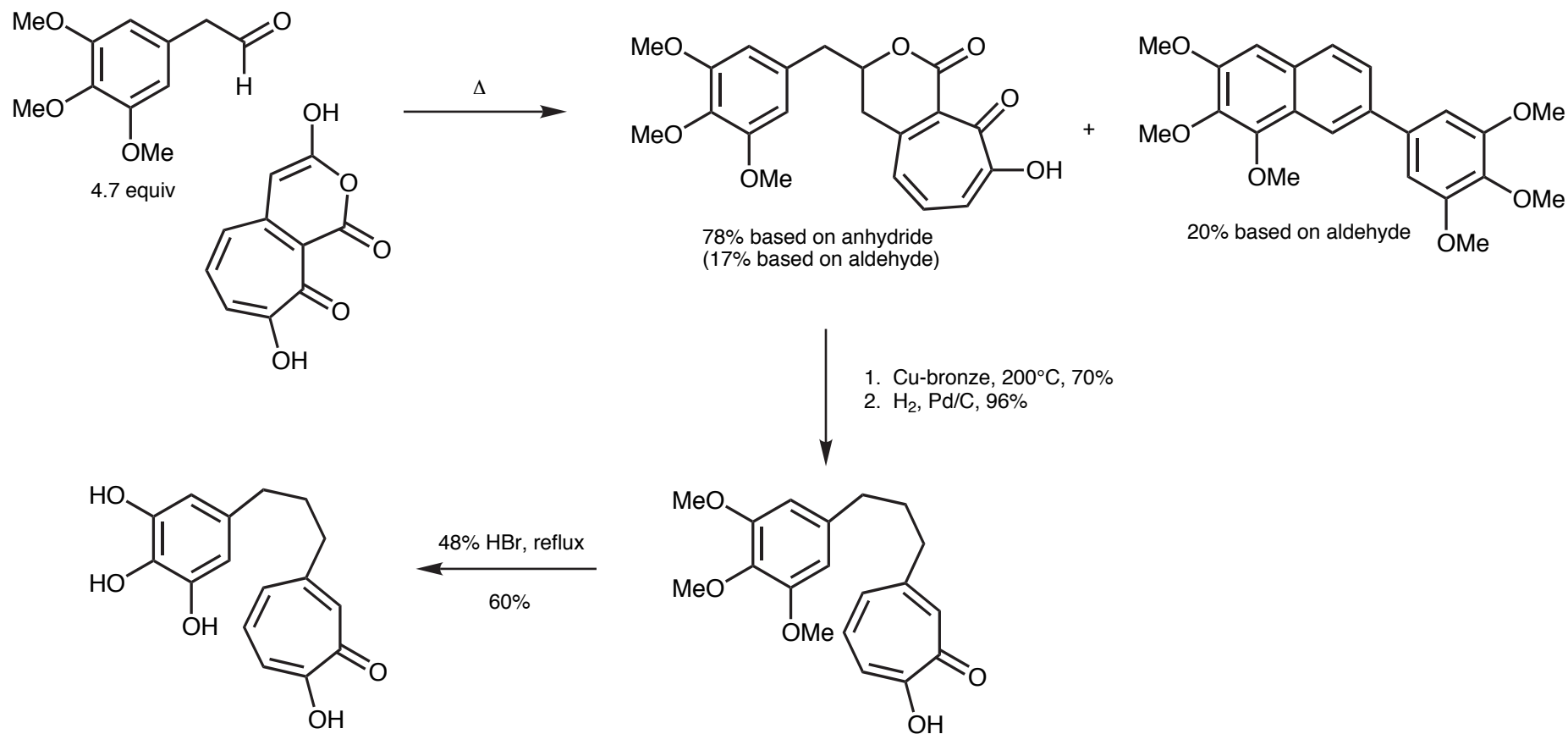
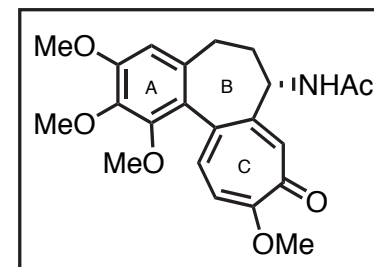
- The hydrazine amination is similar to one performed by Nakamura in his synthesis
- The Eschenmoser transposition of 11-hydroxytropone into 9-hydroxytropone is accomplished by tosylation, aminolysis, and hydrolysis

Boger *J. Am. Chem. Soc.* **1986**, 6713

*Retrosynthetic Analyses of Colchicine-A->AC->ABC via Oxidative Phenolic Coupling of Intact Tropolone*



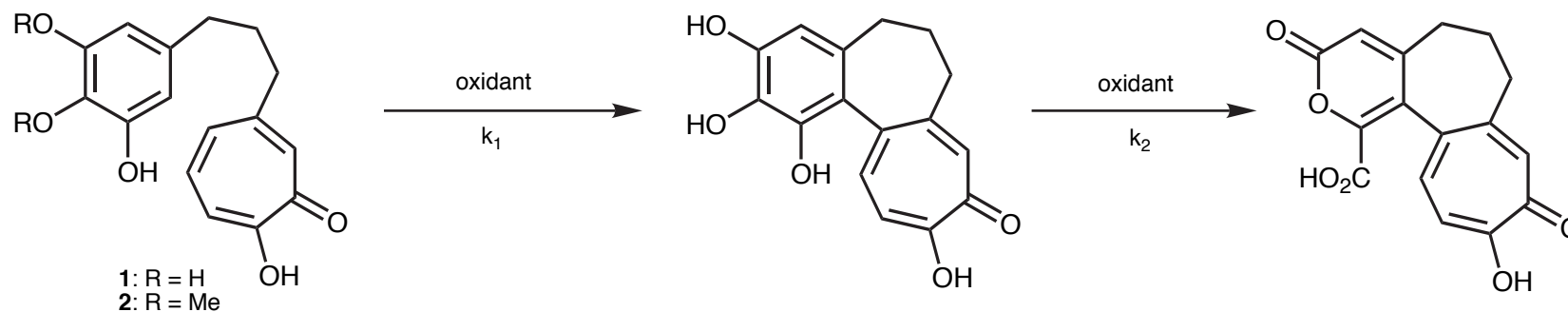
## Scott Synthesis-Set-Up for Phenol Coupling



• The starting anhydride is available in 3 steps (7% yield) from the oxidation of pyrogallol

Scott *Tetrahedron* **1965**, 3605

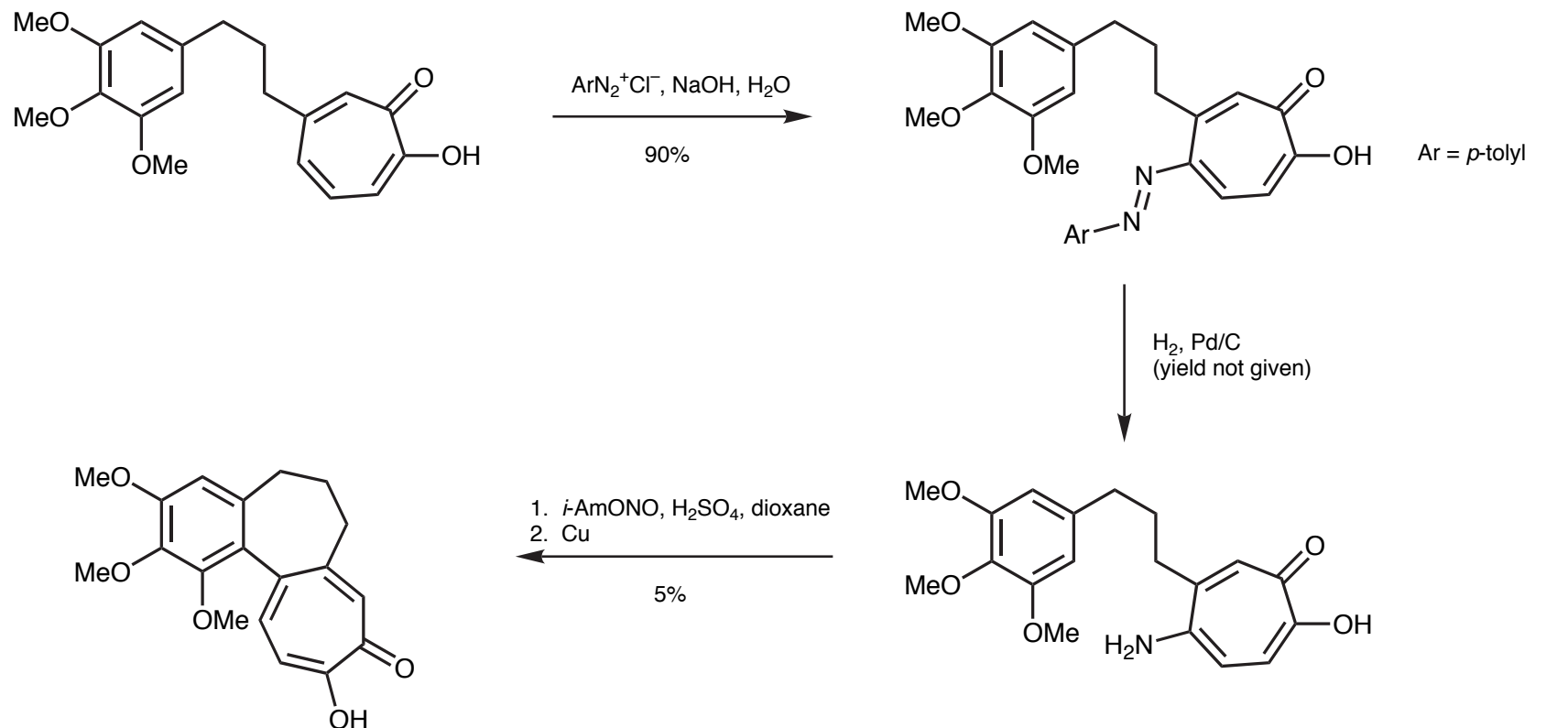
## Scott Synthesis-Phenol Coupling



- Attempted cyclizations of the bismethylated compound **2** with  $\text{MnO}_2$ ,  $\text{K}_3\text{Fe}(\text{CN})_6$ , Pd/C, and  $\text{PbO}_2$ , returned recovered starting material
- Compound **1** and the cyclization product were both extremely sensitive to base, decomposing slowly even in pH 7 aqueous solutions
- Most oxidation conditions resulted in decomposition of **1** and the product: air/ $\text{Na}_2\text{CO}_3$ , air/ $\text{BaOH}$ , air/ $\text{NH}_4\text{OH}$ ,  $\text{PbO}_2$ ,  $\text{MnO}_2$ ,  $\text{KIO}_3$
- Only  $\text{K}_3\text{Fe}(\text{CN})_6$  and  $\text{FeCl}_3$  did not decompose the starting material and product
- For the oxidation with  $\text{K}_3\text{Fe}(\text{CN})_6$ ,  $k_2/k_1 = 1000$ , and the pyrone could be isolated in 20% yield
- The optimized conditions ( $\text{FeCl}_3$ , 6 N  $\text{H}_2\text{SO}_4$ , EtOH,  $\text{CHCl}_3$ , 72h) resulted in a 4-5% yield of desired product by UV spectroscopy. Isolation of the product from this reaction could be accomplished by paper chromatography under inert atmosphere (2%)

Scott *Tetrahedron* **1965**, 3605

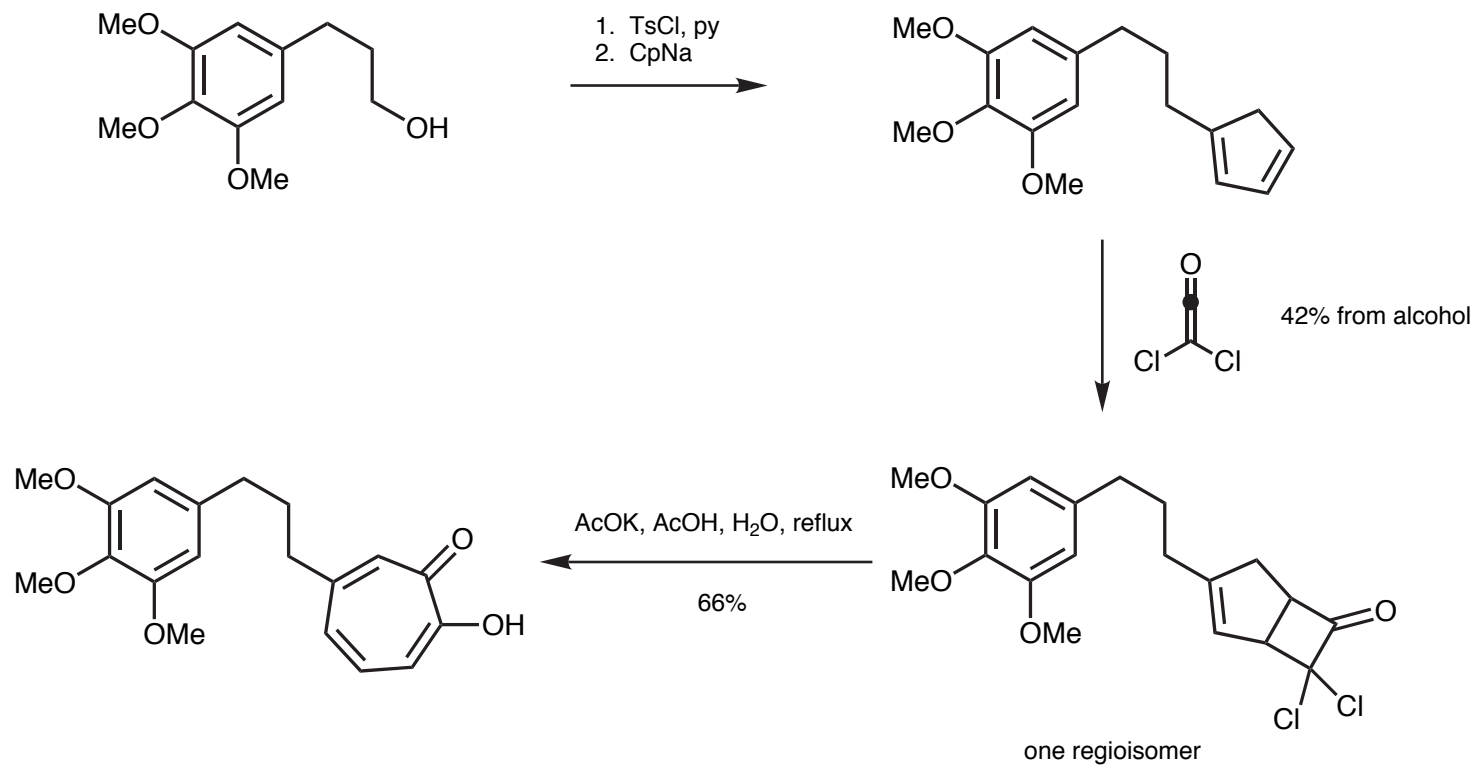
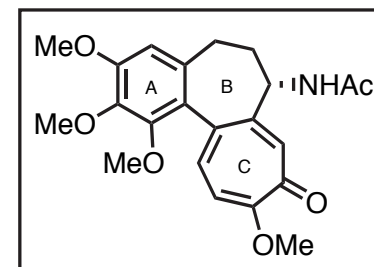
## Matsui Synthesis-B-ring Formation



- The starting material shown was originally synthesized by their own method in 6 steps and 4% overall yield. To illustrate the Pshorr reaction as a phenol coupling method, it was synthesized via the method of Scott (3 steps, 52% yield)
- Attempted cyclization of the diazonium chloride synthesized from the aminotropolone with isoamyl nitrite/HCl failed

Matsui *Agri. Biol. Chem.* **1967**, 675  
 Matsui *Agri. Biol. Chem.* **1968**, 995

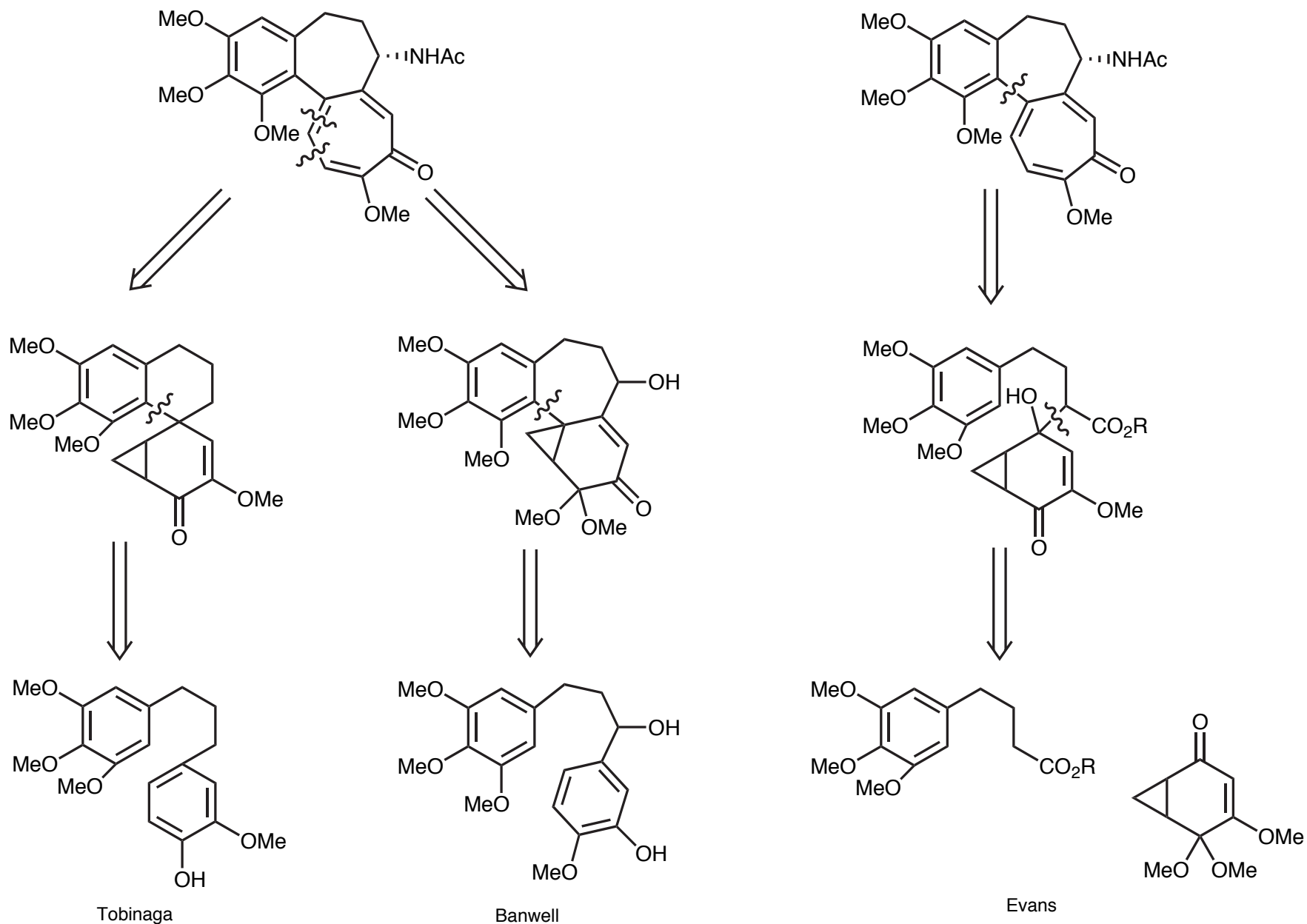
*Kato Synthesis-Synthesis of the Phenol Coupling Intermediate*



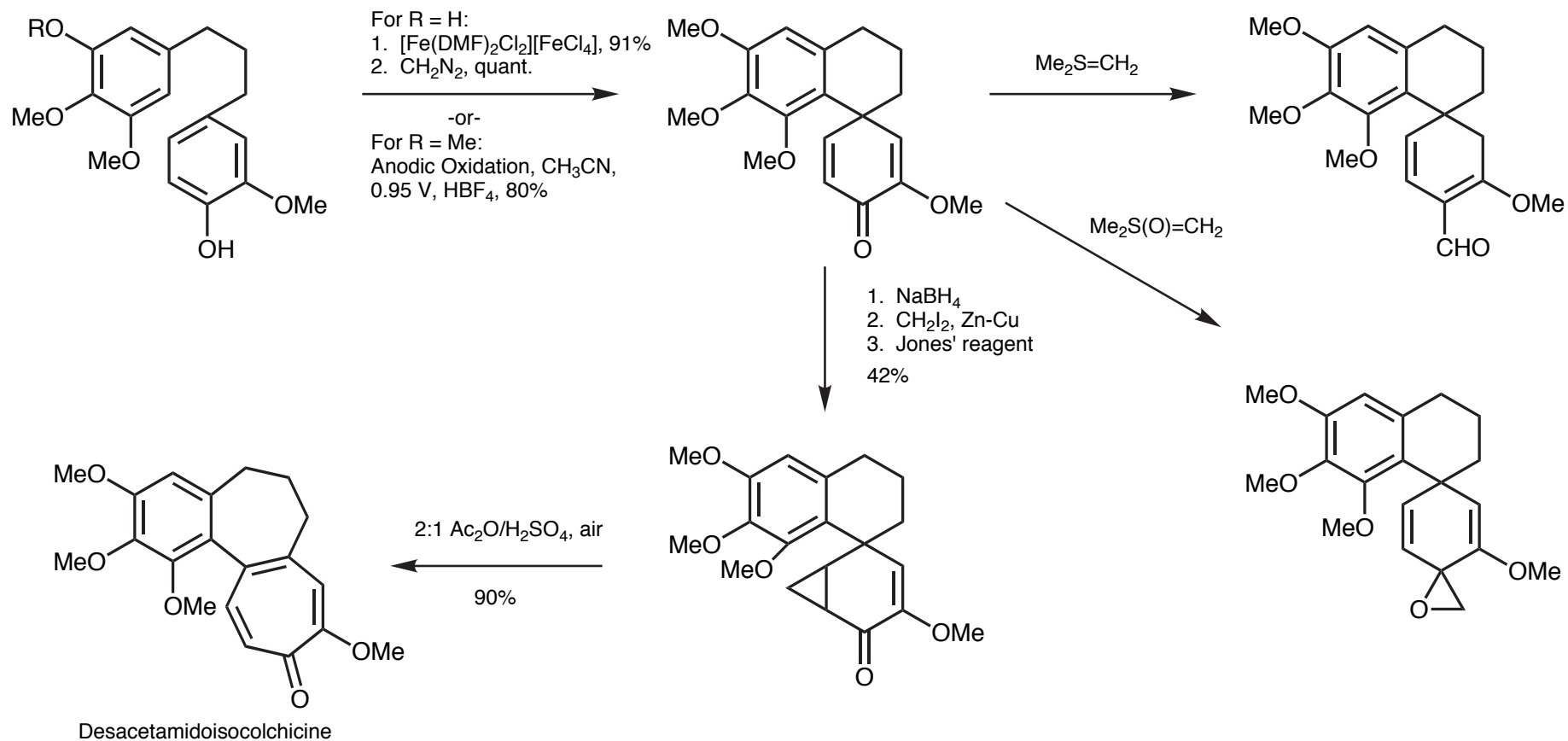
- The starting alcohol was synthesized from the cinnamyl ester in two steps and 92% yield
- The tropolone was previously cyclized to desacetamidocolchicine by Matsui

Kato *Bull. Chem. Soc. Jpn.* **1974**, 1516

Retrosynthetic Analyses of Colchicine-A--AC'--ABC'--ABC via Cyclopropyl Ring Expansion



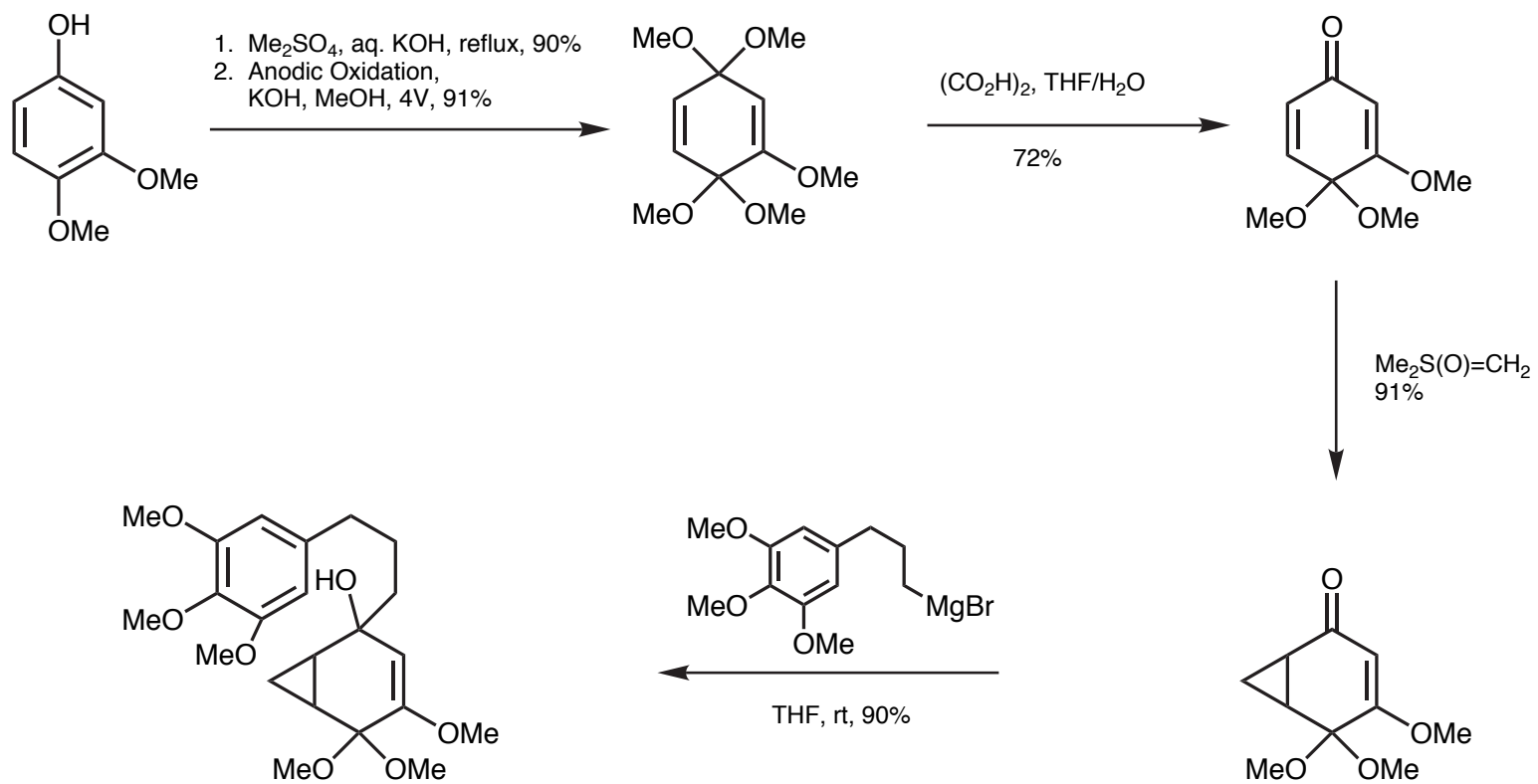
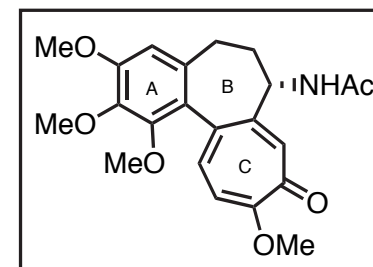
## Tobinaga Synthesis-Oxidative Phenol Coupling



- The iron reagent used for the oxidative coupling is prepared by adding DMF to a  $\text{Et}_2\text{O}$  solution of  $\text{FeCl}_3$
- Other attempts to cyclopropanate the spirodienone directly failed to give the desired product
- The final product has already been transformed to colchicine by Eschenmoser

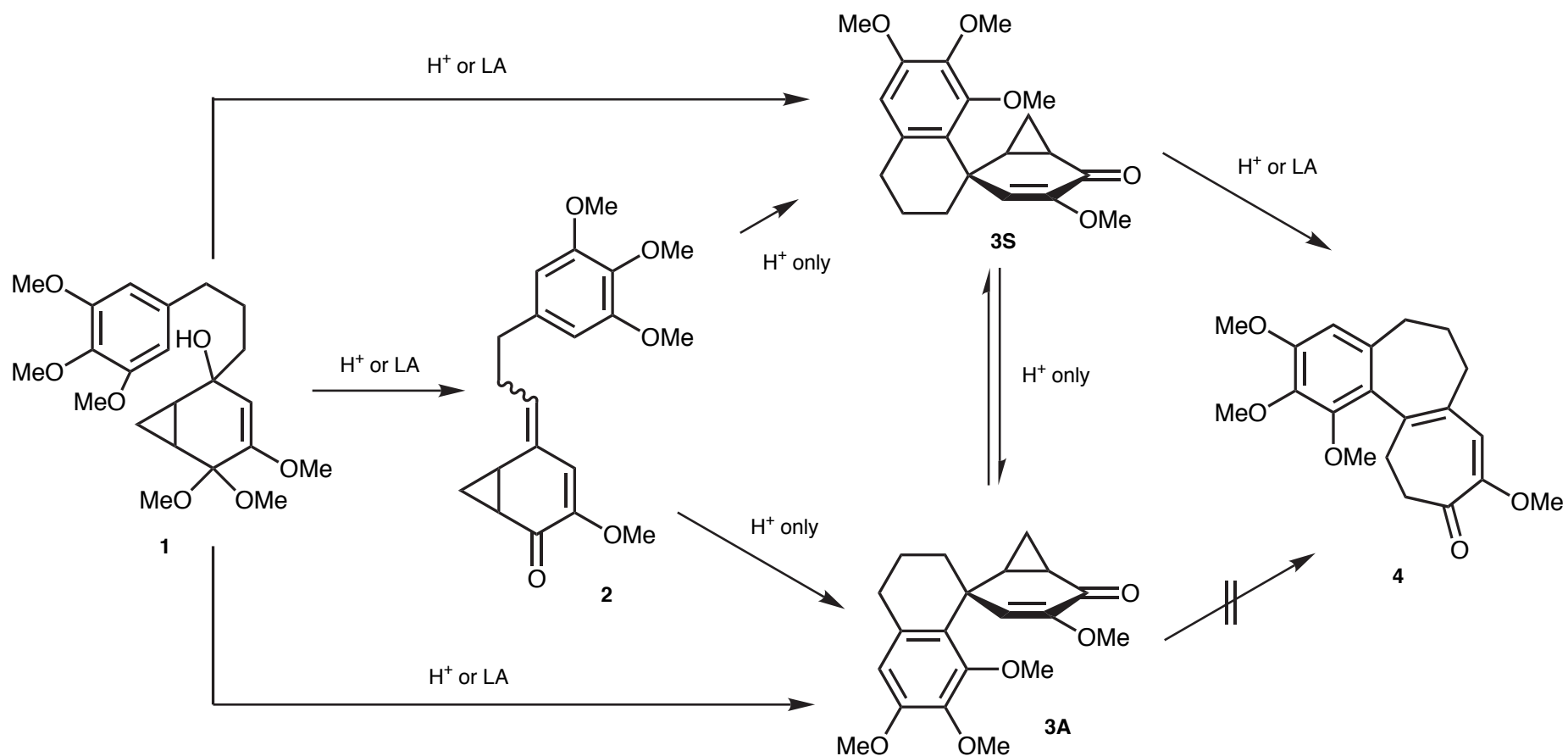
Tobinaga *Chem. Comm.* 1974, 300

Evans Synthesis-Synthesis of Phenol Coupling Intermediate



Evans *J. Am. Chem. Soc.* **1978**, 4593  
 Evans *J. Am. Chem. Soc.* **1981**, 5813

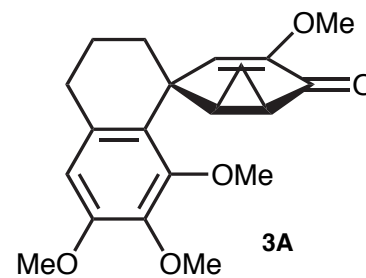
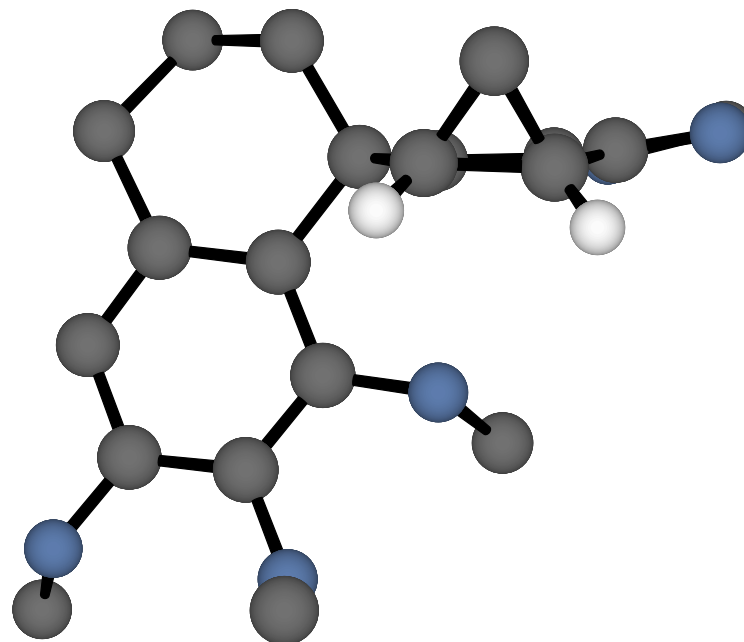
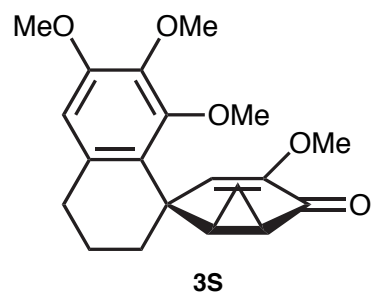
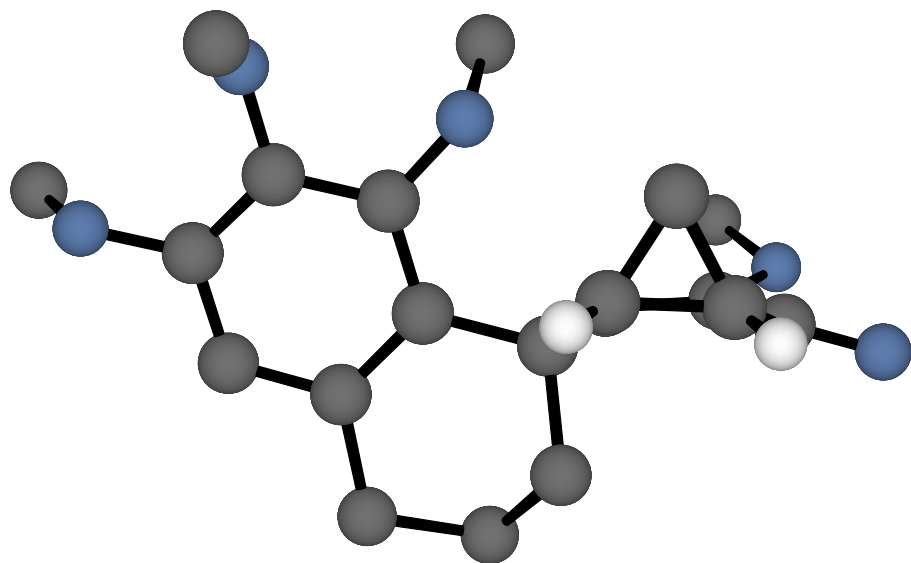
## Evans Synthesis-Cyclization and Rearrangement



- Reaction of **1** with TFA for 18 h gave the dihydrotropolone **4** in 68% yield, whereas  $BF_3 \cdot OEt_2$  gave only a 23% yield
- All intermediates shown could be isolated by stopping the reaction before it went to completion
- Formation of **3A** is favored over **3S** upon initial cyclization
- Treatment of either **3S** or **3A** with TFA resulted in a mixture of **3S**, **3A**, and **4**
- Compound **3S** is identical with the compound synthesized by Tobinaga in the course of his synthesis
- Treatment of **3S** with  $BF_3 \cdot OEt_2$  provided **4** in 40% yield, whereas **3A** failed to react under the same conditions
- The **3S/3A** interconversion is postulated to proceed through a retro-Friedel-Crafts type mechanism
- Compound **4** can be converted to desacetamidoisocolchicine by the action of DDQ in 72% yield

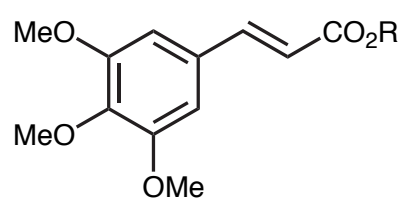
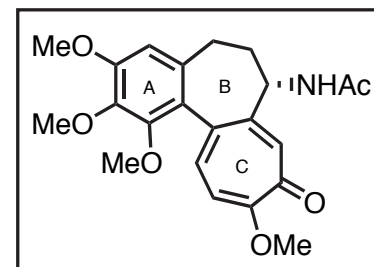
Evans *J. Am. Chem. Soc.* **1978**, 4593  
 Evans *J. Am. Chem. Soc.* **1981**, 5813

# Evans Synthesis-Spirocycles



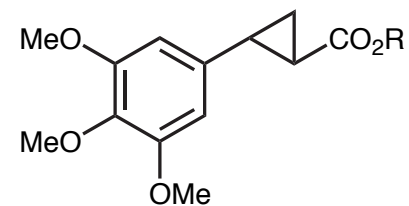
• MM2 minimized structures

Evans Synthesis-Synthesis of Phenol Coupling Intermediate

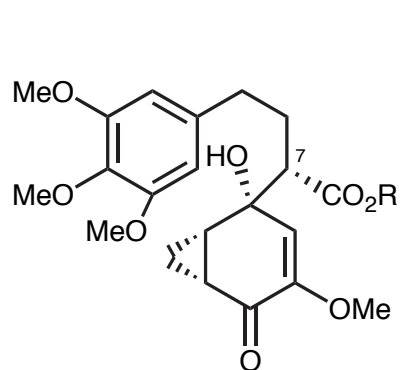
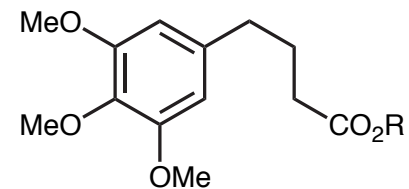


For R = *t*-Bu:  
Me<sub>2</sub>S(O)CH<sub>2</sub>, 69%

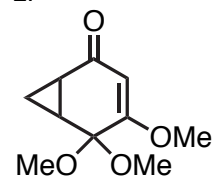
For R = Me:  
CH<sub>2</sub>N<sub>2</sub>, Pd(OAc)<sub>2</sub>, 98%



H<sub>2</sub>, Pd/C  
R = *t*-Bu: 70%  
R = Me: quant.



1. LDA, THF  
2.



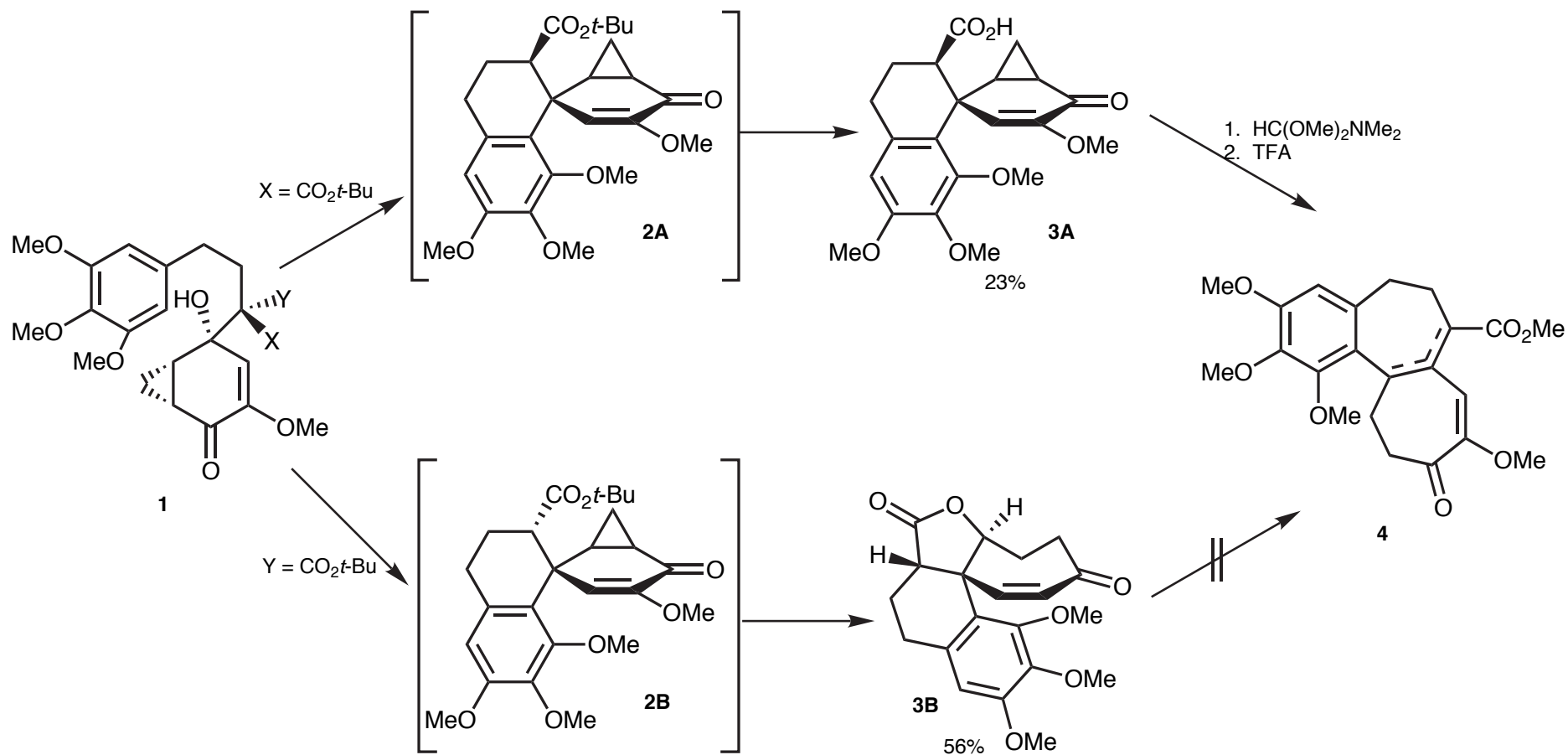
3. (CO<sub>2</sub>H)<sub>2</sub>, H<sub>2</sub>O/THF

R = *t*-Bu: 3:2:1 mixture of diastereomers, 75%

R = Me: 1:1 mixture of diastereomers at C-7, 95%

Evans *J. Am. Chem. Soc.* **1978**, 4593  
Evans *J. Am. Chem. Soc.* **1981**, 5813

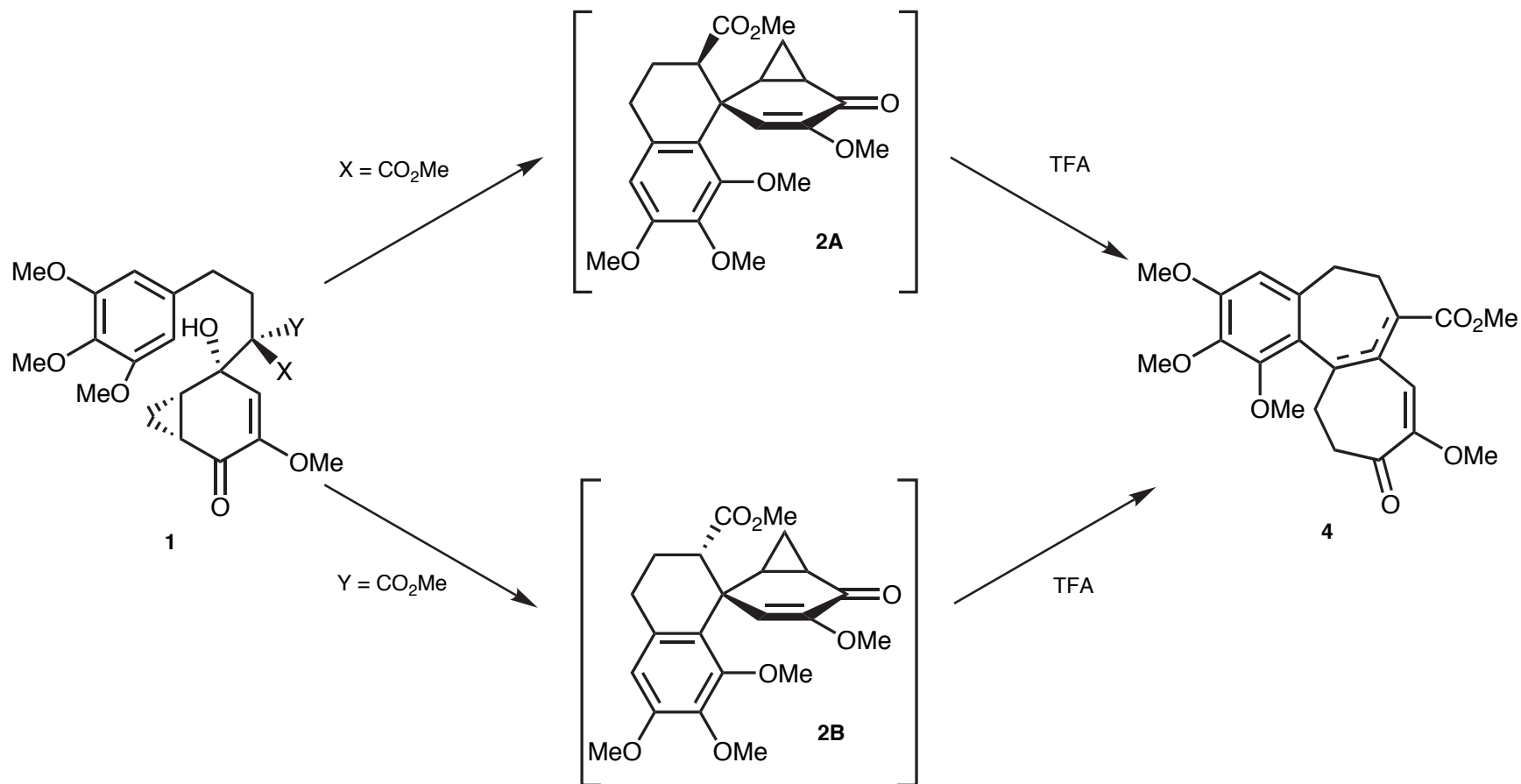
## Evans Synthesis-Cyclization and Rearrangement



- Spirocyclization of the 3:2:1 mixture of diastereomers with  $\text{BF}_3 \cdot \text{OEt}_2$  afforded acid **3A** and lactone **3B** in 23 and 56% yields respectively
- No trace of the syn spiro compounds seen in the previous case was observed
- Spontaneous loss of the *t*-Bu ester occurred under the reaction conditions
- The acid from **2B** is the only one stereoelectronically aligned to open the cyclopropyl ketone
- As expected, treatment of **3A**-methyl ester with  $\text{BF}_3 \cdot \text{OEt}_2$  did not result in formation of **4**
- **3A**-methyl ester was converted to the desired product **4** with TFA, but lactone **3B** was left unchanged

Evans *J. Am. Chem. Soc.* **1978**, 4593  
 Evans *J. Am. Chem. Soc.* **1981**, 5813

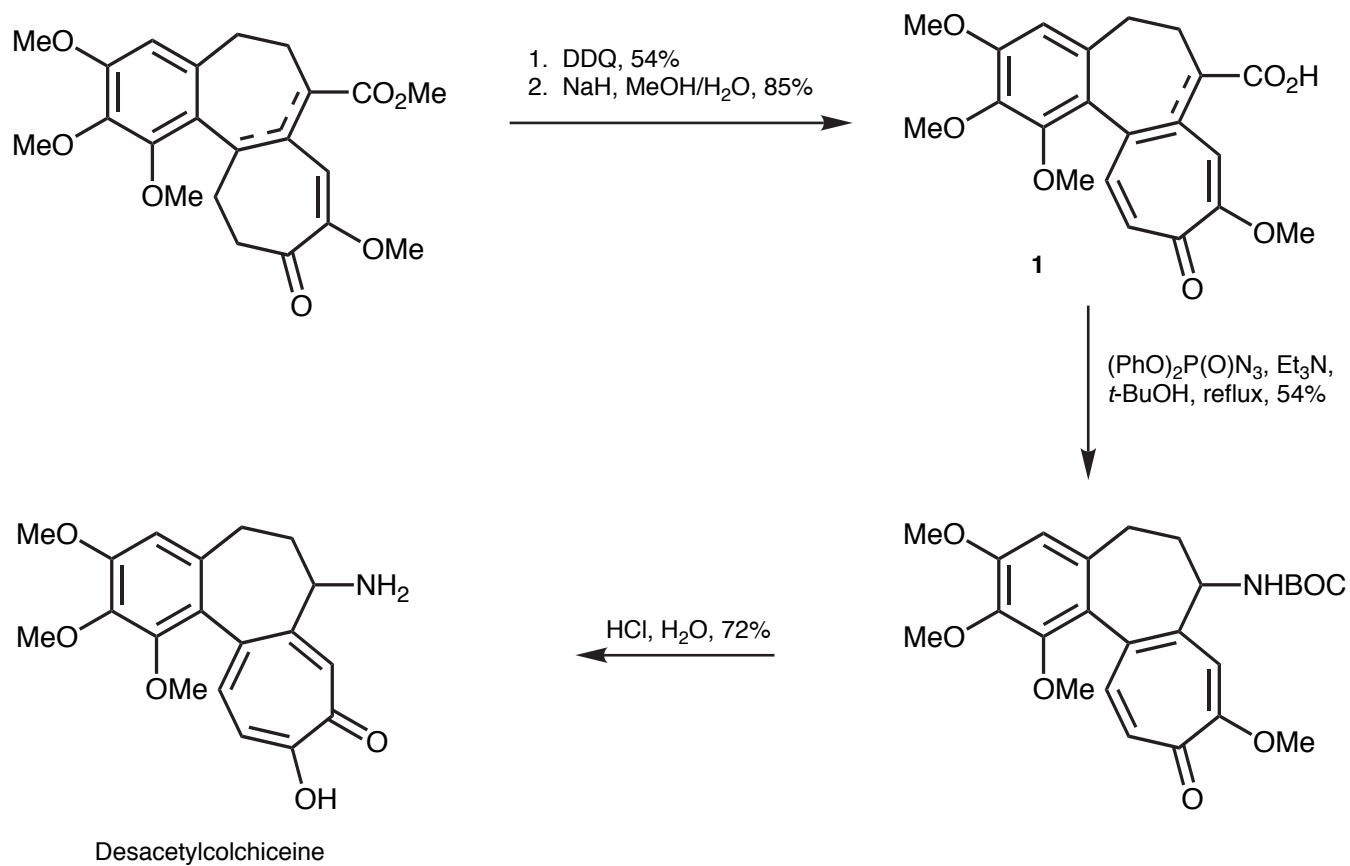
## Evans Synthesis-Cyclization and Rearrangement



- Spirocyclization of the 1:1 mixture of diastereomers with BF<sub>3</sub>•OEt<sub>2</sub> afforded a 1:1 mixture of **2A** and **2B** in 71% yield
- No trace of the syn spiro compounds was observed
- Equilibration of pure **2A** and the 1:1 **2A/2B** mixture with NaOMe/DMF gave the same 40:60 mixture of **2A** and **2B**
- **4** could be produced in 92% yield by reaction of the ketal precursor to **1** in TFA

Evans *J. Am. Chem. Soc.* **1978**, 4593  
 Evans *J. Am. Chem. Soc.* **1981**, 5813

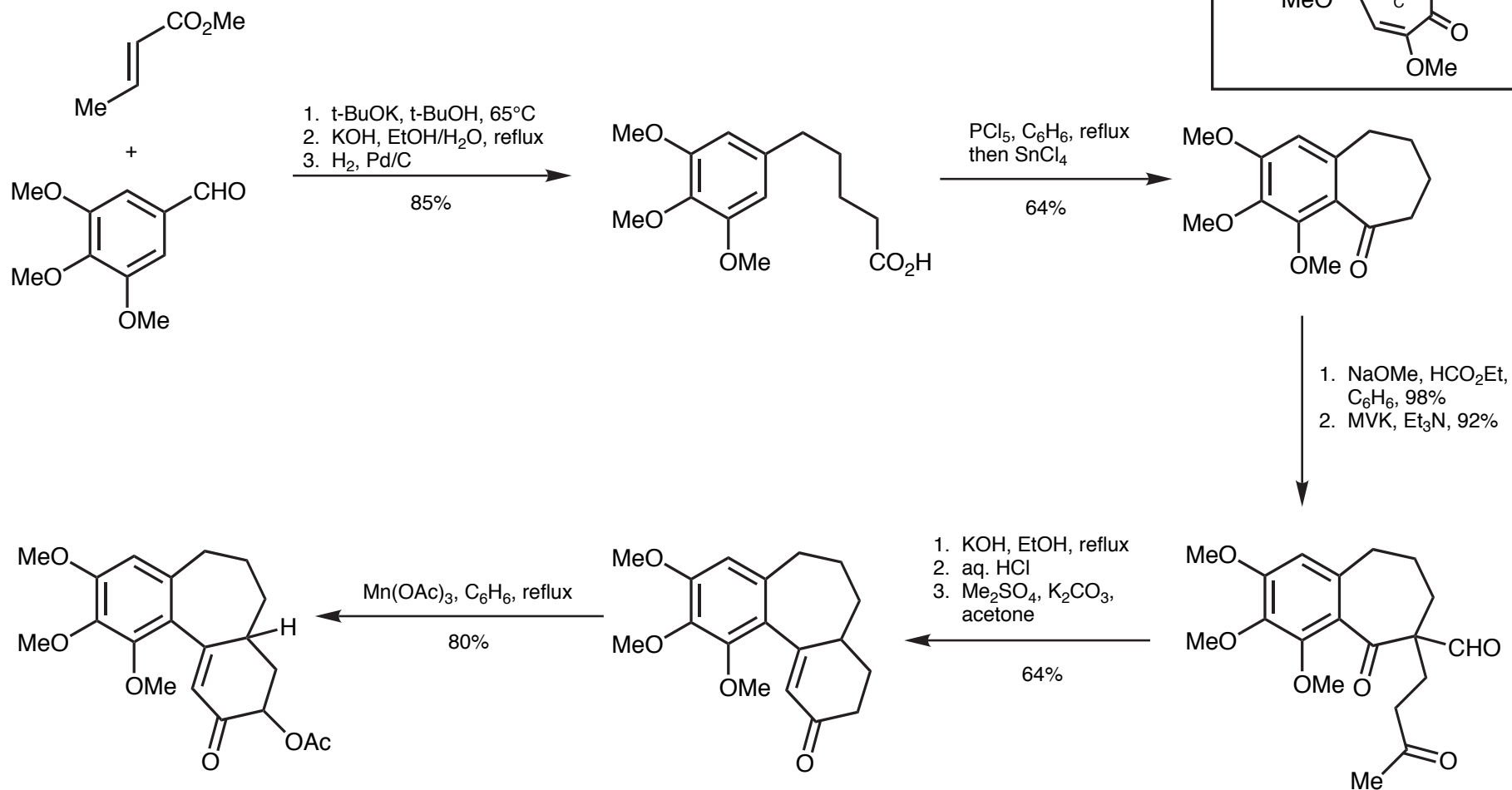
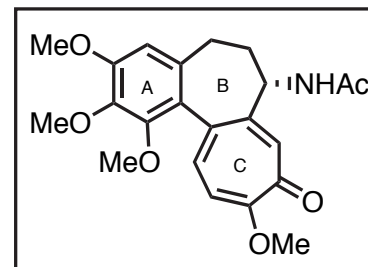
## Evans Synthesis-Completion of the Synthesis



- Compound **1** was isolated as a separable 7:3 mixture of the tropolone and its heptafulvene tautomer.
- Upon sitting in CDCl<sub>3</sub> purified samples of either tautomer were reconverted to the 7:3 mixture.

Evans *J. Am. Chem. Soc.* **1978**, 4593  
Evans *J. Am. Chem. Soc.* **1981**, 5813

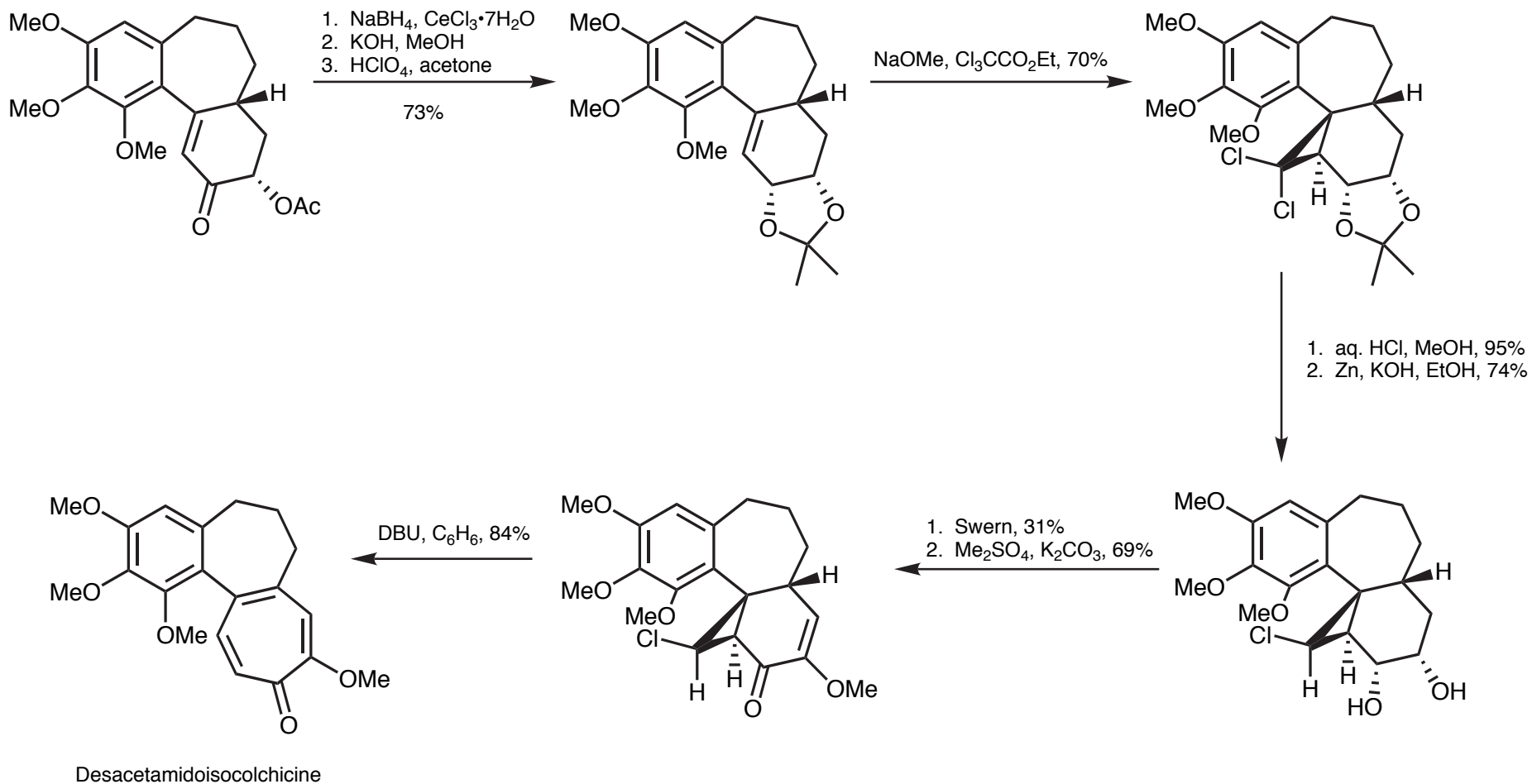
Banwell Synthesis-B and C-ring synthesis



1:1 mixture of diastereomers

- Direct Robinson annulation failed due to insufficient reactivity of the starting ketone
- NMR analysis of the crude reaction mixture after enone formation and decarboxylation indicated some demethylation had occurred, but methylation of the crude reaction mixture alleviated this problem

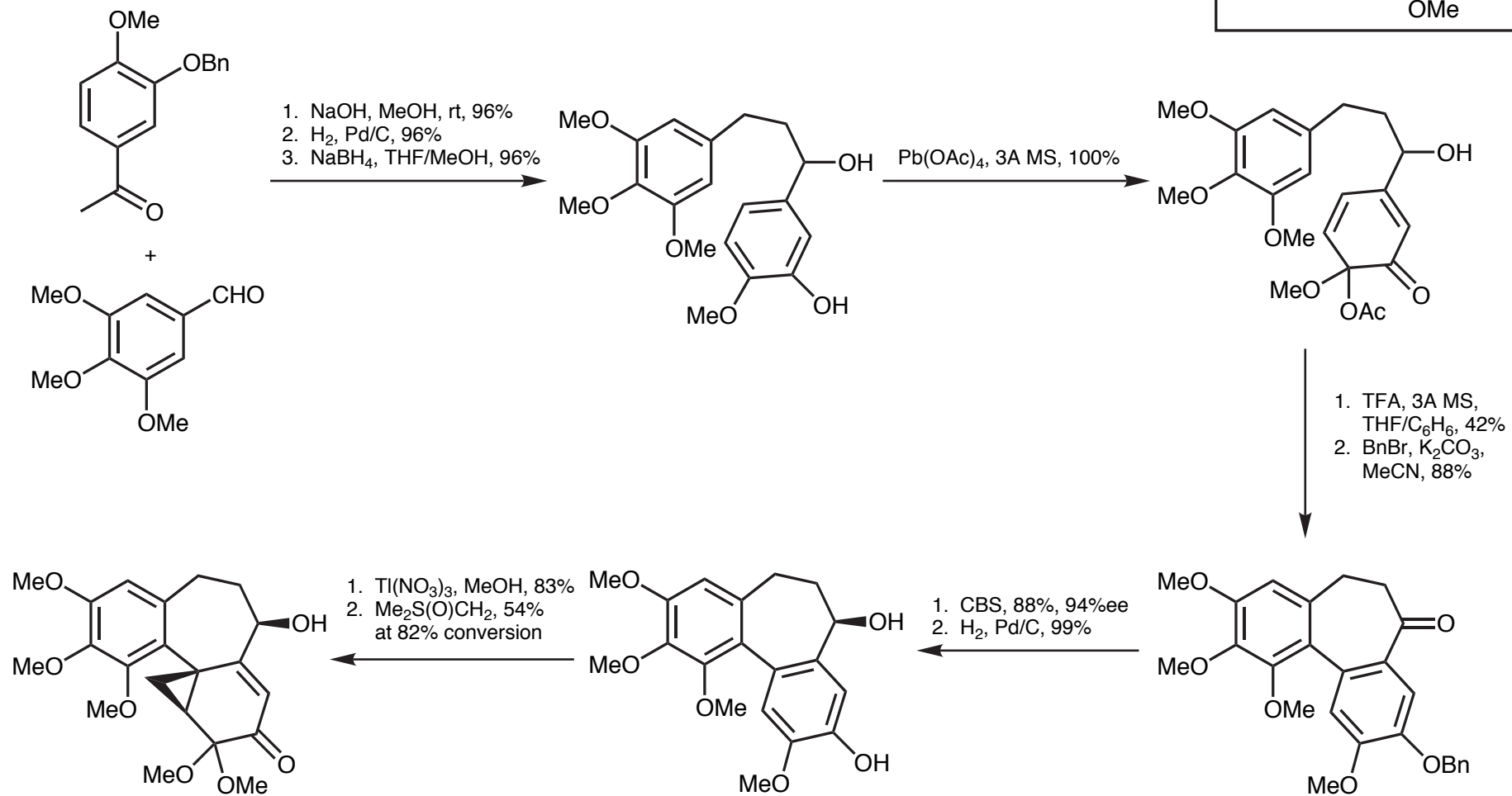
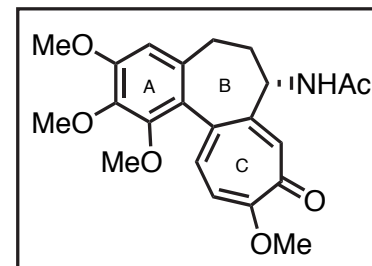
## Banwell Synthesis-Tropolonization



- The initial 3-step sequence to the acetonide was also performed on the other diastereomer in similar yields
- Dichlorocarbene addition to the other diastereomer resulted in a low yield of a C-H insertion product due to steric shielding of the olefin
- Reversing the order of the Zn reduction and acetal removal steps fails due to the extreme acid sensitivity of the monochlorocyclopropane
- This same acid sensitivity may be the cause of the low yield in the Swern oxidation
- Base-promoted rearrangement of a dichlorocyclopropyl enone was unsuccessful

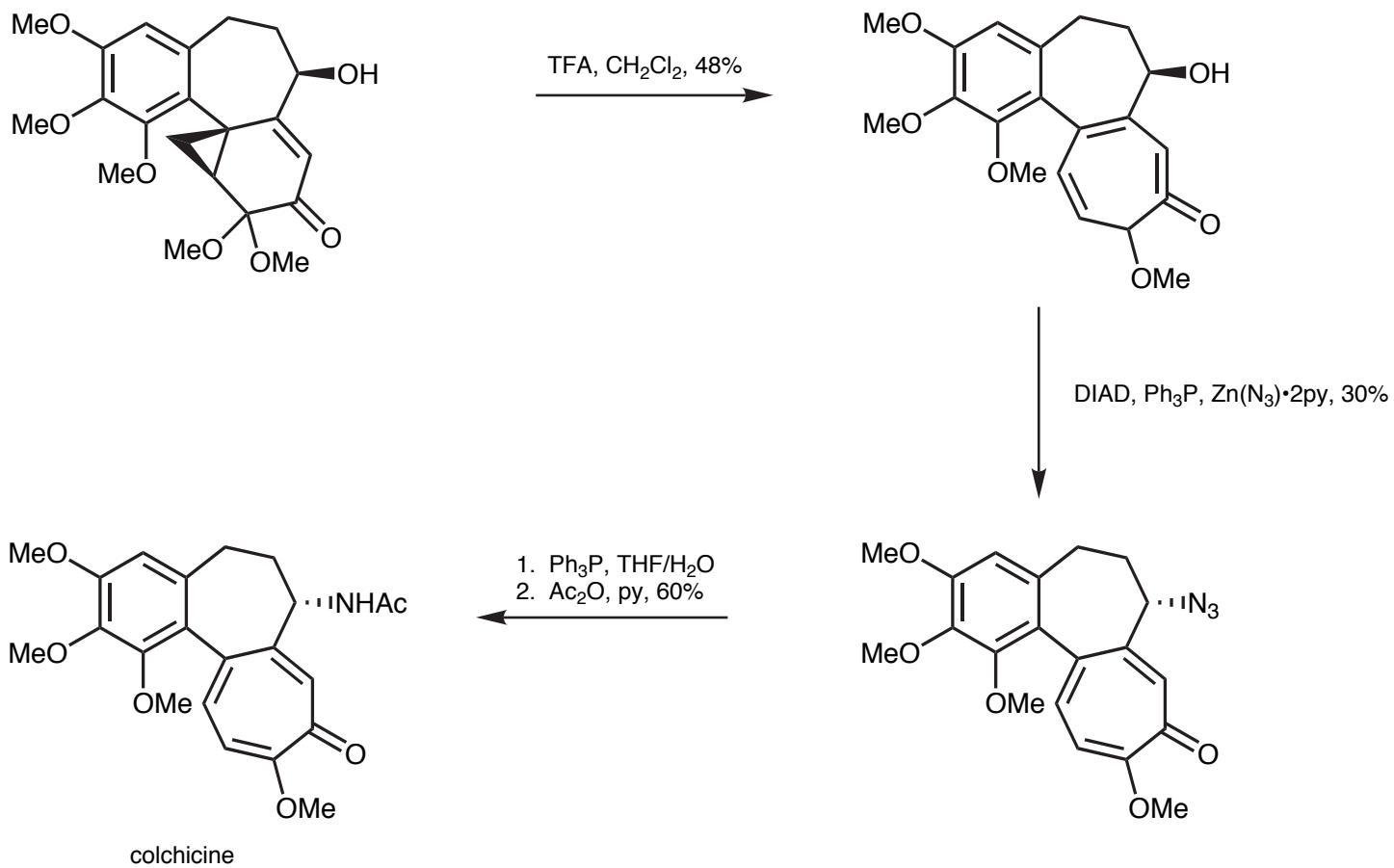
Banwell *J. Chem. Soc. Perkin Trans 1* **1992**, 1415

*Banwell Synthesis-New and Improved*



• The penultimate product of the sequence was crystallized up to 98% ee and its structure confirmed by X-ray crystallography

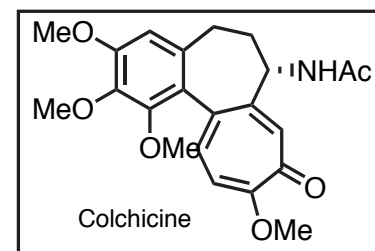
## Banwell Synthesis-New and Improved



- This marks the only synthesis of optically active colchicine that does not involve a resolution
- It is also the only synthesis that selectively produces the correct troponone isomer
- The final ee of colchicine produced is only 81%-racemization occurred during the Staudinger reduction

Banwell *Pure and Appl. Chem.* 1996, 539

## Summary-The Numbers



Synthesis	Starting material	(±)-Desacetaminocolchiceine	(±)-Colchicine
Eschenmoser	pyrogallol	17 steps, 0.234%	24 steps, 0.00243%
van Tamelen	pyrogallol	14 steps, 0.0425%	21 steps, 0.000442%
Nakamura	monomethylpyrogallol	N/A	22 steps, 0.0000675%
Woodward	aminocrotonate	N/A	24 steps, ???
Martel	trimethoxyphenylpropylchloride	15 steps, 0.298%	22 steps, 0.00310%
Scott	pyrogallol	8 steps, 0.000462%	15 steps, 0.0000481%
Boger	pyrogallol	11 steps, 3.66%	18 steps, 0.038%
Matsui	trimethoxyphenylacetaldehyde	7 steps, 2.36%	14 steps, 0.0245%
Kato	trimethoxyphenylpropanol	8 steps, 1.25%	15 steps, 0.013%
Tobinaga	bis(aryl)propane	6 steps, 34.4%	12 steps, 1.02%
Evans	3,4-dimethoxyphenol	7 steps, 23.6%	13 steps, 3.03%
Banwell	trimethoxybenzaldehyde	17 steps, 0.810%	14 steps, 1.1% (84% ee)