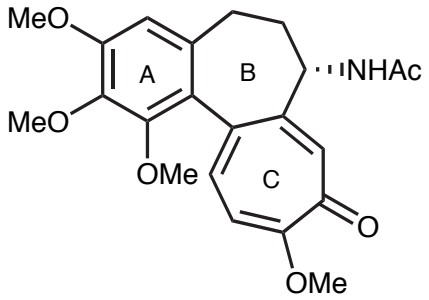
Colchicine

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:

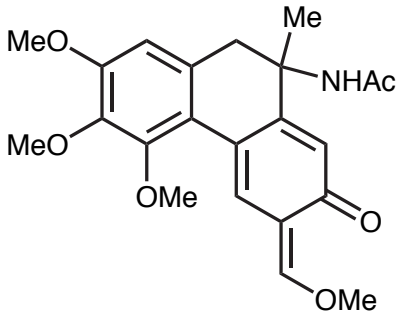
Eigsti "Colchicine in agriculture, medicine, biology, and chemistry"

Most Recent Synthesis:

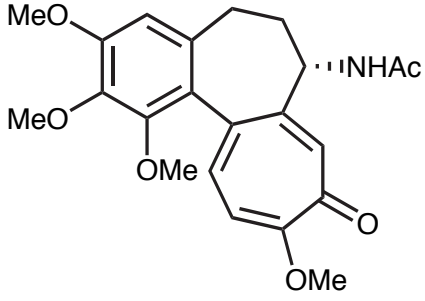
Banwell, *Pure and Appl. Chem.*, **1996**, 539

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



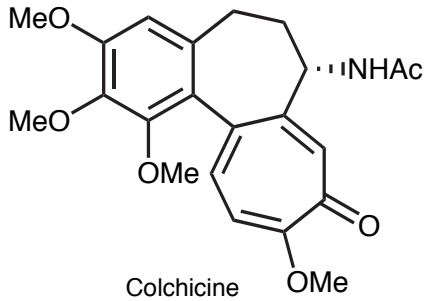
Windaus, 1924



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



Colchicine

- 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

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

Structure-Activity Relationship

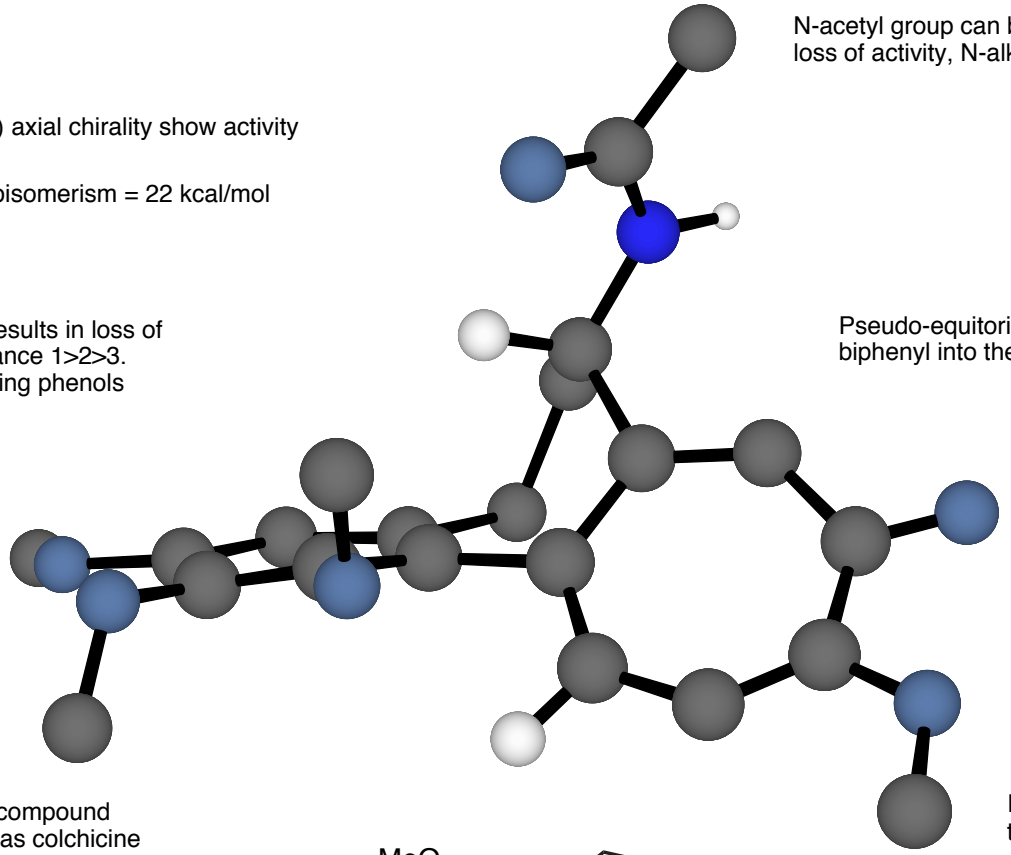
N-acetyl group can be replaced with almost acyl group without loss of activity, N-alkyl versions are slightly less active

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.

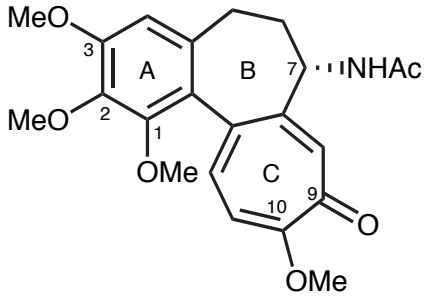
Pseudo-equitorial NHAc group gears the biphenyl into the (aS)-atropdiastereomeric form



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

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

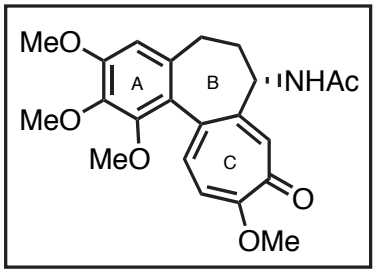
In the 10-position activity decreases in the series SMe>NR_2>OMe>OH>>H. An Et substituent in this position is also active

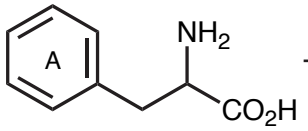


Contraction of the tropolone ring to a phenyl ring results in a slight decrease in activity

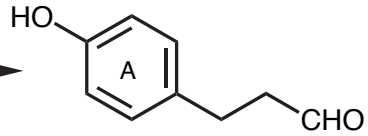
Brossi "The Alkaloids" v.23, p.1
Brossi "The Alkaloids" v.41, p.125

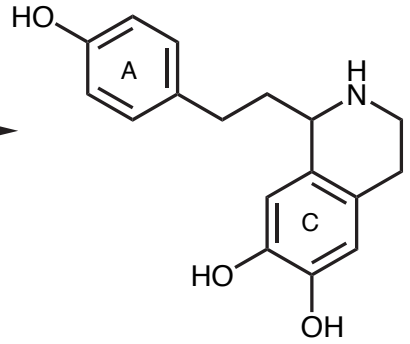
Biosynthesis of Colchicine

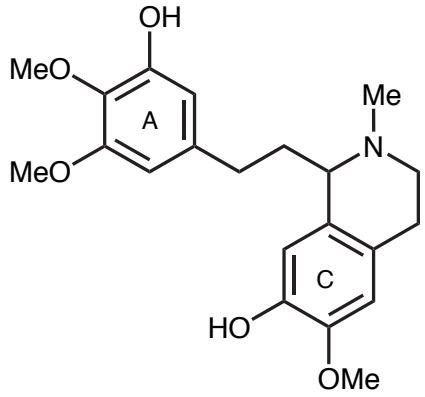




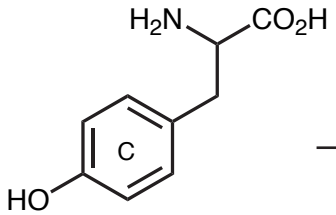
Phenylalanine



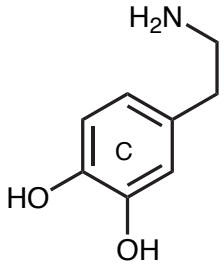




Autumnaline



Tyrosine

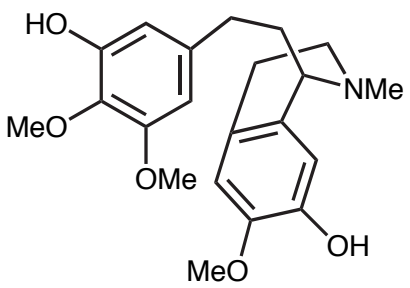


Dopamine

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

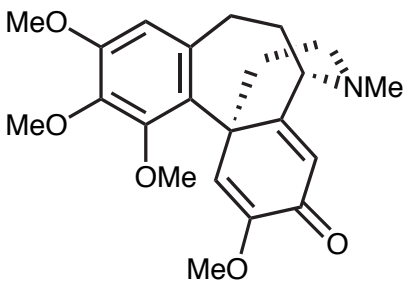
Brossi "The Alkaloids" v.23, p.1
Brossi "The Alkaloids" v.41, p.125
Herbert *Tetrahedron*, **1990**, 7119

Biosynthesis of Colchicine

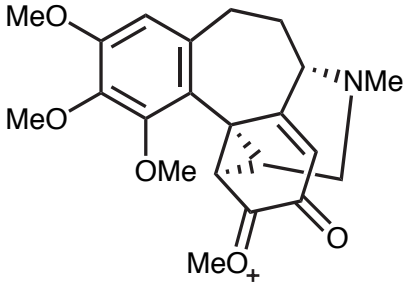


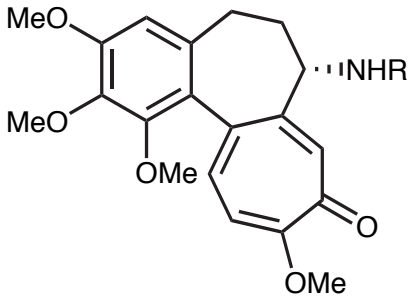
Autumnaline

Cytochrome P-450



O-Methylandrocymbine



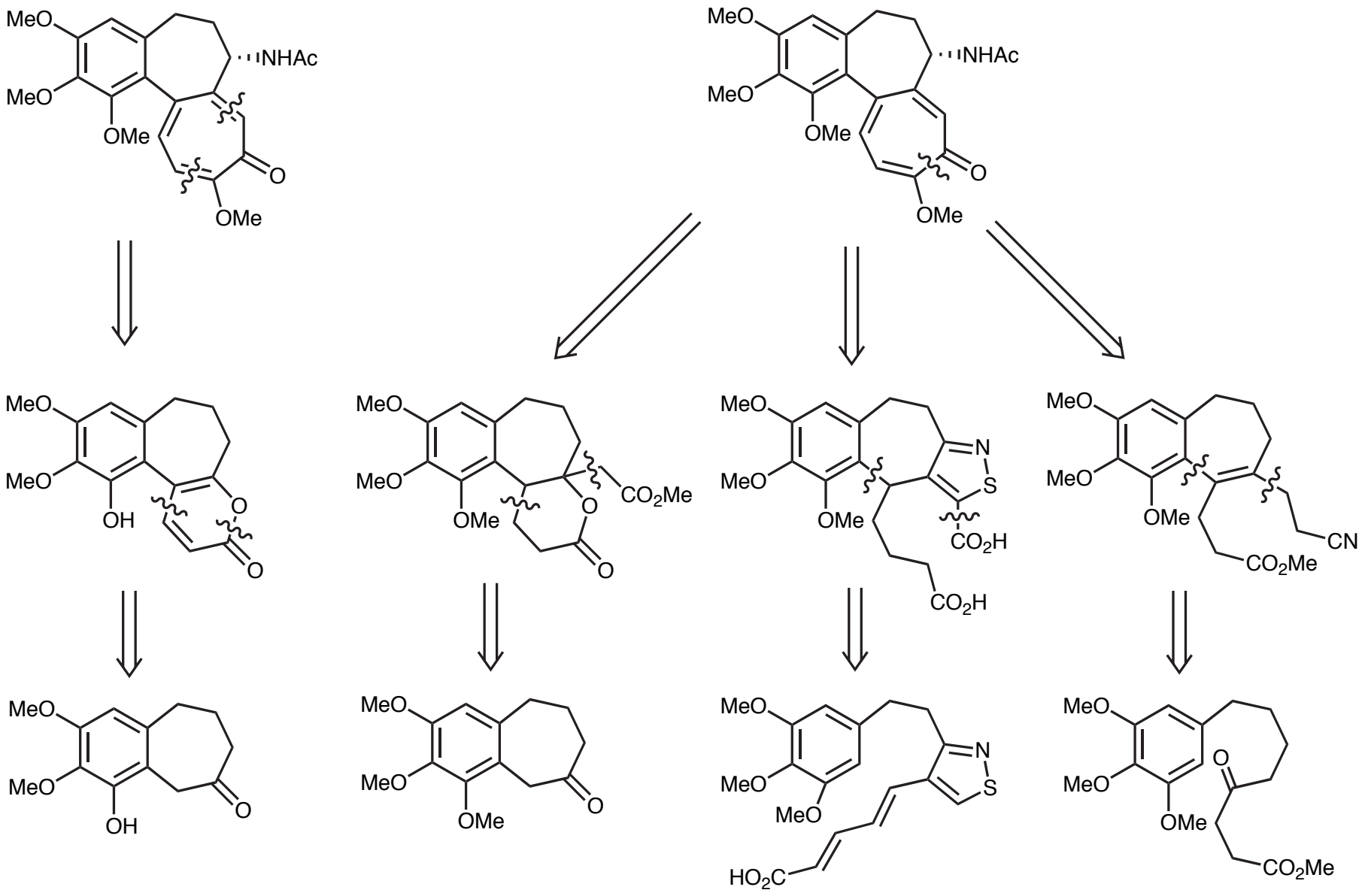


Demecolcine R = Me

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*



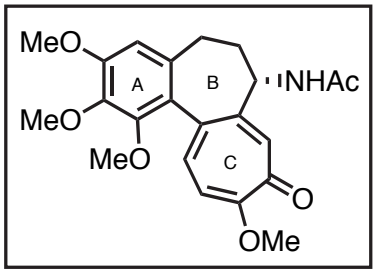
Eschenmoser, Boger

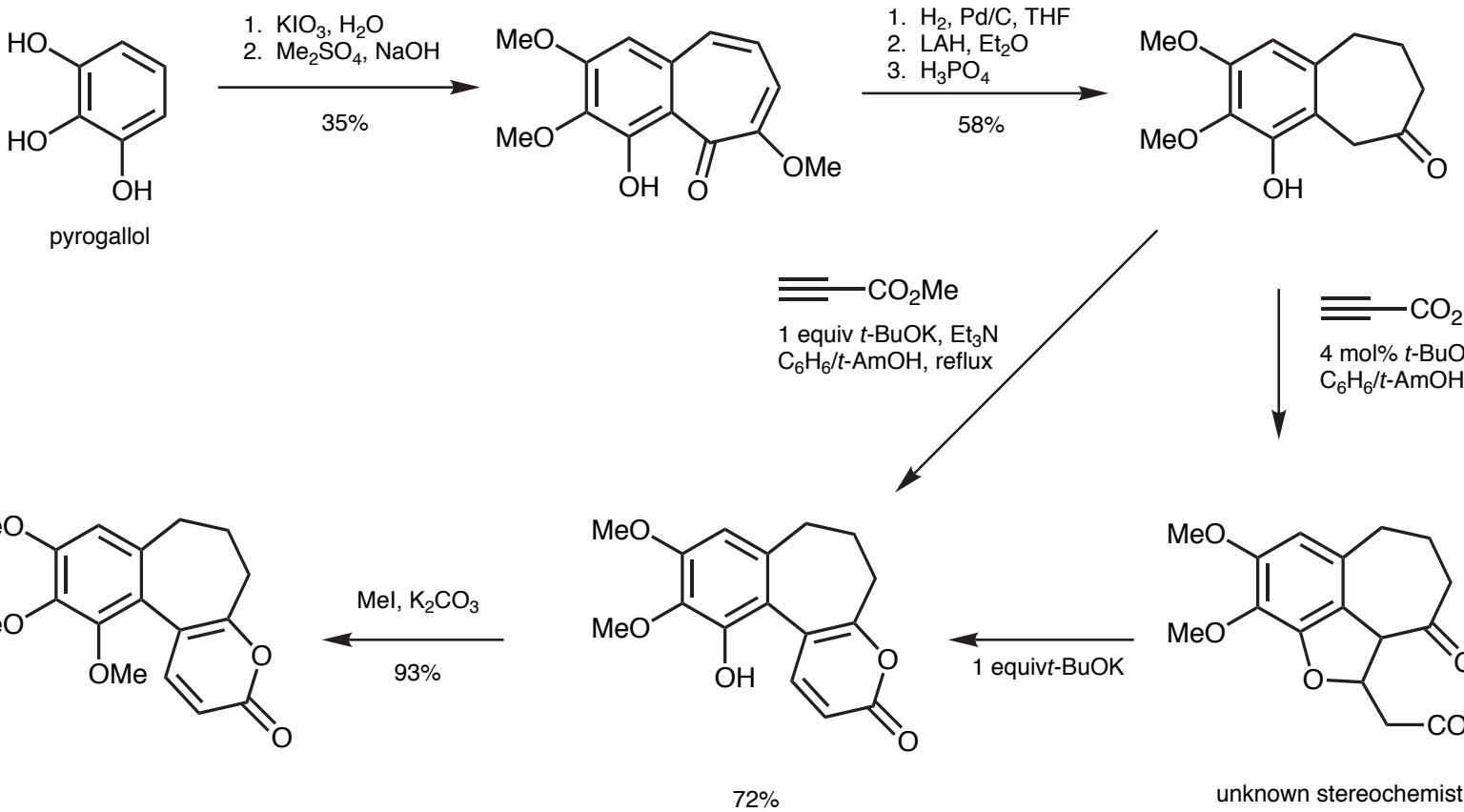
van Tamelen

Woodward

Martel

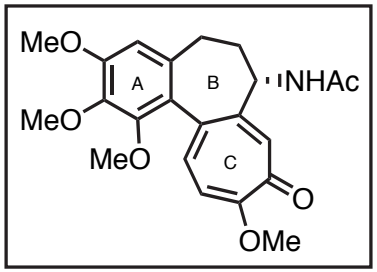
Eschenmoser Synthesis-Formation of the B ring

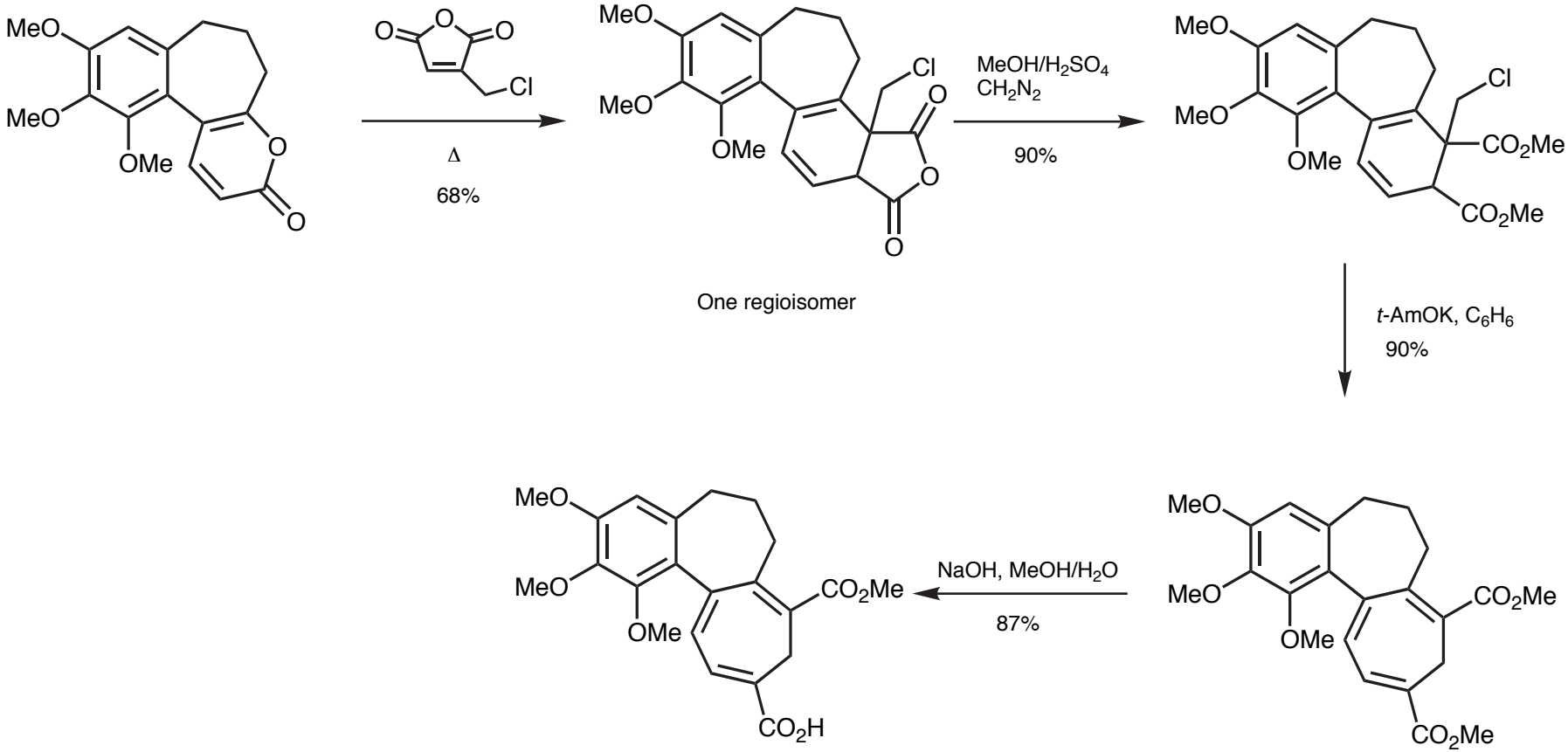




A. Eschenmoser *Helv. Chim. Acta* **1961**, 540

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

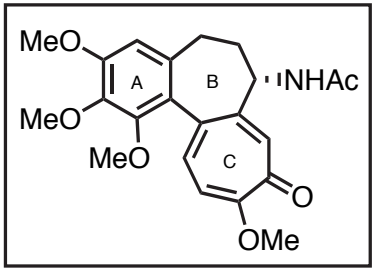


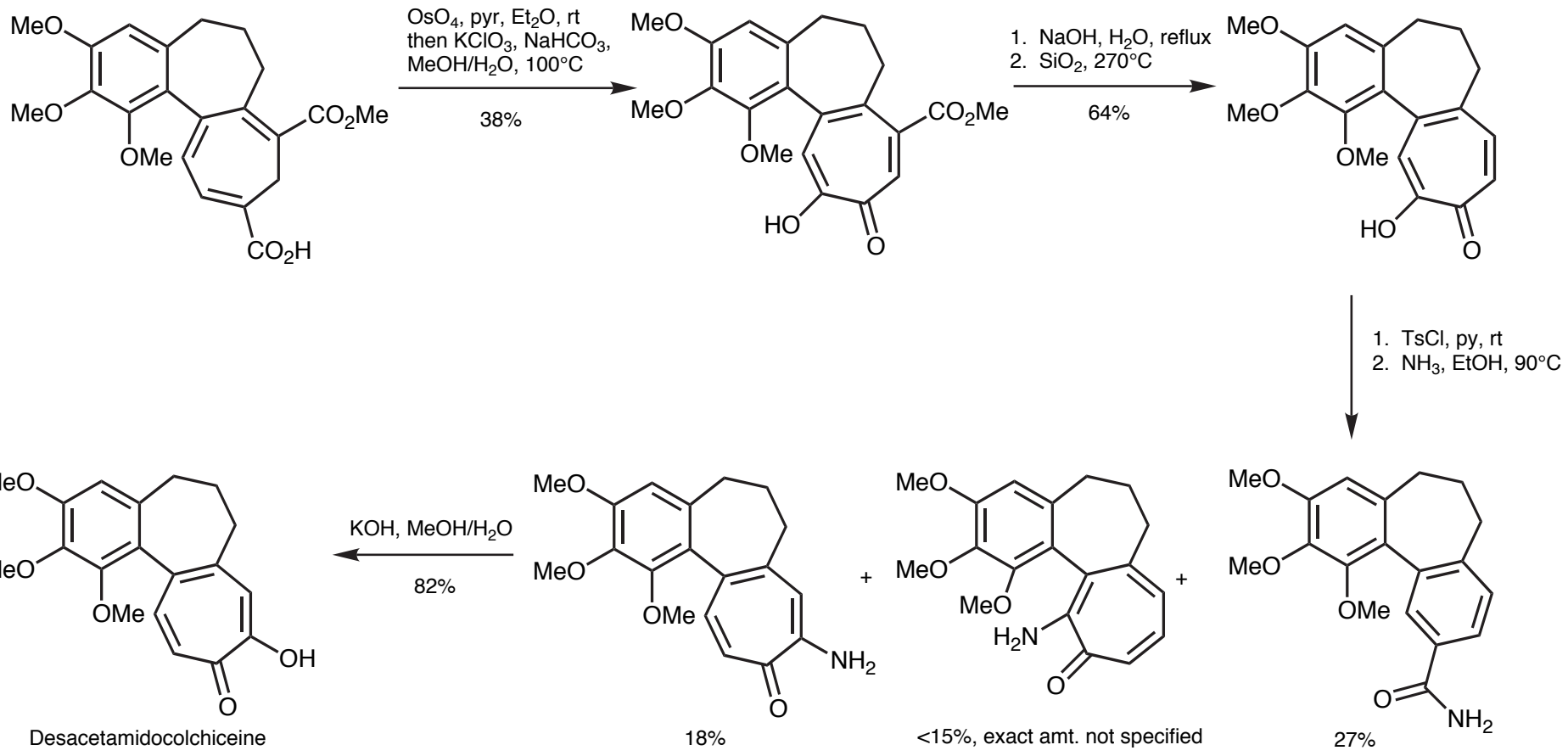


•Reaction of the α-pyrone with methyl propiolate gave a 1:1 mixture of regioisomers
•Norcaradiene form preferred when carboxylates are tied back as the anhydride
•No trace of other cycloheptatriene isomers resulting from ε-attack observed

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

Eschenmoser Synthesis-Tropolonization (Lee Van Cleef)

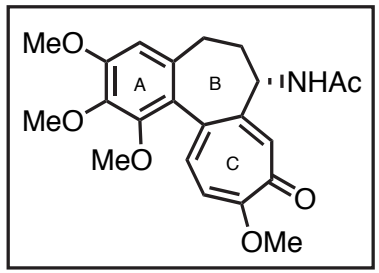


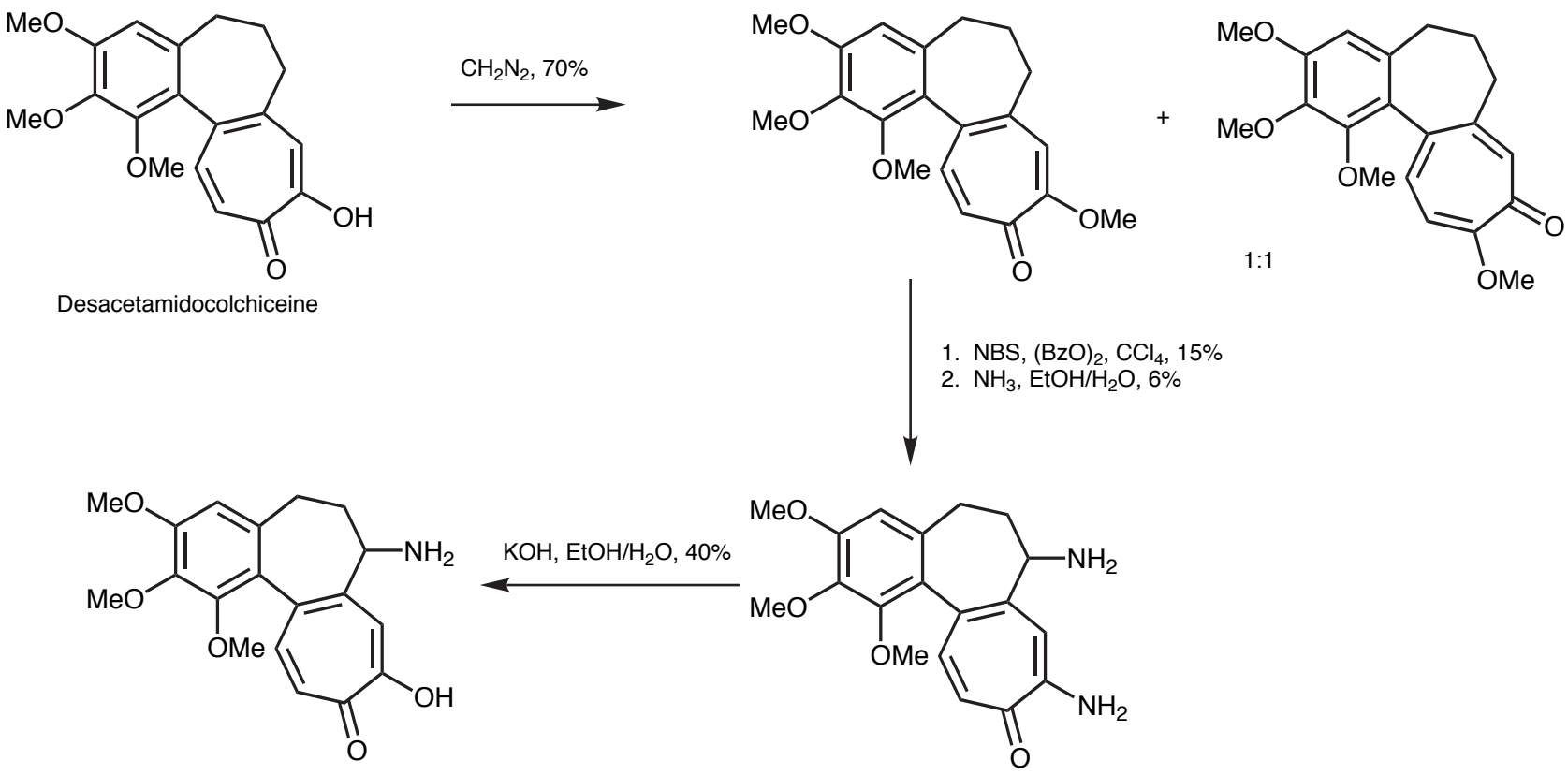


- $KClO_3$ not necessary for decarboxylation, but improves the yield somewhat
- Significant losses occured during the isolation of the tropolone (spectroscopic yield 54%)

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

Eschenmoser Synthesis-Amination (The Ugly)

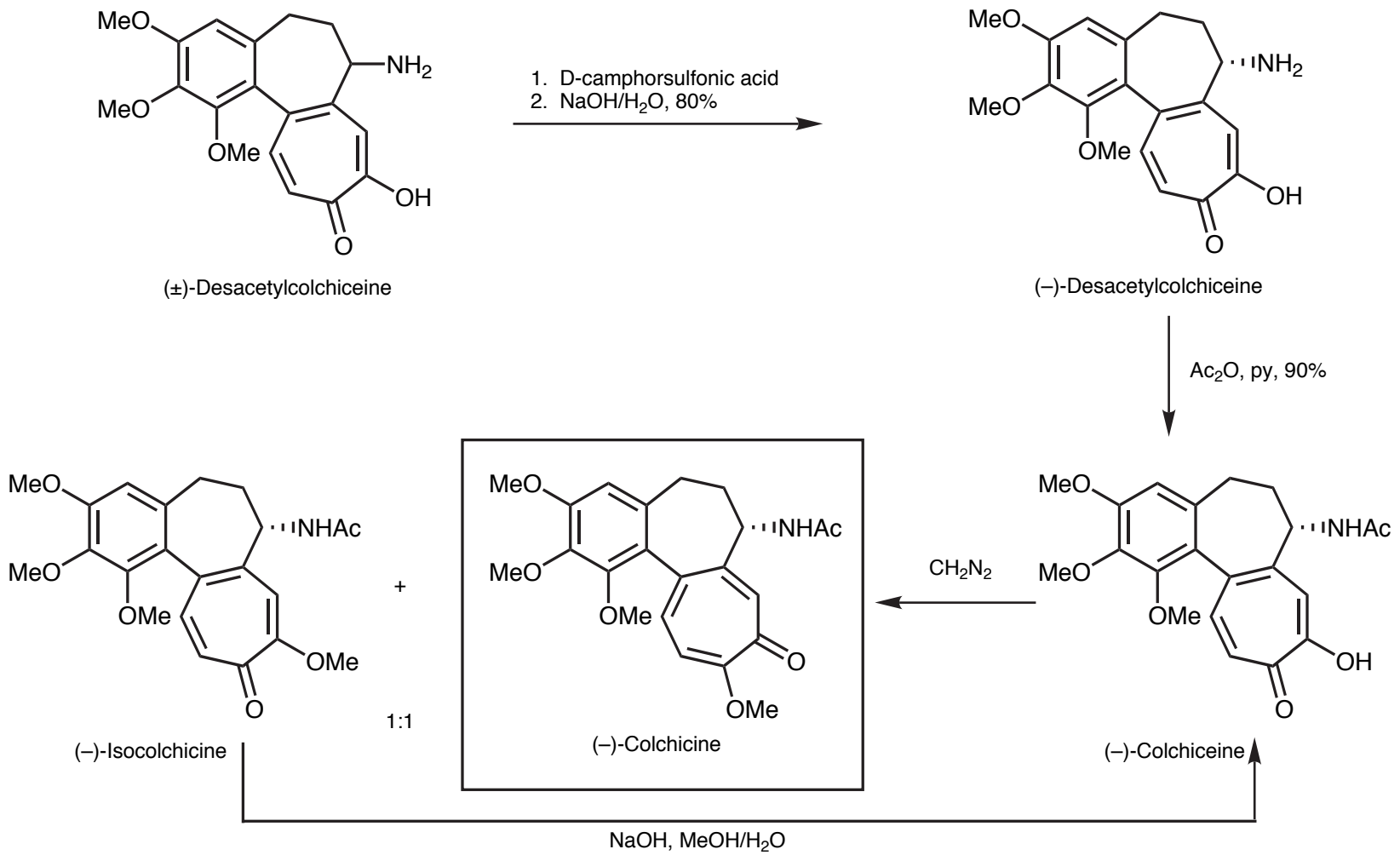




- Attempted bromination of the other tropolone isomer gave no desired product
- The major product from ammonolysis was elimination (50%)

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

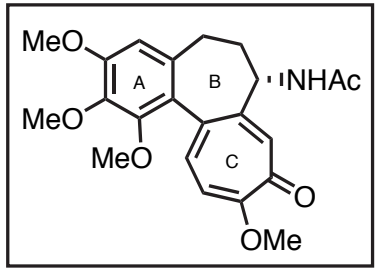
Resolution, Acetylation, and Methylation

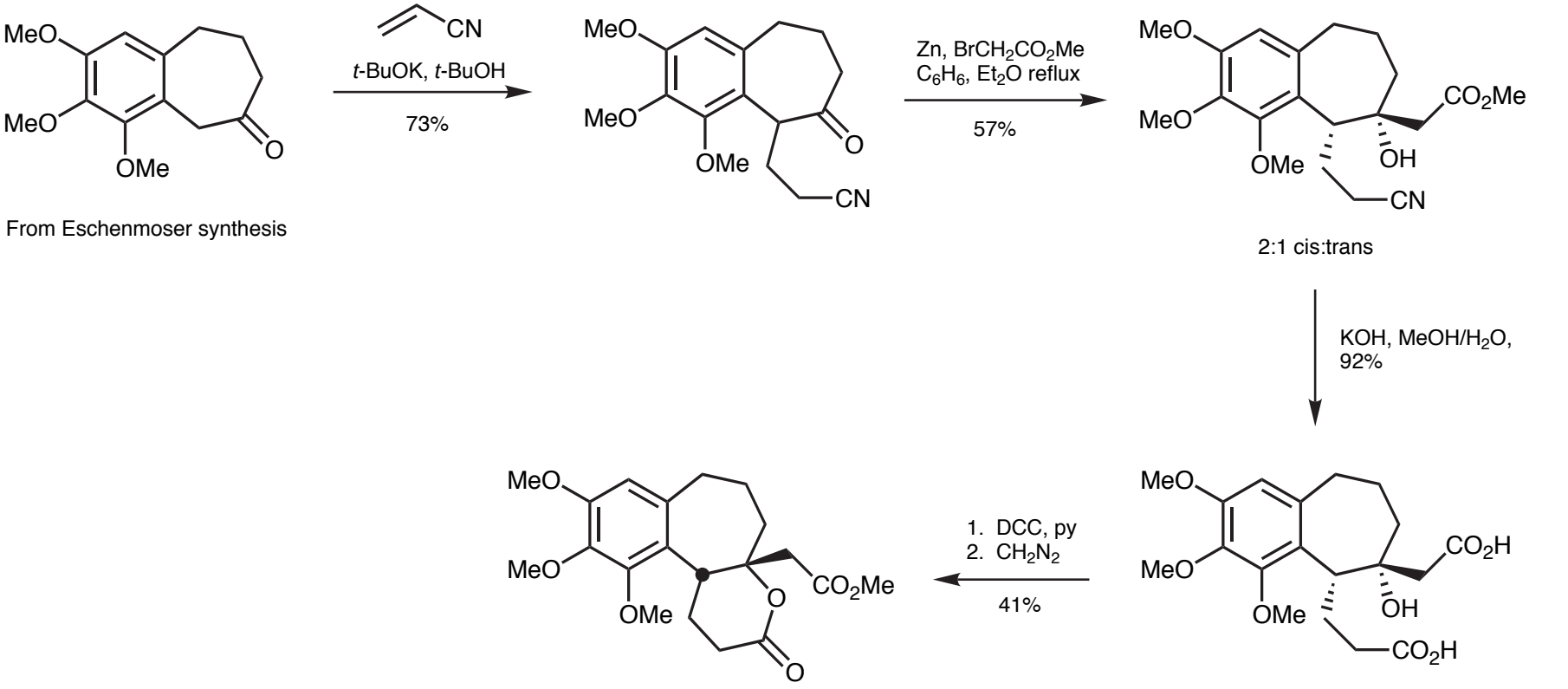


• (+)-Desacetylcolchiceine could be isolated from the mother liquor and crystallized to enantiomeric purity

Hardegger *Helv. Chim. Acta* **1957**, 193

van Tamelen Synthesis-C-ring Formation





From Eschenmoser synthesis

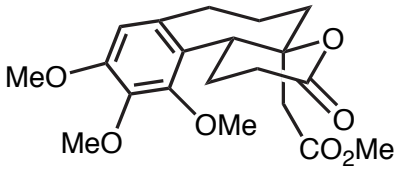
2:1 cis:trans

- 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

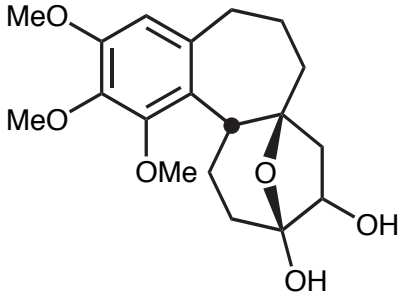
van Tamelen Synthesis-Acyloin Condensation

trans ester-lactone



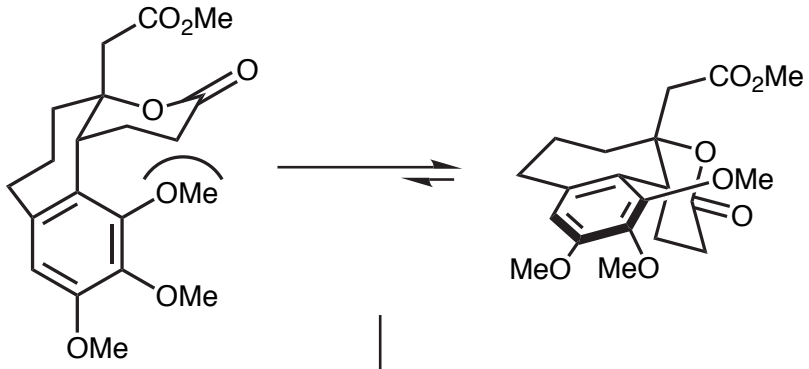
Na, NH_3

10%

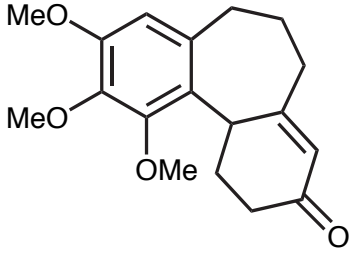


• isolated as a 9:1 mixture of diastereomers at C-9
• Na in xylenes yielded no recognizeable products

cis ester-lactone



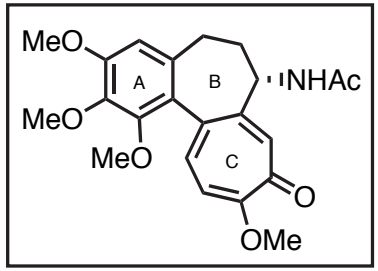
Na, xylenes

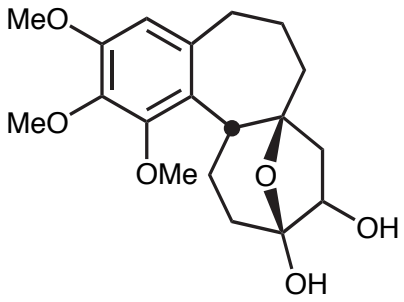


• Na in NH_3 yielded no recognizeable products

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

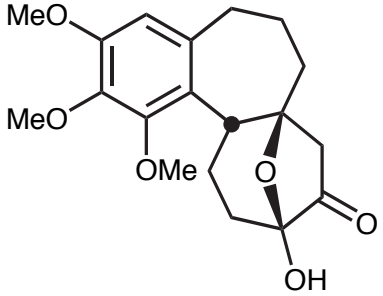
van Tamelen Synthesis-Completion



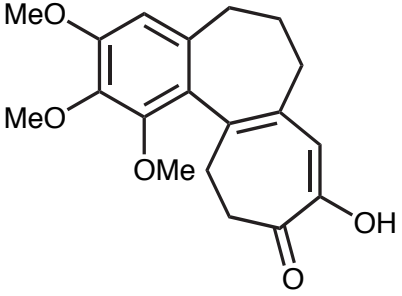


$Cu(OAc)_2$, MeOH

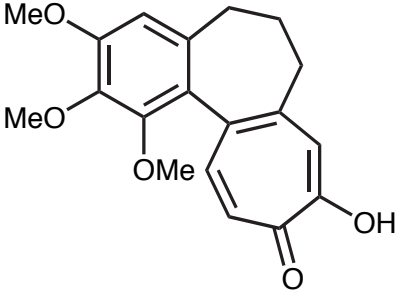
quant.



TsOH, C_6H_6
reflux



NBS, $CHCl_3$, reflux

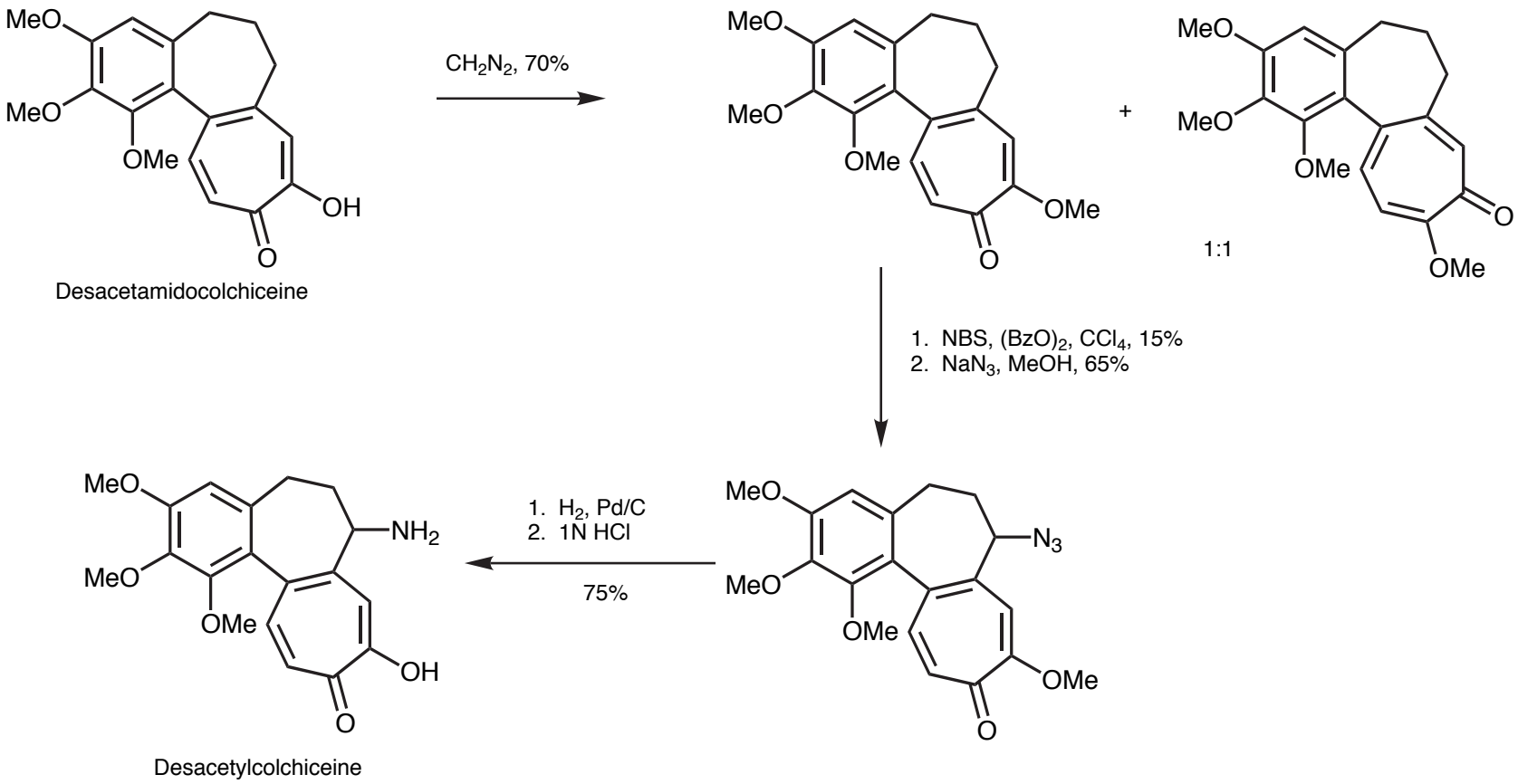


desacetamidocolchiceine

40%

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

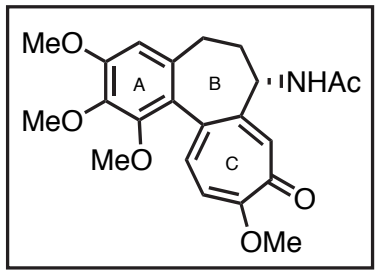
van Tamelen Synthesis-The Not-Quite-So-Ugly

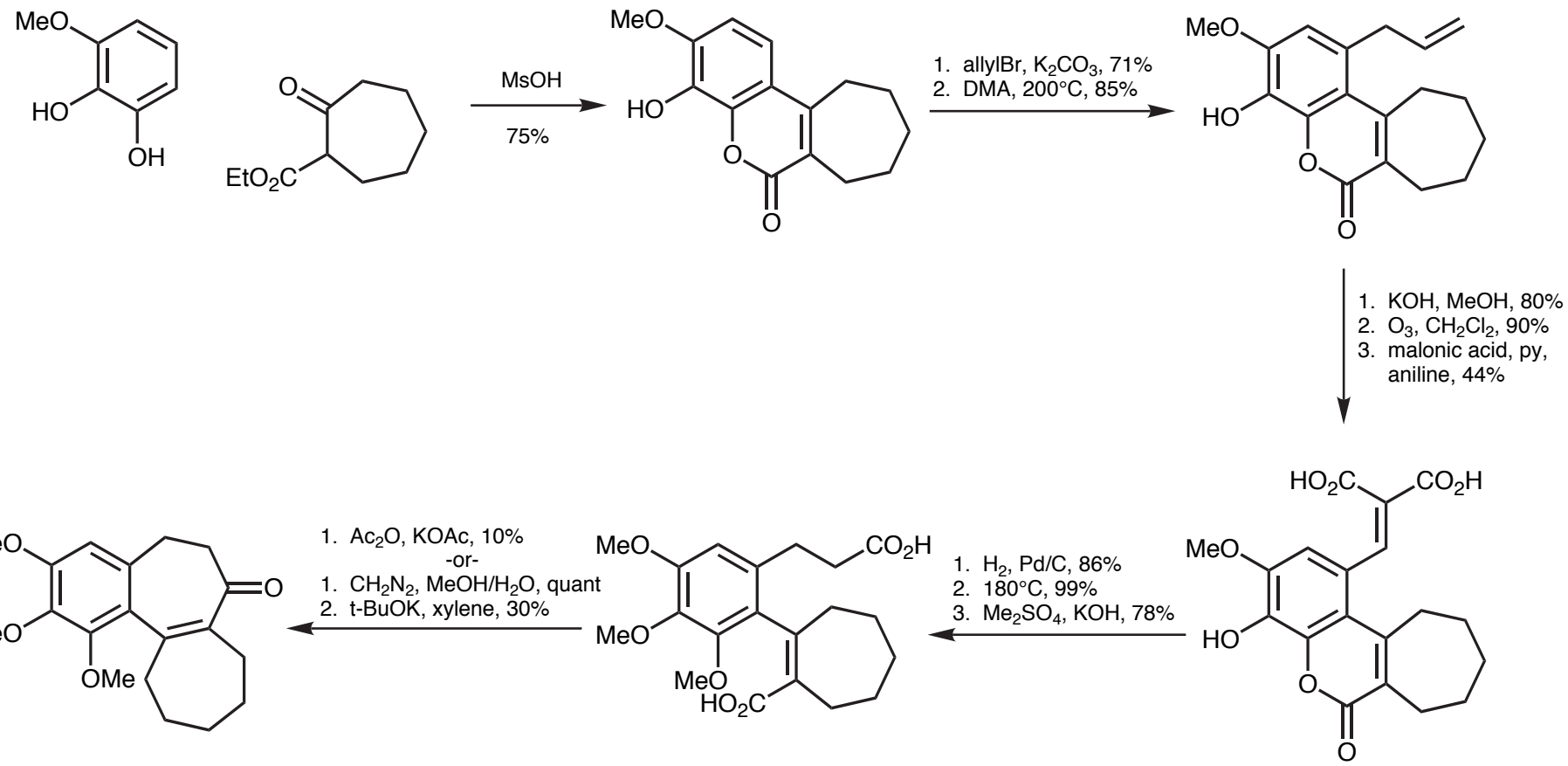


• Attempted bromination of the other tropolone isomer gave no desired product

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

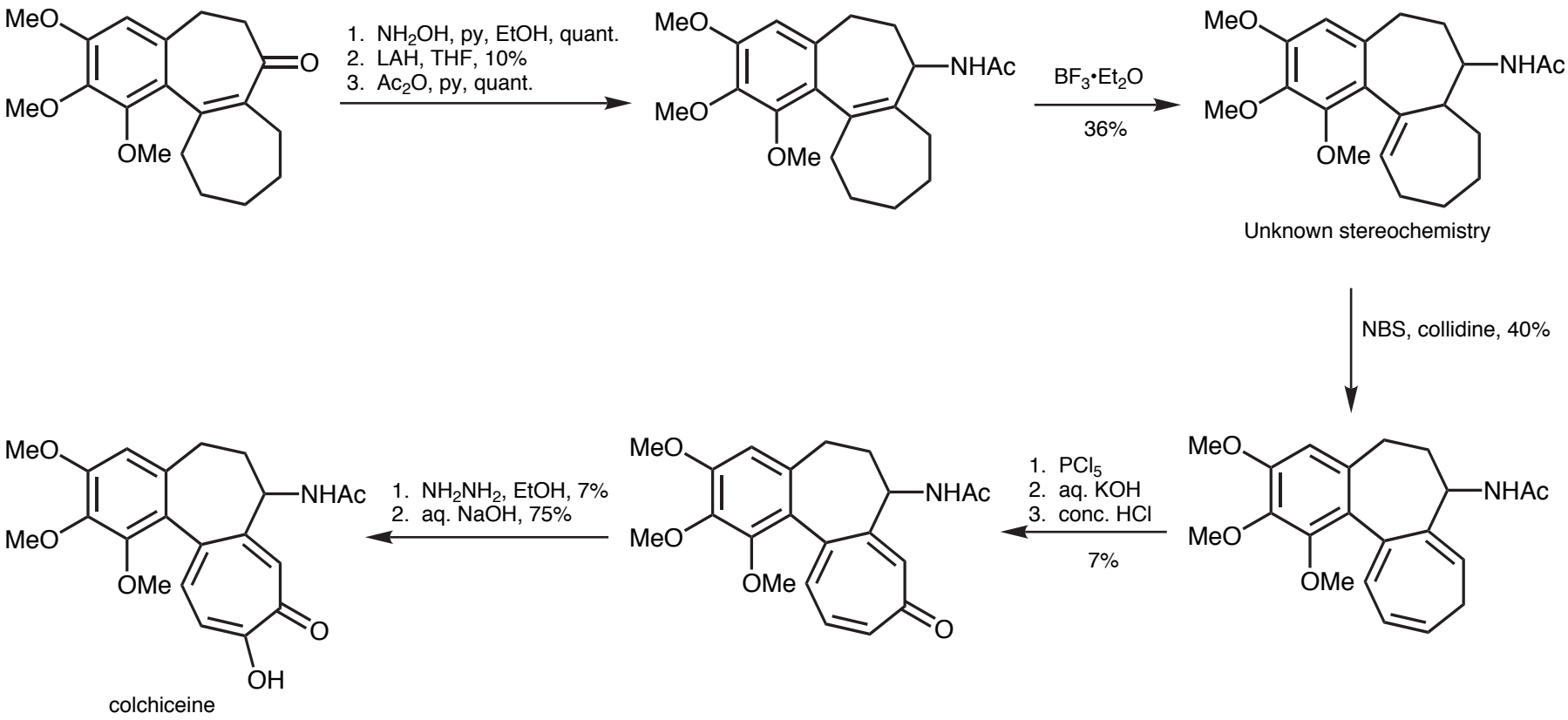
Nakamura Synthesis-B ring closure





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

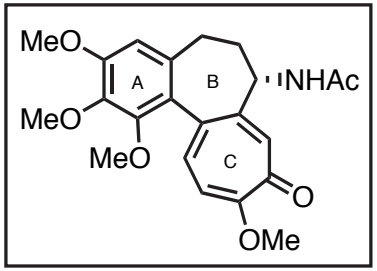
Nakamura Synthesis-Tropolonization

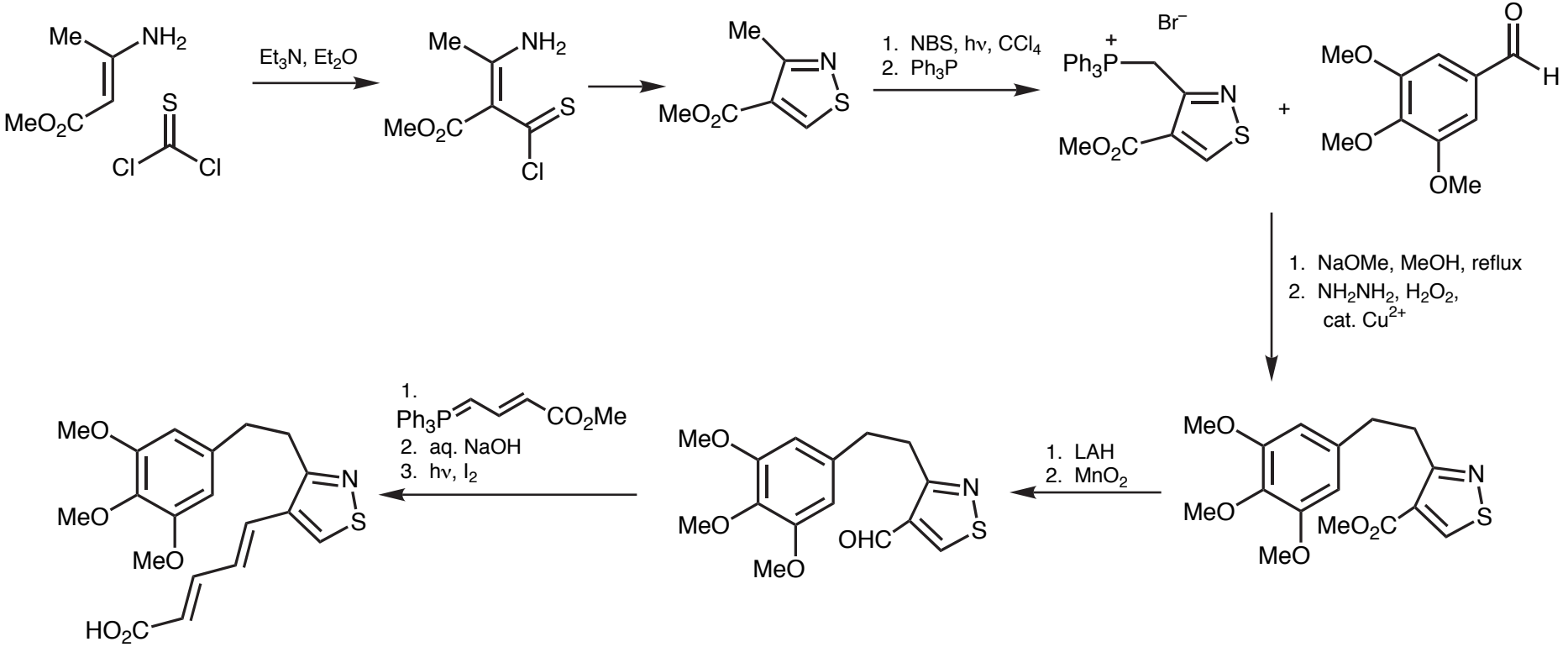


- Yield of LAH reduction before recrystallization was about 40%
- Resolution of free amine with tartaric acid or camphorsulfonic acid failed
- The major product from the bromination reaction was a bromodiene that could not be converted to the desired triene

Nakamura *Chem. Pharm. Bull.* **1962**, 291, 299

Woodward Synthesis-Isothiazole Formation and Elaboration

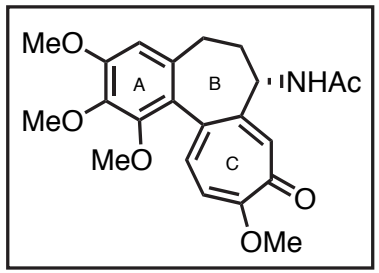


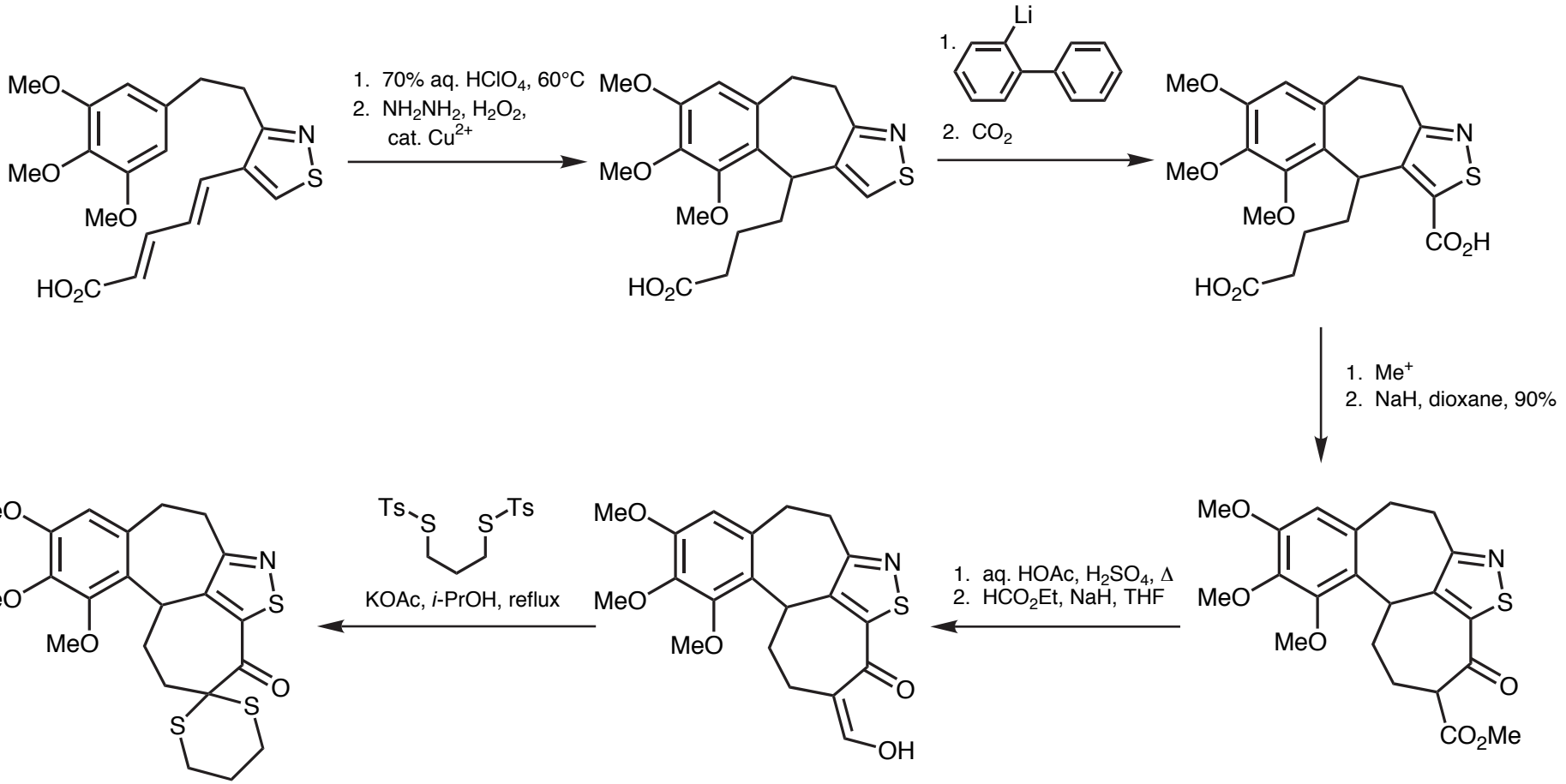


• "One aspect of our plan to base a synthesis of colchicine upon a simple isothiazole intermediate might well have given us pause. A forceful reminder of the fantastic multiformity of organic chemistry is provided by the fact the although literally millions of different organic molecules were known at 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 hν, I_2 procedure

Woodward *The Harvey Lecture Series* **1963**, 31

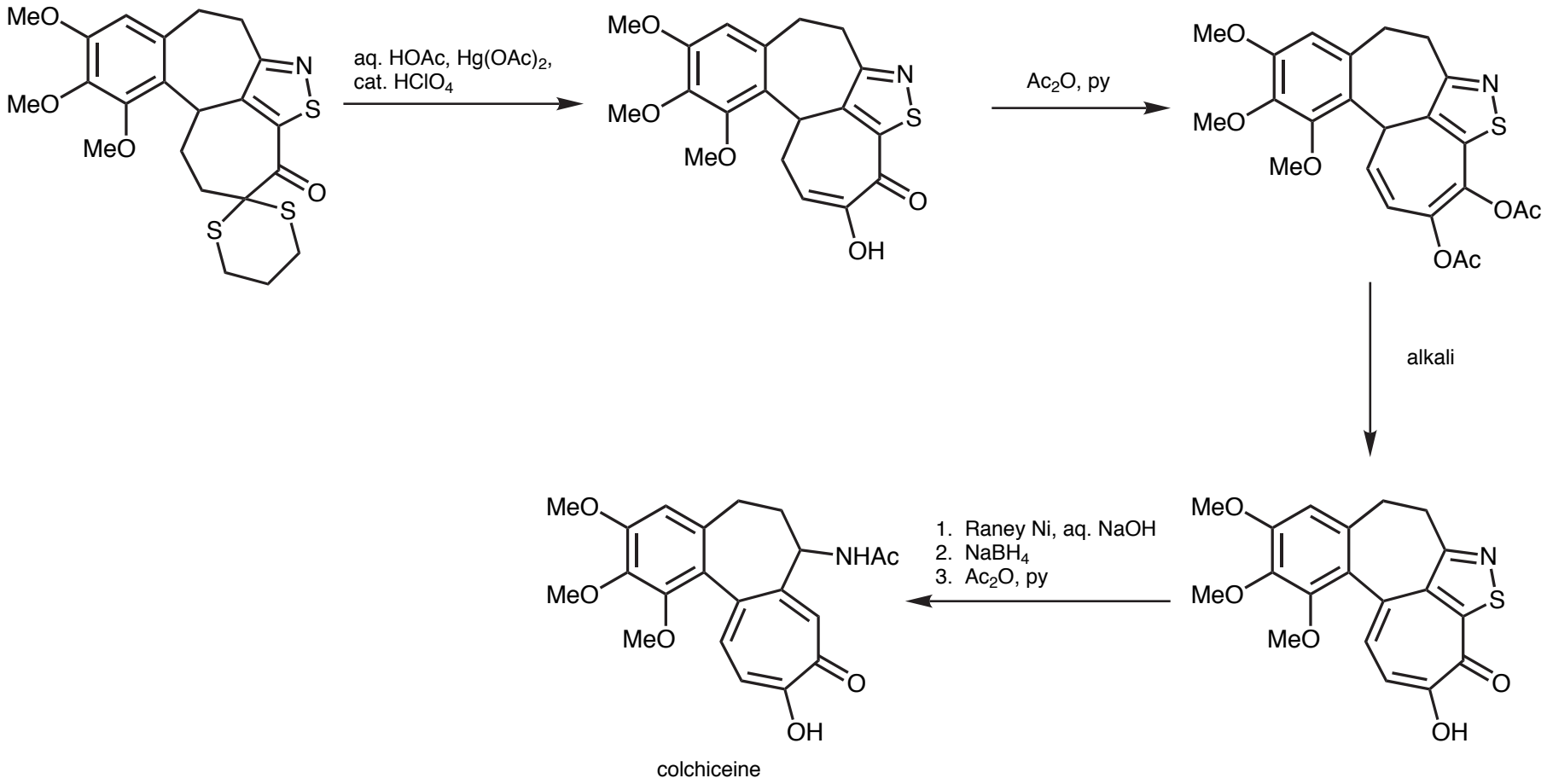
Woodward Synthesis-B and C-ring Formation





Woodward *The Harvey Lecture Series* **1963**, 31

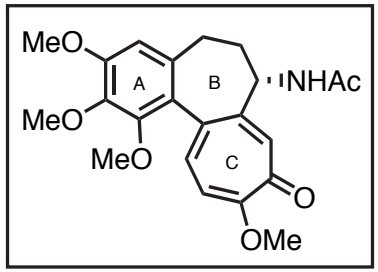
Woodward Synthesis-Tropolonization

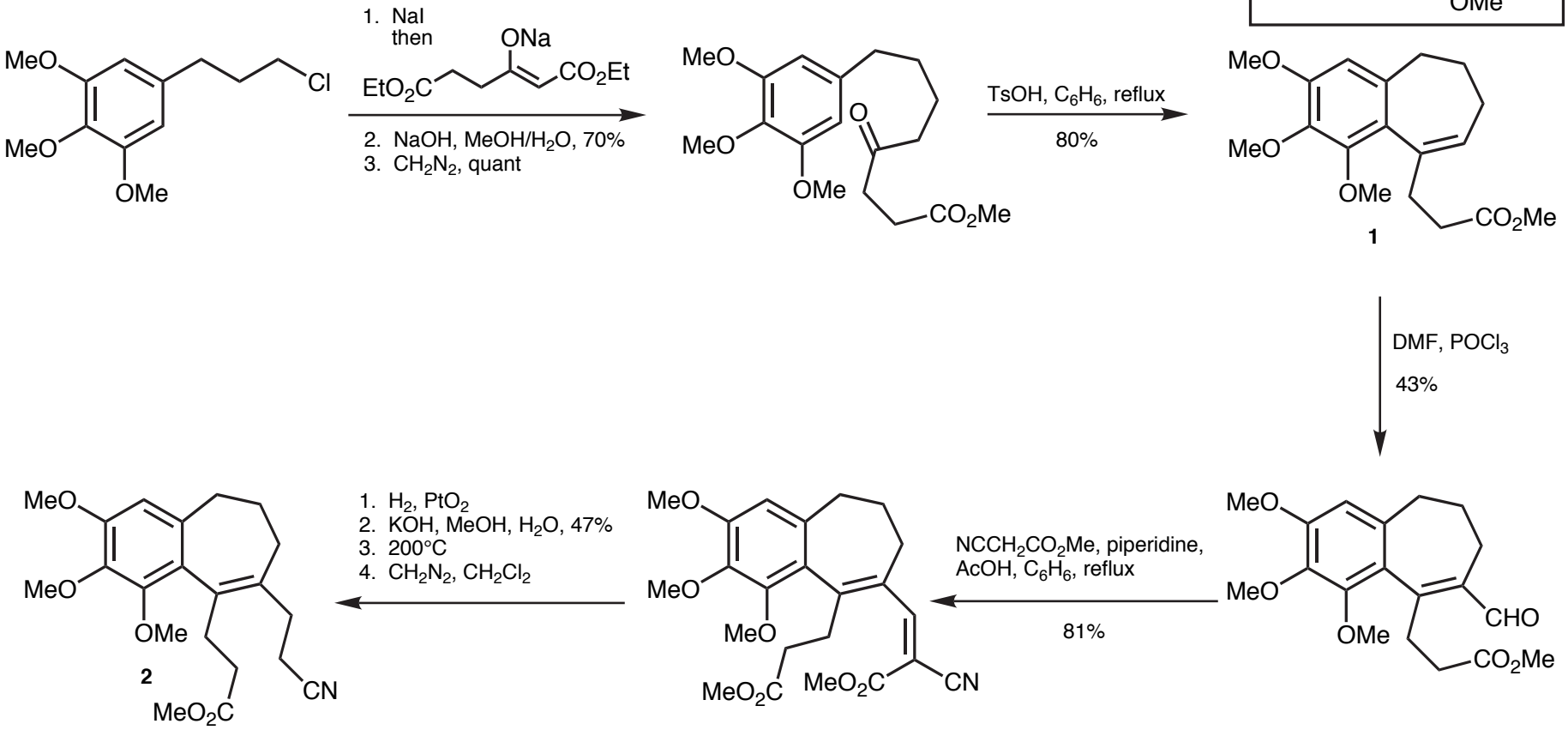


colchiceine

Woodward *The Harvey Lecture Series* **1963**, 31

Martel Synthesis-B-ring Closure

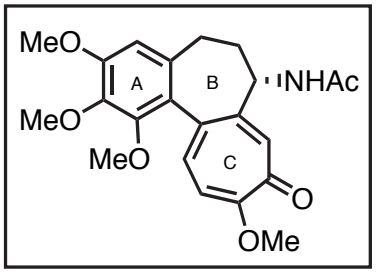


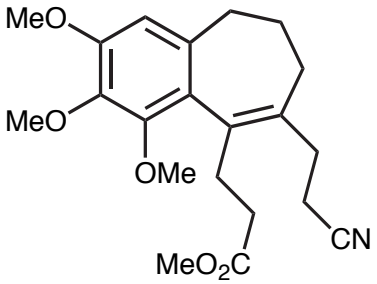


- If not rigorously dried by azeotropic removal of water, the acid-catalyzed cyclization did not stop at **1**, but cyclized further to give the tricyclic ketone product of Friedel-Crafts type acylation
- "The yields given in this series of reaction [*sic*] [from **1** to **2**] are those obtained in 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

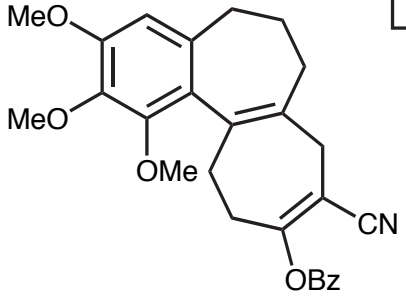
Martel *J. Org. Chem.* **1965**, 1752

Martel Synthesis-C-ring Formation

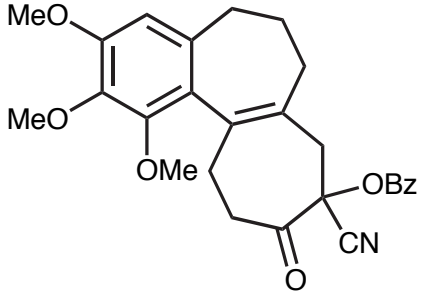




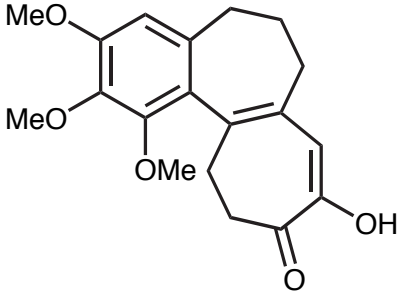
K, toluene, reflux
then BzCl, py, 17%



1. KOH, $MeOH/H_2O$, 90%
2. Na, C_6H_6, reflux
   then $(BzO)_2$, rt, 76%



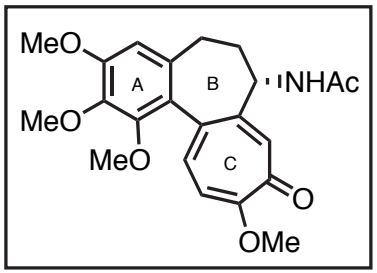
aq. $NaHCO_3$, EtOH, 70%

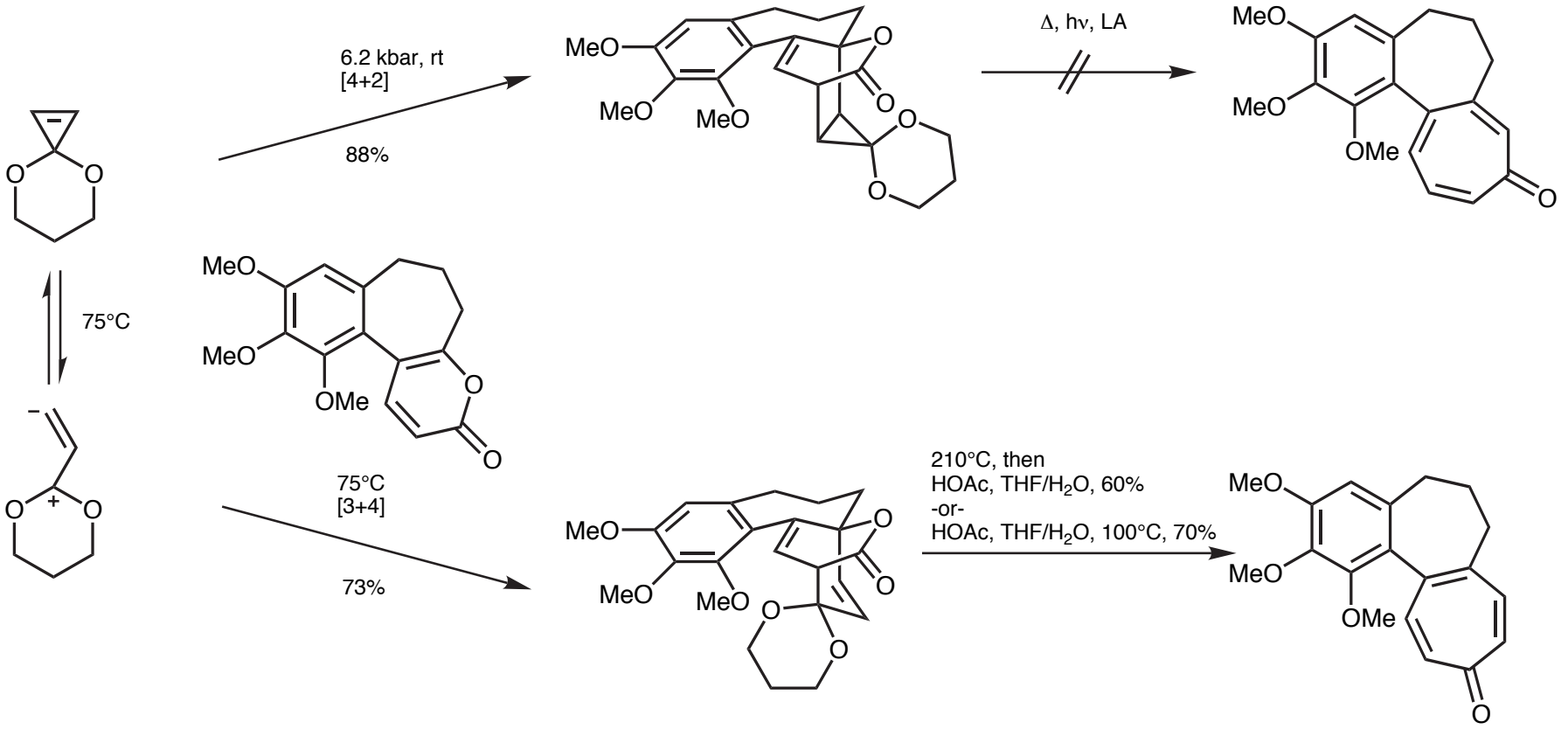


• The final compound has already been converted to desacetamidocolchiceine in 40% yield in the synthesis by van Tamelen

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

Boger Synthesis-[3+4] Cycloaddition

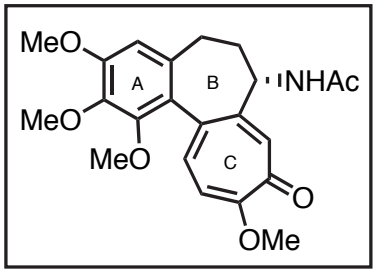


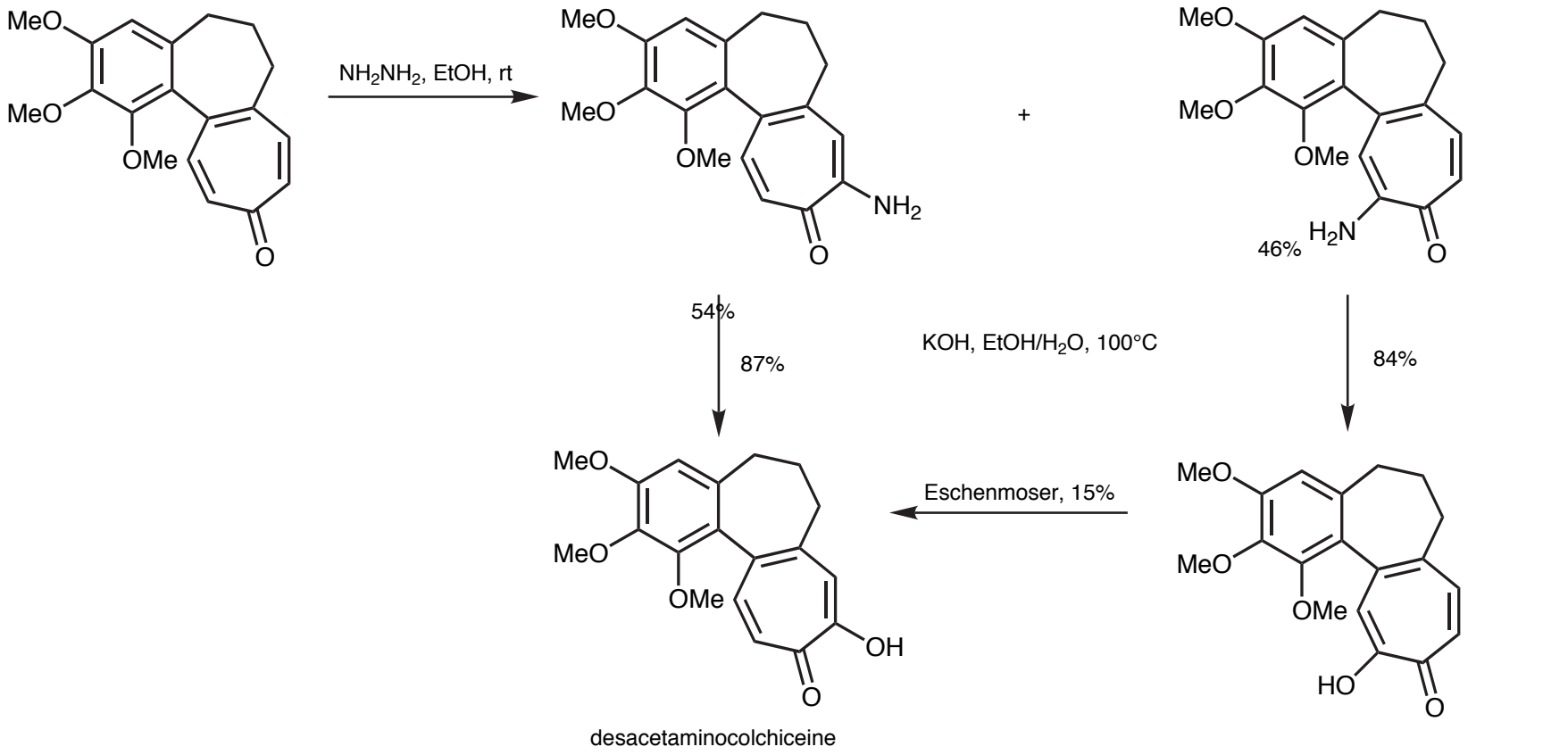


- The pyrone used in the cycloaddition is an intermediate on Eschenmoser's route to colchicine
- Steric hinderance disfavors the [4+2] cycloaddition at higher temperatures

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

Boger Synthesis-Completion

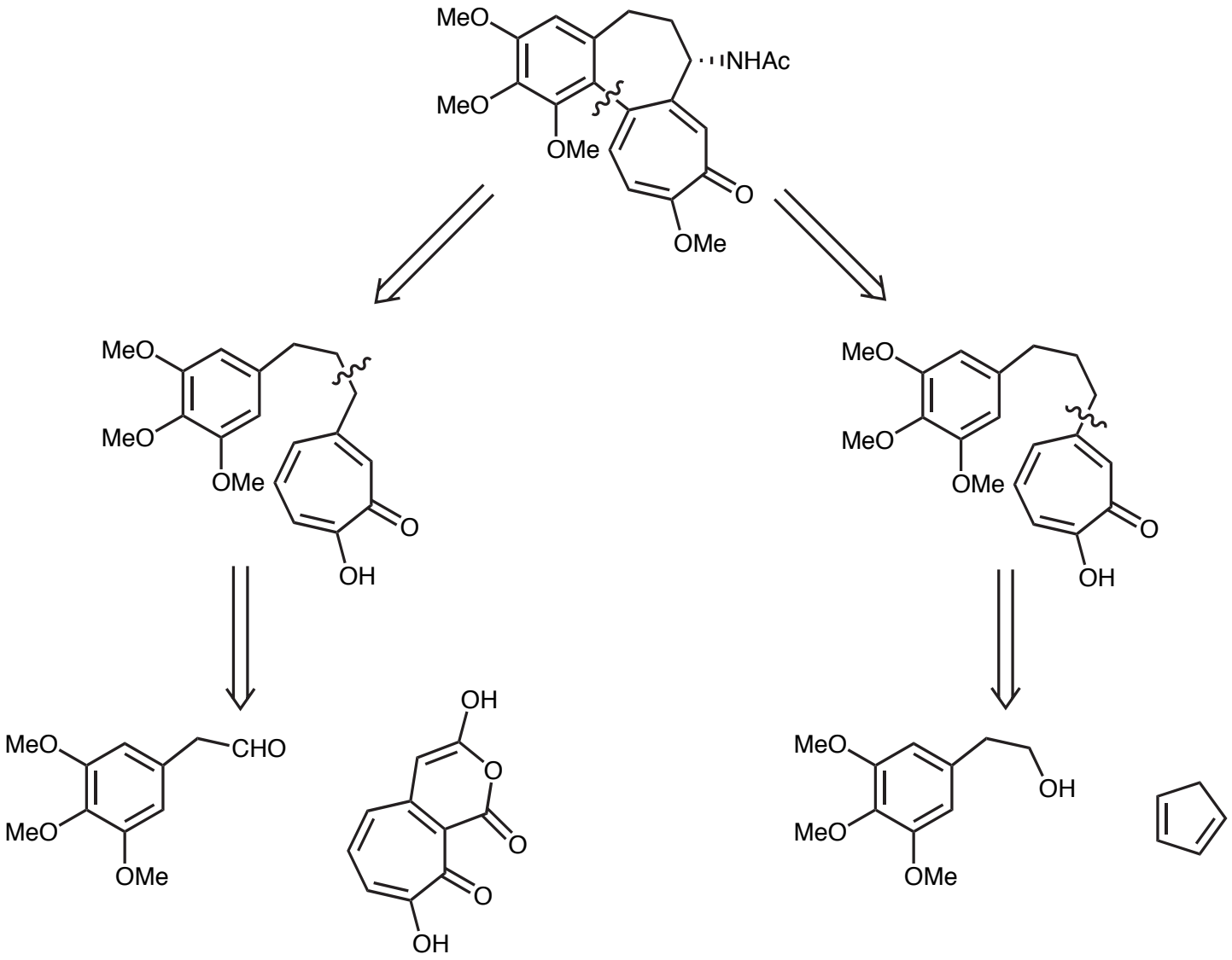




- The hydrazine amination is similar to one performed by Nakamura in his synthesis
- The Eschenmoser transposition of 11-hydroxytropone into 9-hydroxytropone is accomplished by tosylation, aminolysis, and hydrolysis

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

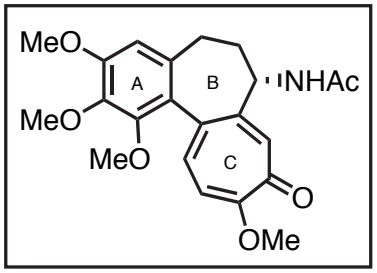
Retrosynthetic Analyses of Colchicine-A->AC->ABC via Oxidative Phenolic Coupling of Intact Tropolone

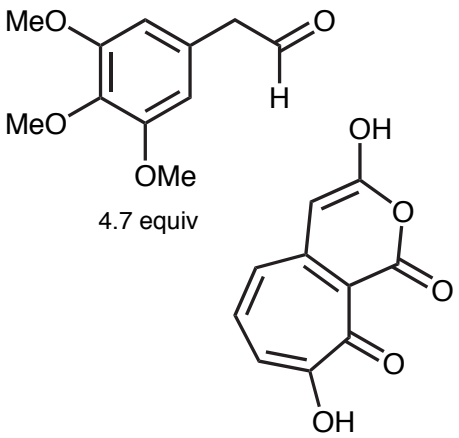


Scott, Matsui

Kato

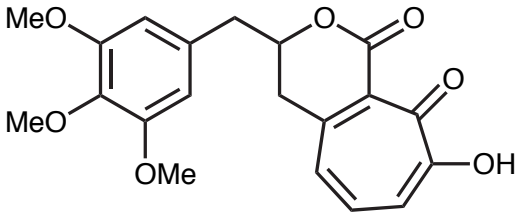
Scott Synthesis-Set-Up for Phenol Coupling





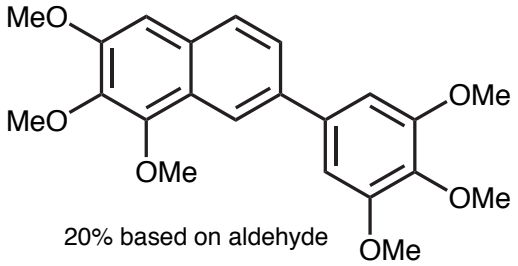
4.7 equiv

Δ



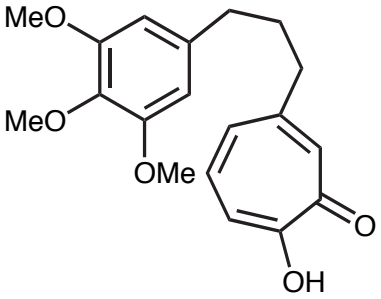
78% based on anhydride
(17% based on aldehyde)

+



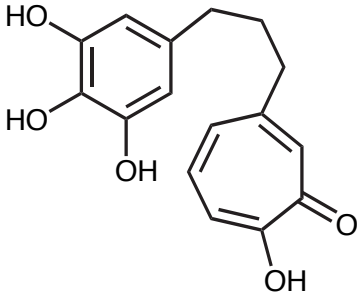
20% based on aldehyde

1. Cu-bronze, 200°C, 70%
2. H_2, Pd/C, 96%



48% HBr, reflux

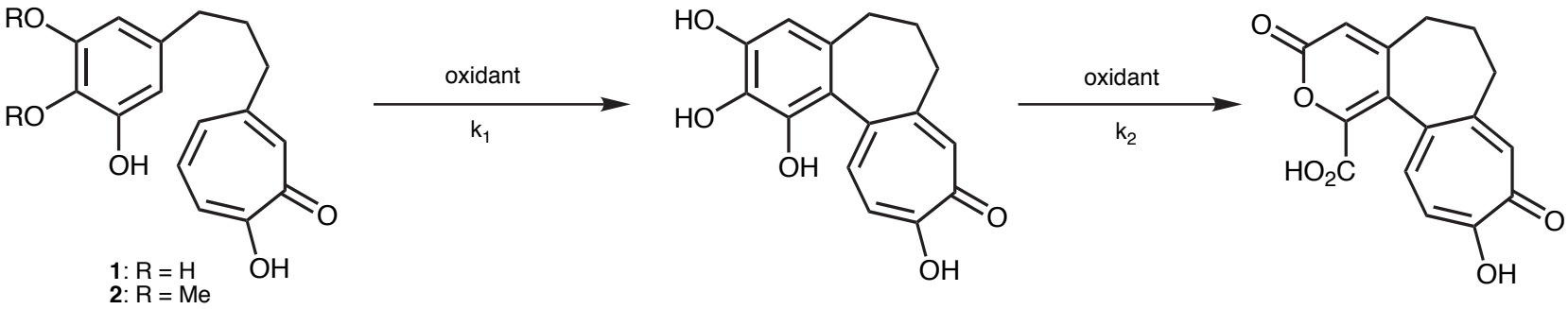
60%



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

Scott *Tetrahedron* **1965**, 3605

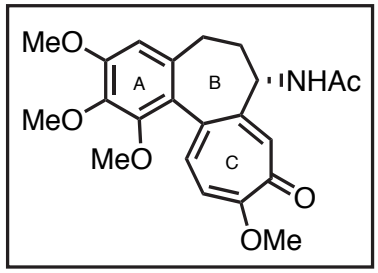
Scott Synthesis-Phenol Coupling

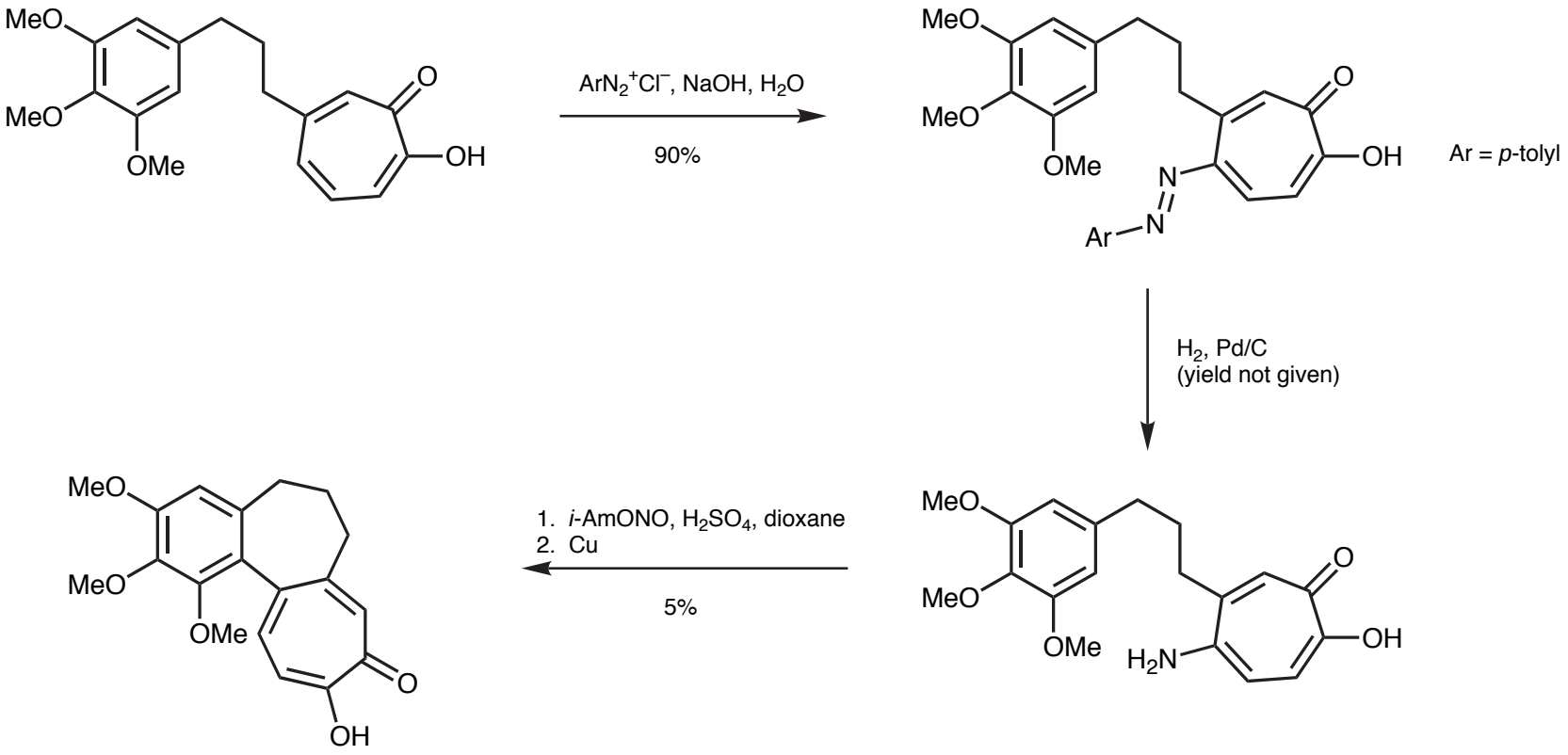


- Attempted cyclizations of the bismethylated compound **2** with MnO_2, $K_3Fe(CN)_6$, Pd/C, and PbO_2, returned recovered starting material
- Compound **1** and the cyclization product were both extremely sensitive to base, decomposing slowly even in pH 7 aqueous solutions
- Most oxidation conditions resulted in decomposition of **1** and the product: air/Na_2CO_3, air/BaOH, air/NH_4OH, PbO_2, MnO_2, KIO_3
- Only $K_3Fe(CN)_6$ and $FeCl_3$ did not decompose the starting material and product
- For the oxidation with $K_3Fe(CN)_6$, $k_2/k_1 = 1000$, and the pyrone could be isolated in 20% yield
- The optimized conditions ($FeCl_3$, 6 N H_2SO_4, EtOH, $CHCl_3$, 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

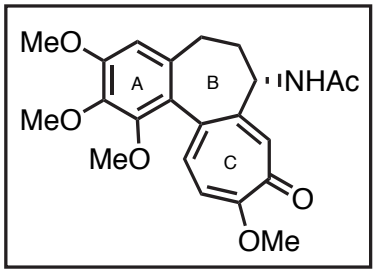


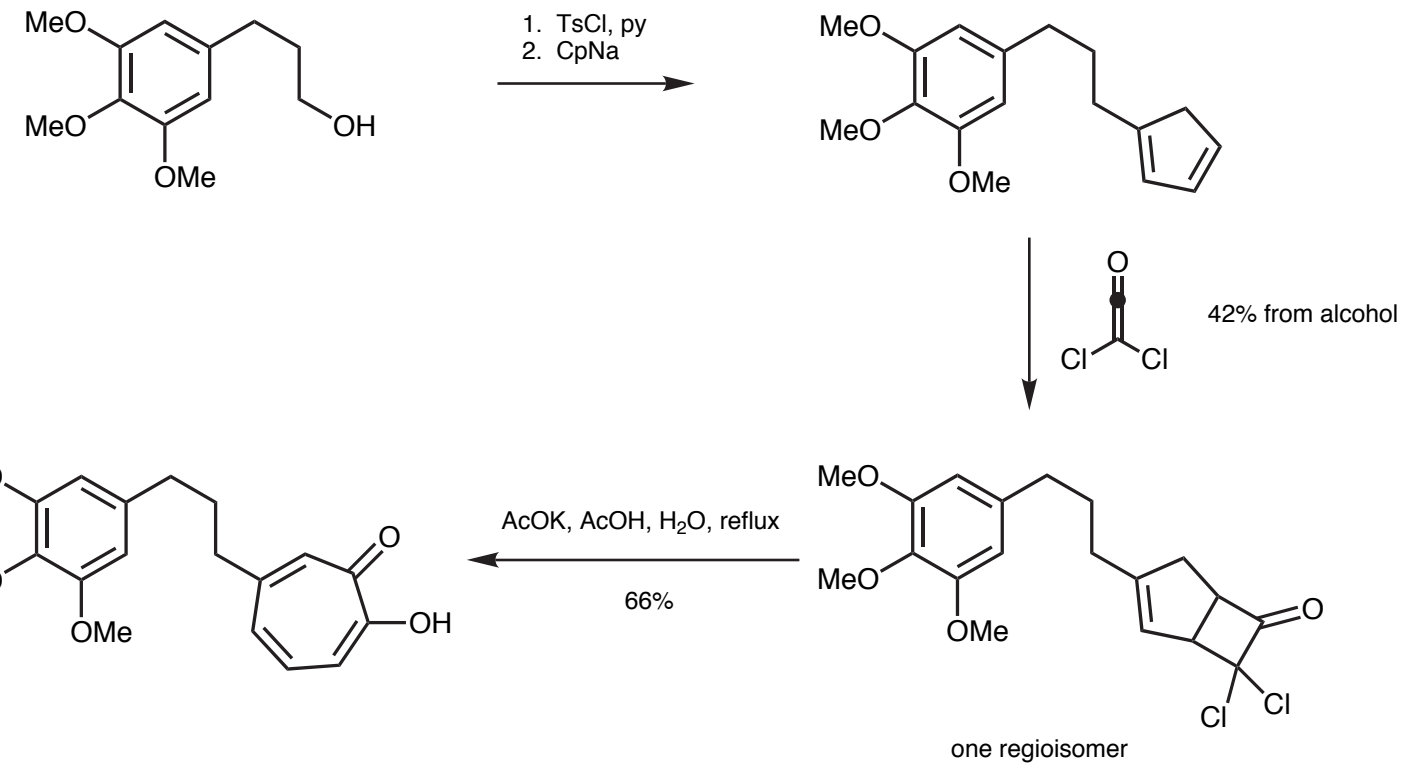


- The starting material shown was originally synthesized by their own method in 6 steps and 4% overall yield. To illustrate the Pshorr reaction as a phenol coupling method, it was synthesized via the method of Scott (3 steps, 52% yield)
- Attempted cyclization of the diazonium chloride synthesized from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

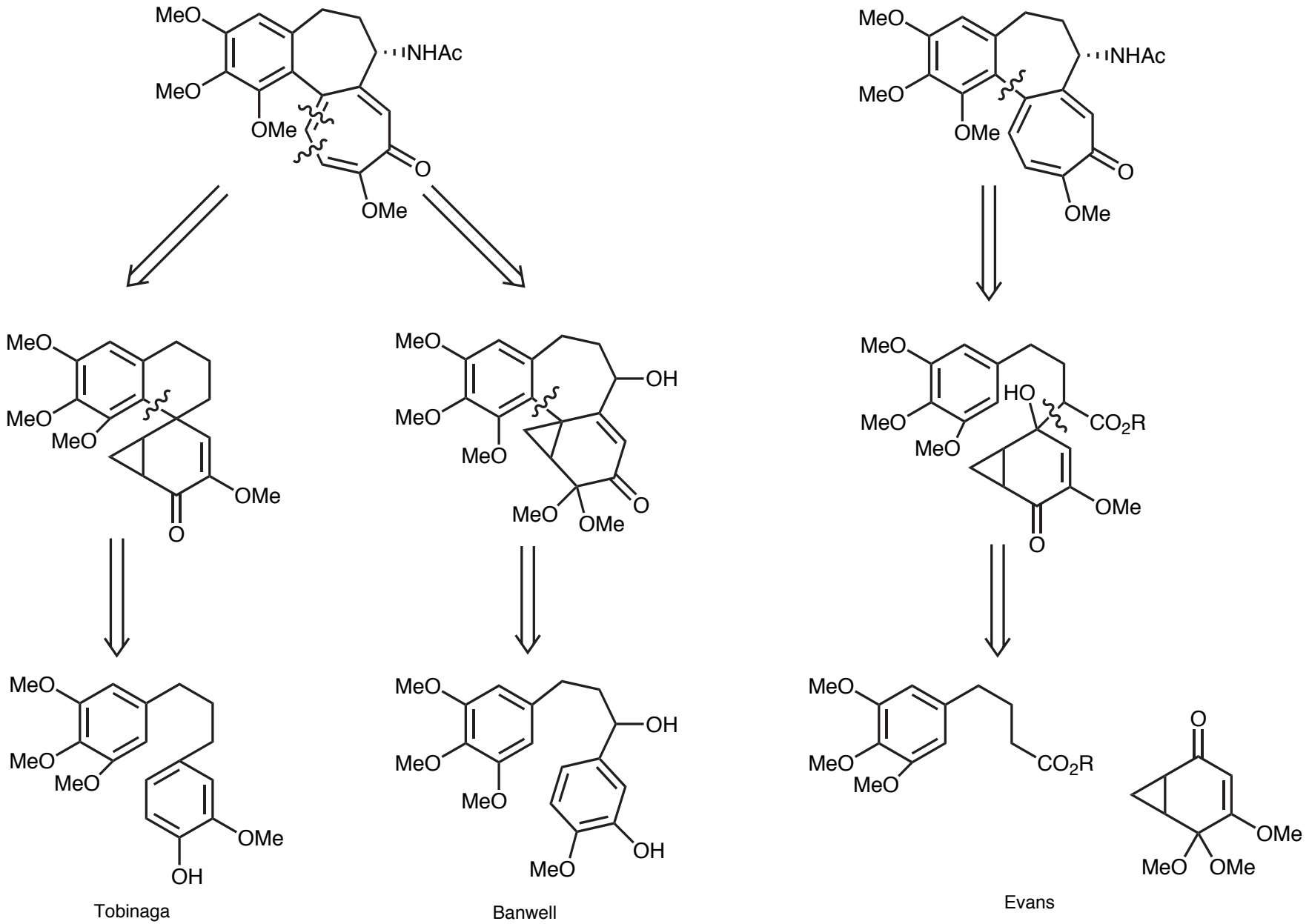




- The starting alcohol was synthesized from the cinnamyl ester in two steps and 92% yield
- The tropolone was previously cyclized to desacetamidocolchiceine by Matsui

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

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

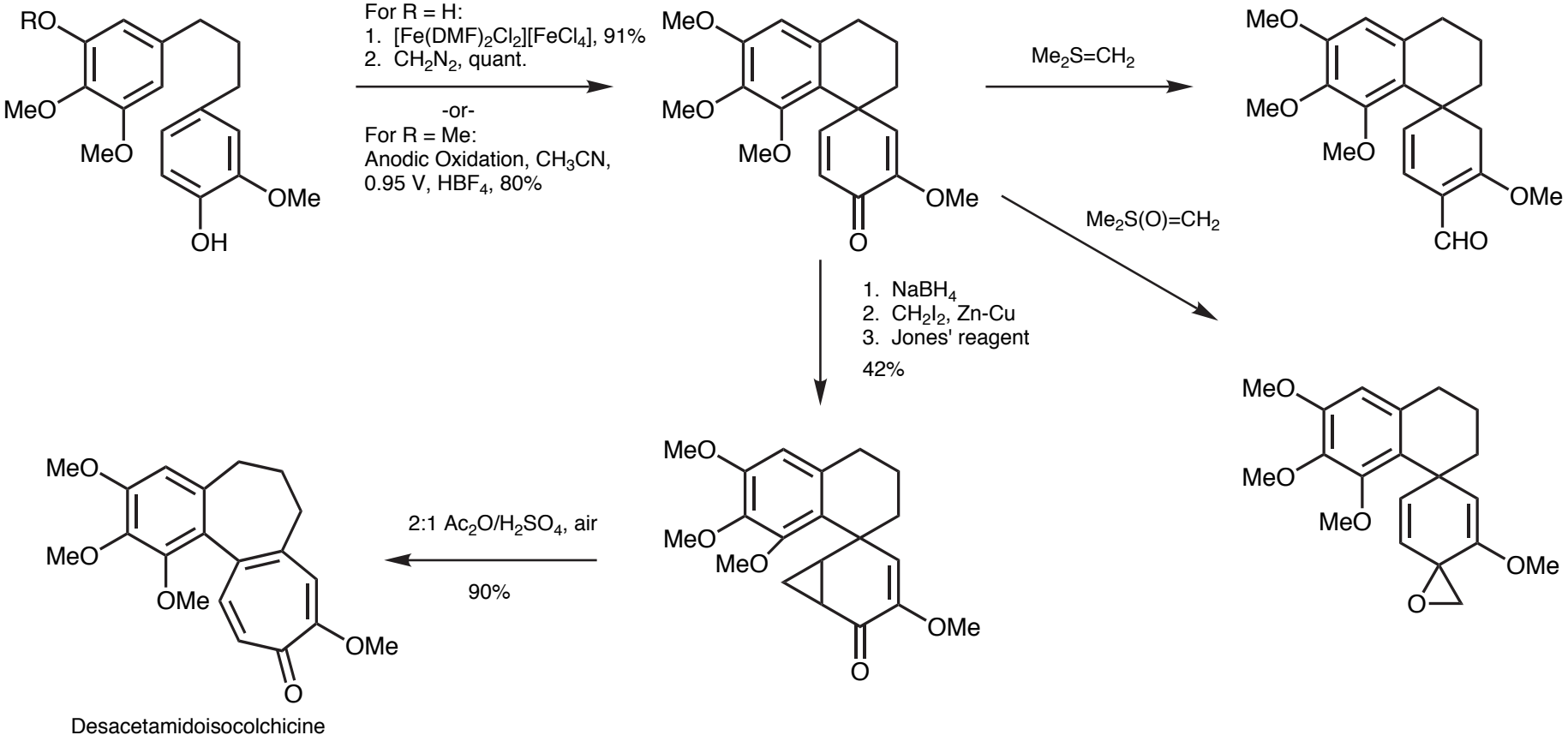


Tobinaga

Banwell

Evans

Tobinaga Synthesis-Oxidative Phenol Coupling

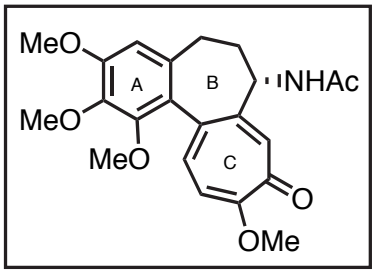


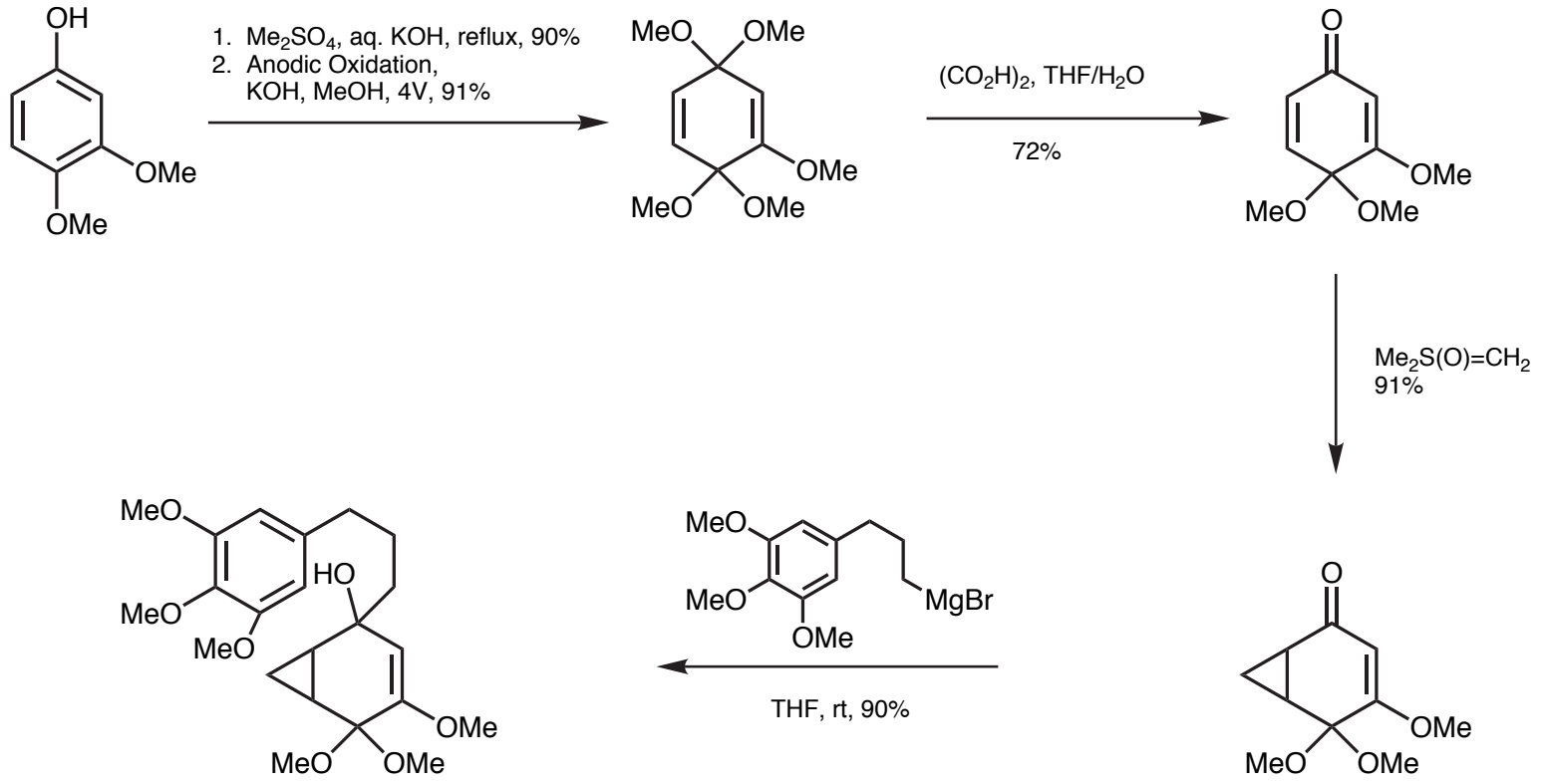
Desacetamidoisocolchicine

- The iron reagent used for the oxidative coupling is prepared by adding DMF to a Et_2O solution of $FeCl_3$
- 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

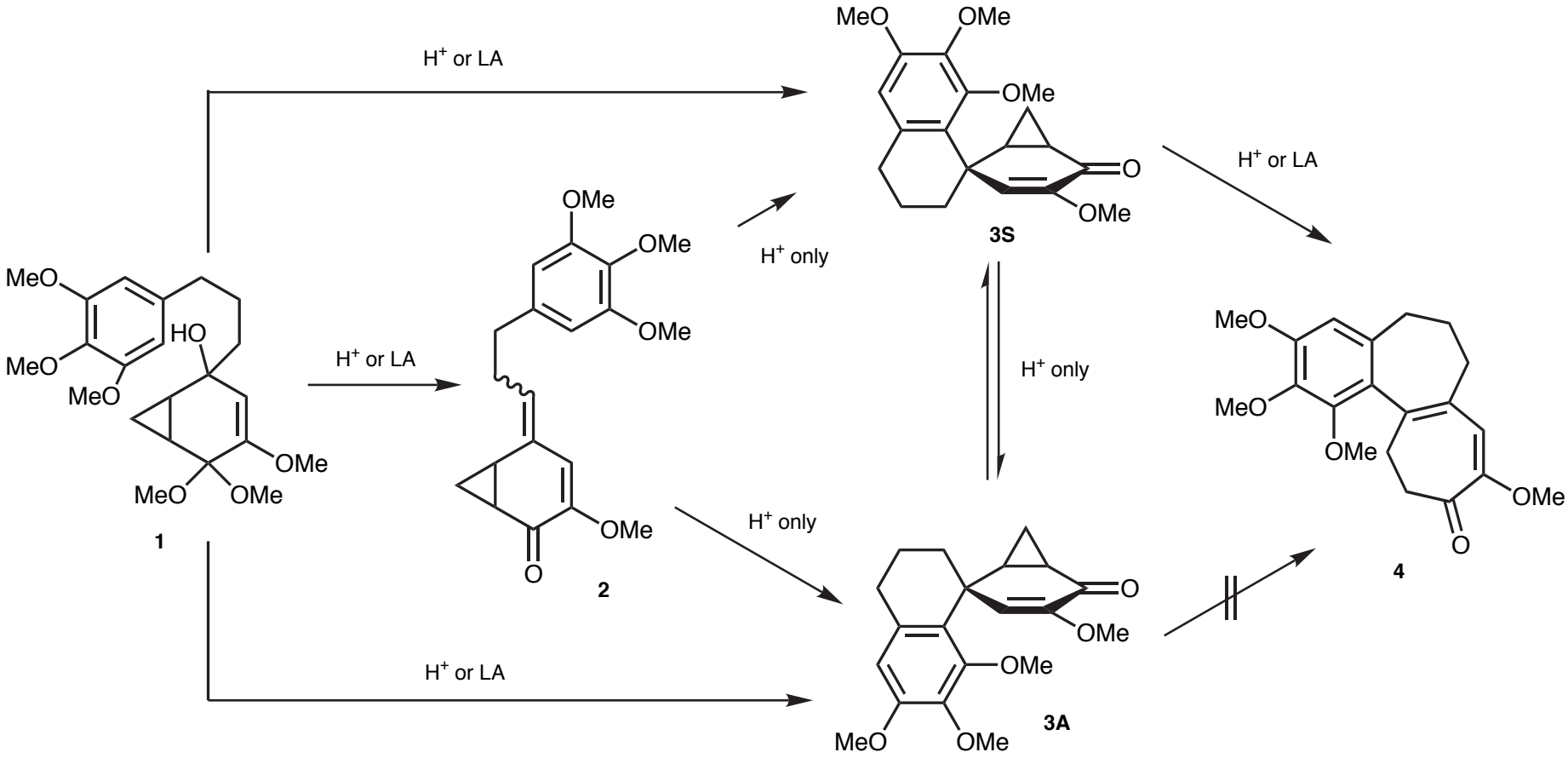
Evans Synthesis-Synthesis of Phenol Coupling Intermediate





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

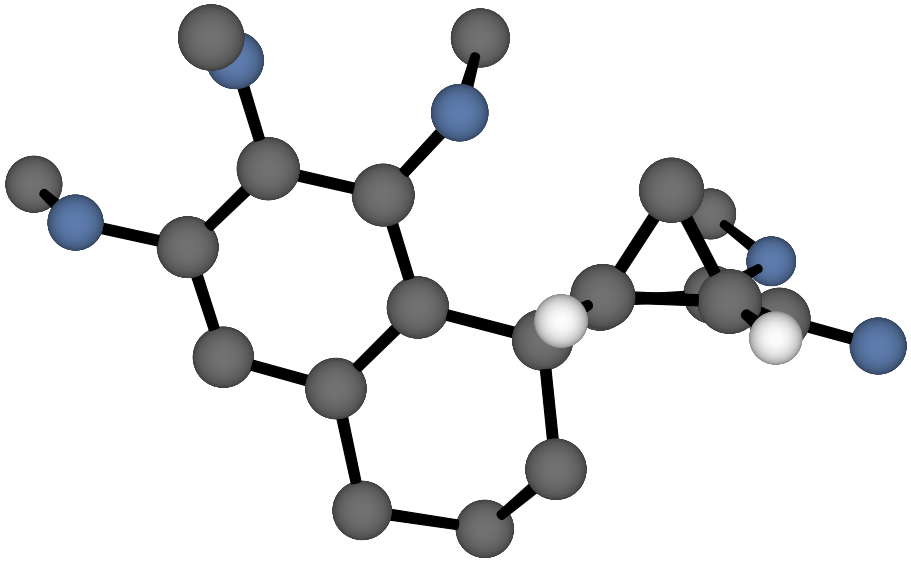
Evans Synthesis-Cyclization and Rearrangement

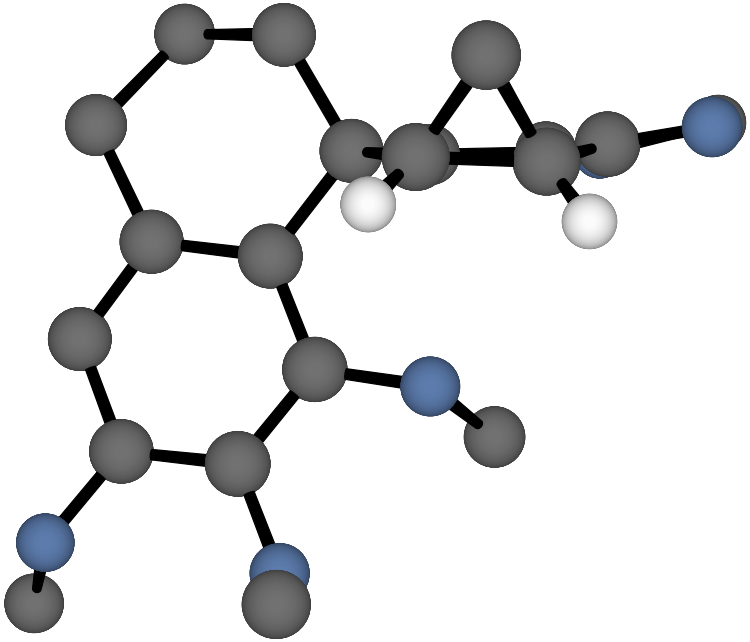


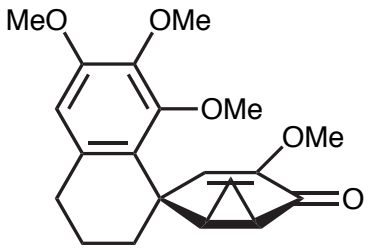
- Reaction of **1** with TFA for 18 h gave the dihydrotropolone **4** in 68% yield, whereas BF_3•OEt_2 gave only a 23% yield
- All intermediates shown could be isolated by stopping the reaction before it went to completion
- Formation of **3A** is favored over **3S** upon initial cyclization
- Treatment 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•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

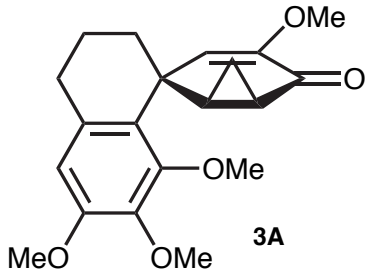
Evans Synthesis-Spirocycles







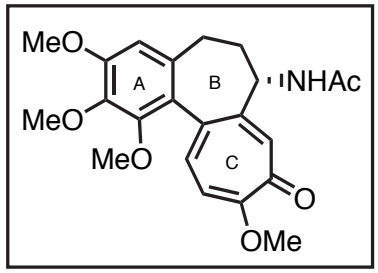
3S

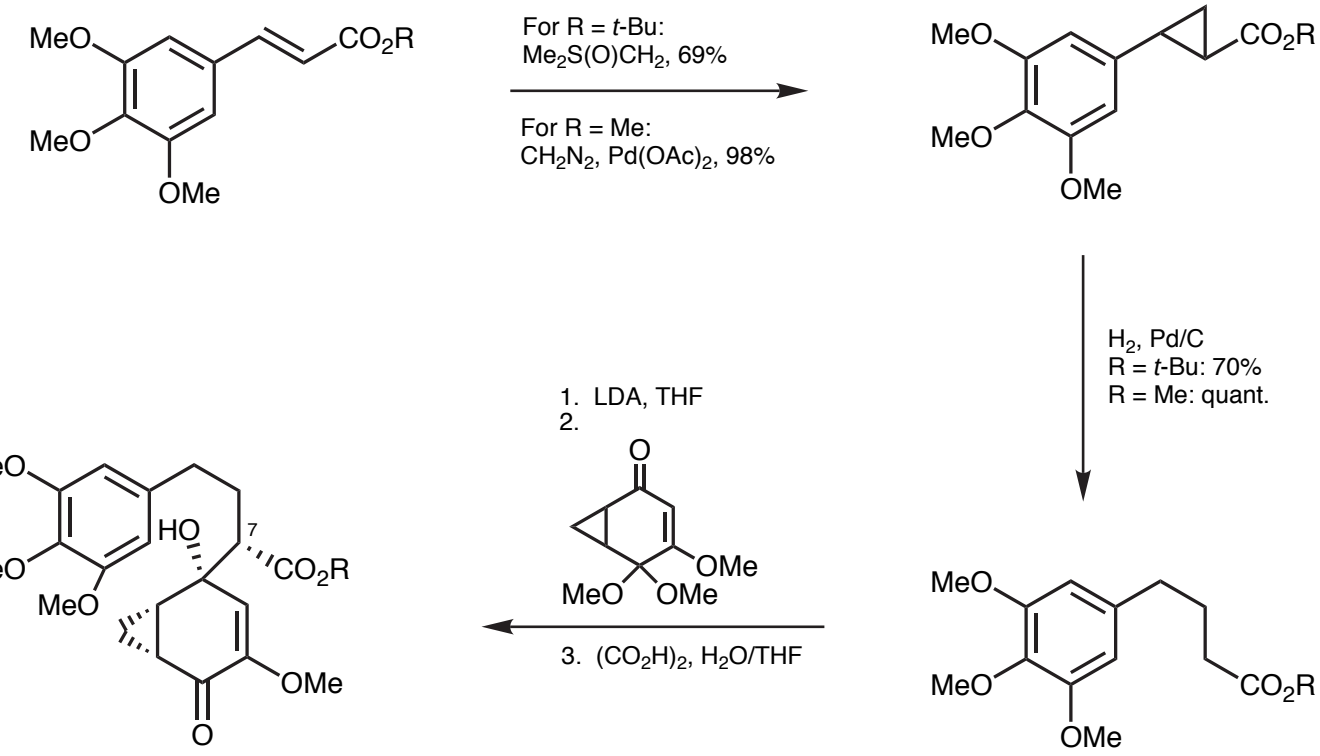


3A

• MM2 minimized structures

Evans Synthesis-Synthesis of Phenol Coupling Intermediate

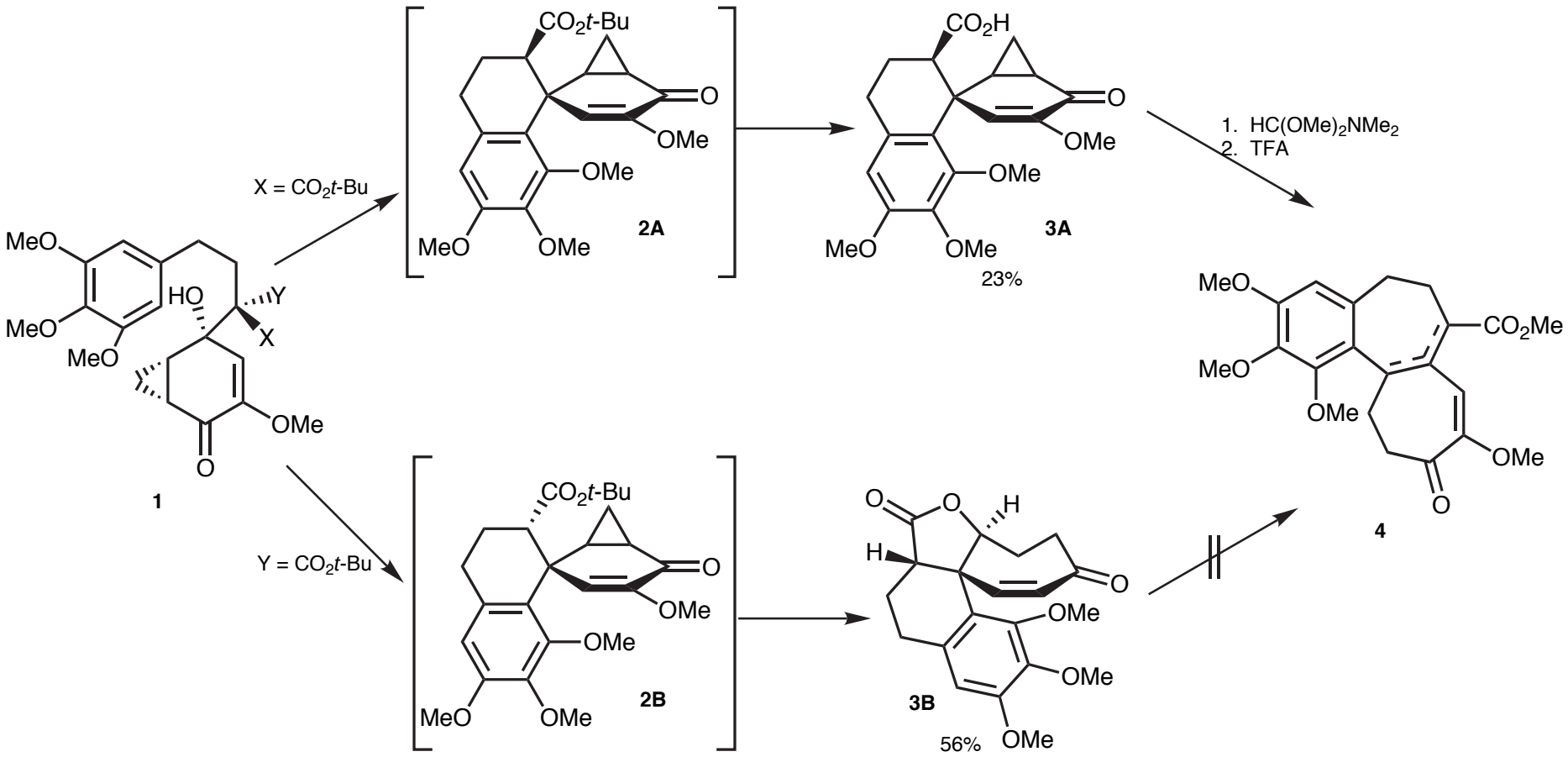




R = *t*-Bu: 3:2:1 mixture of diastereomers, 75%
R = Me: 1:1 mixture of diastereomers at C-7, 95%

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

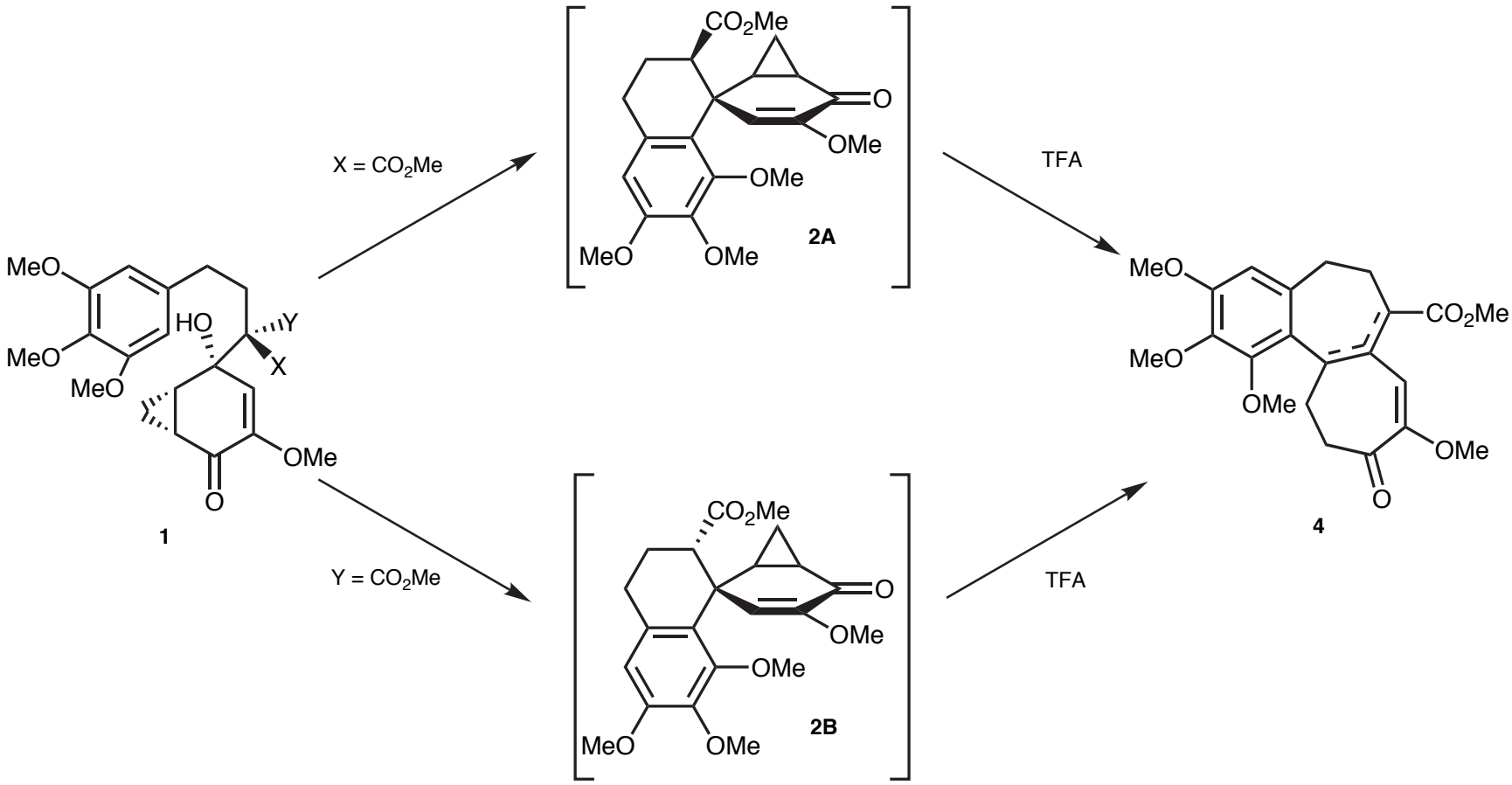
Evans Synthesis-Cyclization and Rearrangement



- Spirocyclization of the 3:2:1 mixture of diastereomers with BF_3•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 occured 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 BF_3•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

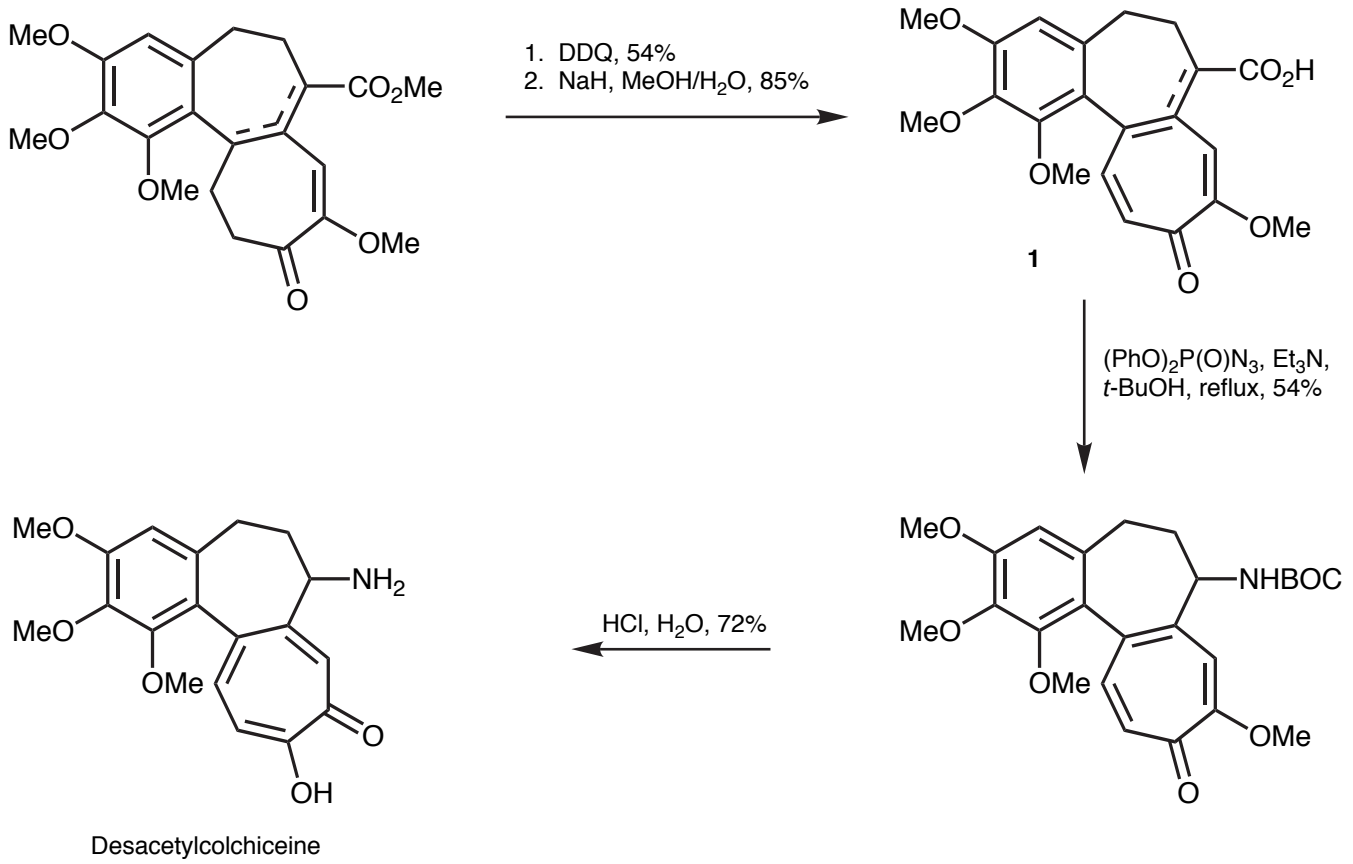
Evans Synthesis-Cyclization and Rearrangement



- Spirocyclization of the 1:1 mixture of diastereomers with $BF_3 \cdot OEt_2$ 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

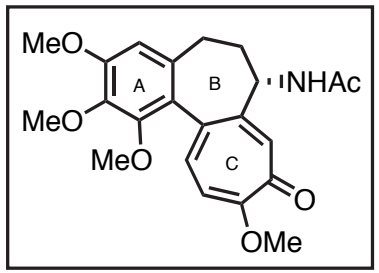


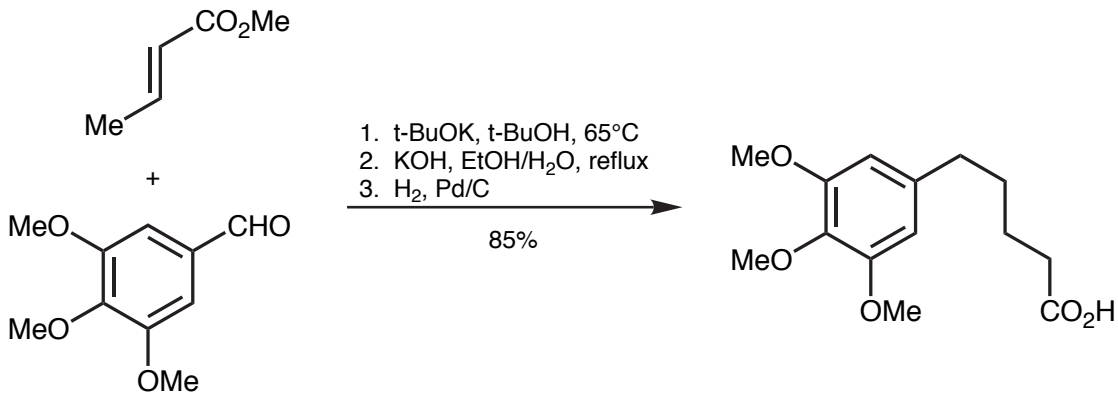
Desacetylcolchiceine

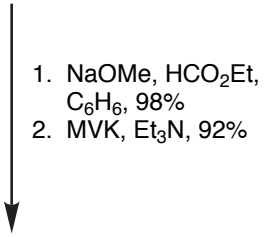
- Compound **1** was isolated as a separable 7:3 mixture of the tropolone and its heptafulvene tautomer.
- Upon sitting in $CDCl_3$ purified samples of either tautomer were reconverted to the 7:3 mixture.

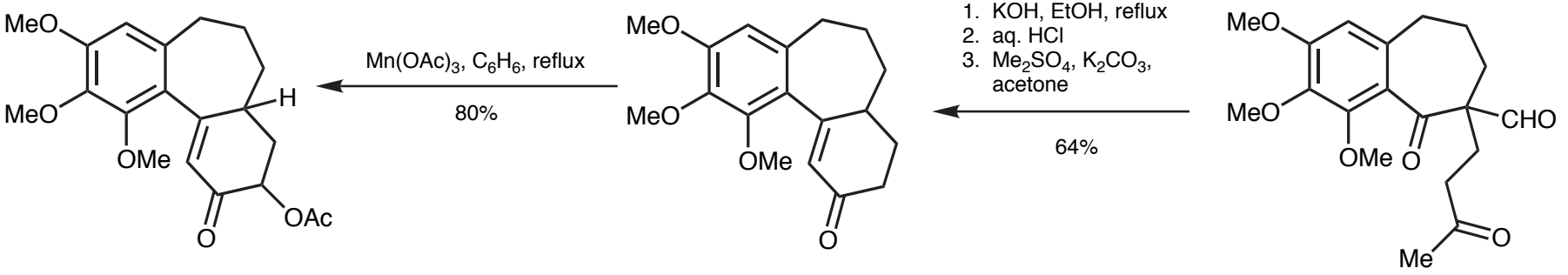
Evans *J. Am. Chem. Soc.* **1978**, 4593
Evans *J. Am. Chem. Soc.* **1981**, 5813

Banwell Synthesis-B and C-ring synthesis







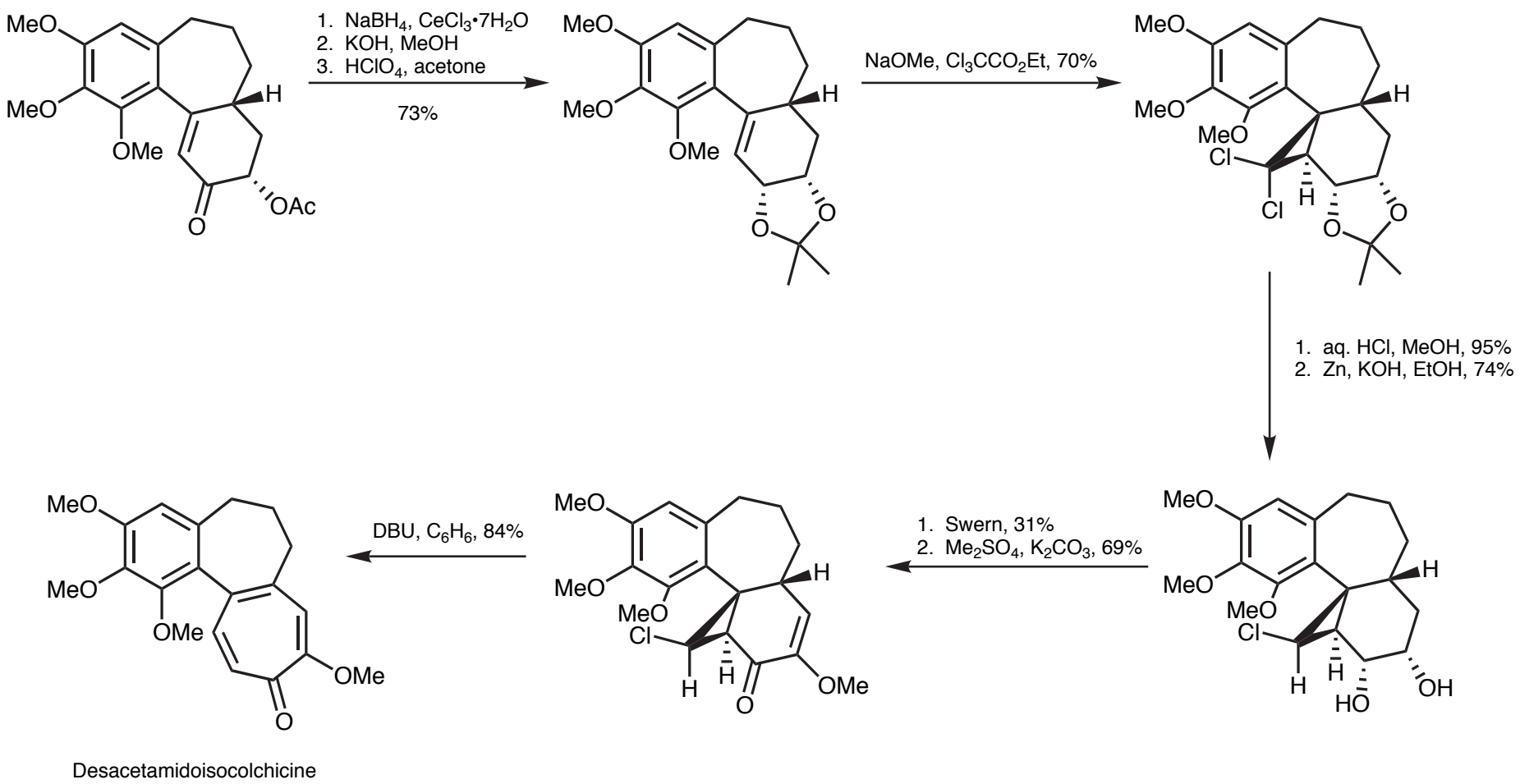


1:1 mixture of diastereomers

- 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 occured, but methylation of the crude reaction mixture alleviated this problem

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

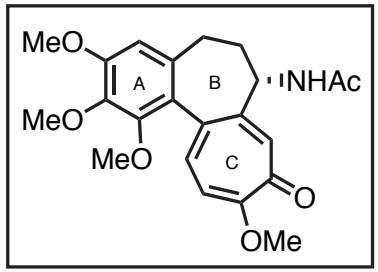
Banwell Synthesis-Tropolonization

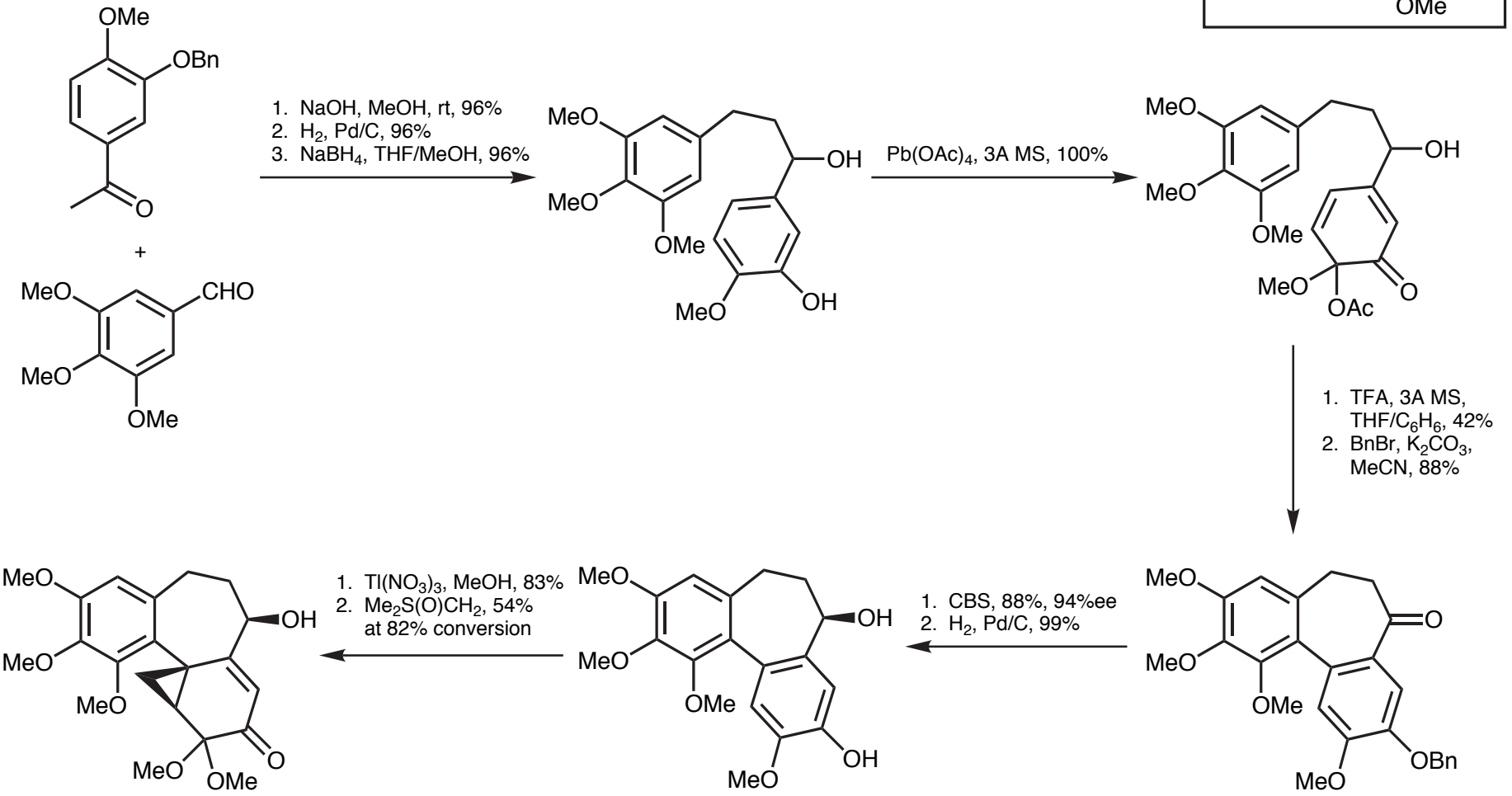


- The initial 3-step sequence to the acetonide was also performed on the other diastereomer in similar yields
- Dichlorocarbene addition to the other diastereomer resulted in a low yield of a C-H insertion product due to steric shielding of the olefin
- Reversing the order of the Zn reduction and acetal 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

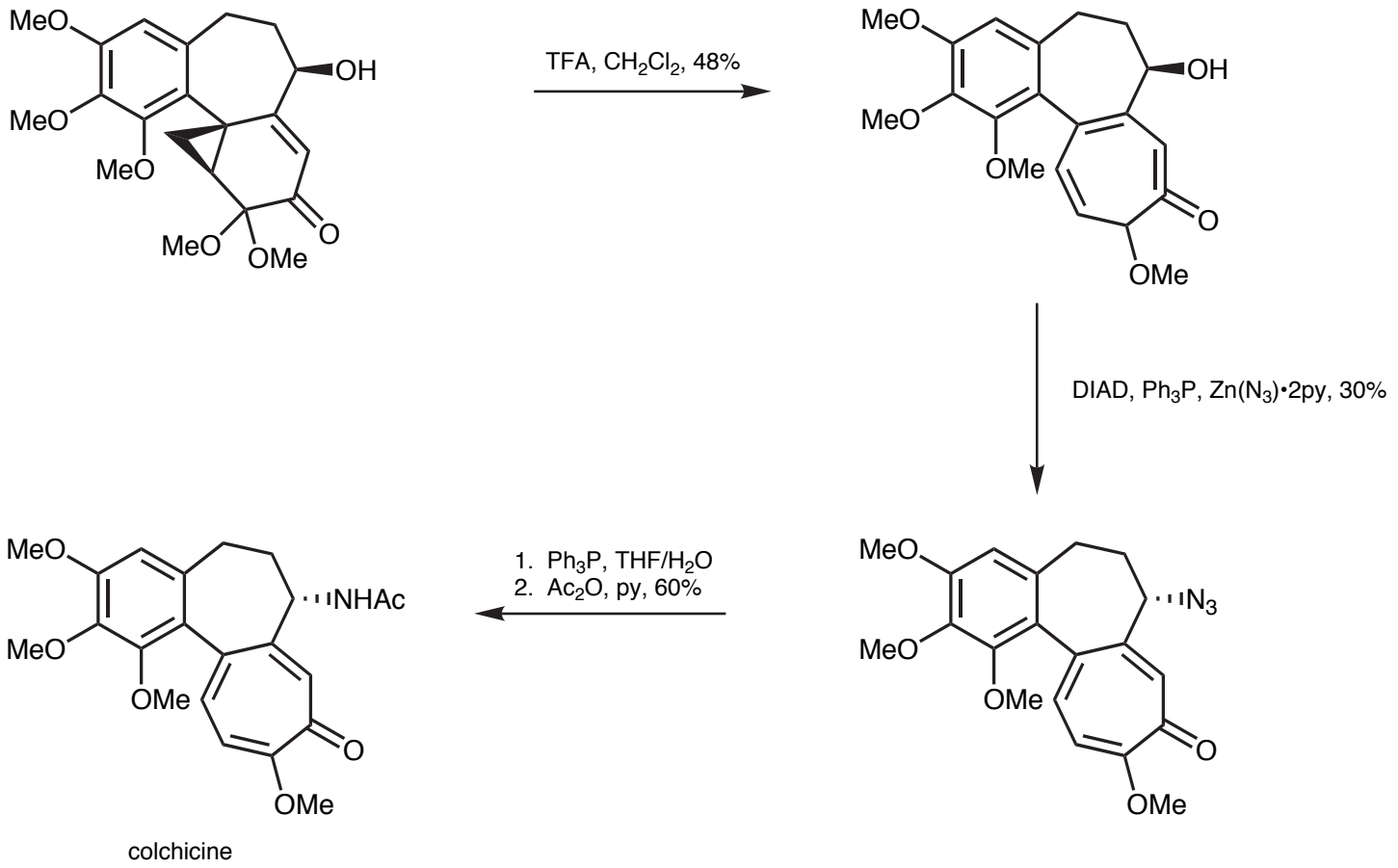




• The penultimate product of the sequence was crystallized up to 98% ee and its structure confirmed by X-ray crystallography

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

Banwell Synthesis-New and Improved

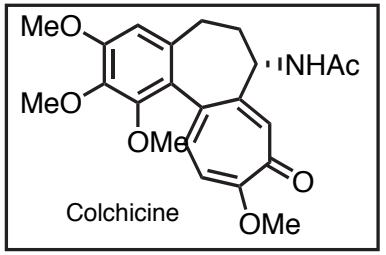


colchicine

- 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 tropolone isomer
- The final ee of colchicine produced is only 81%-racemization occured during the Staudinger reduction

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

Summary-The Numbers



Colchicine

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, 0.00000481%
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)