



The Staunton-Weinreb Annulation

SED Group meeting | Guanqun Zhang | 2015.04.21

Steven M. Weinreb



- Brooklyn, NY – May 10, 1941 (Age 73)
- Cornell University, A.B. – 1963
- University of Rochester, Ph.D. – 1967
 - Advisor: Marshall Gates
- NIH Postdoc Fellow
 - Columbia; Gilbert Stork: 1966-1967
 - MIT: George Buchi: 1967-1970
- Fordham University – 1970
 - Associate professor - 1975
- Penn State University – 1978
 - Professor of chemistry – 1980
 - Russell and Mildred Marker Professor of Natural Products Chemistry – 1987

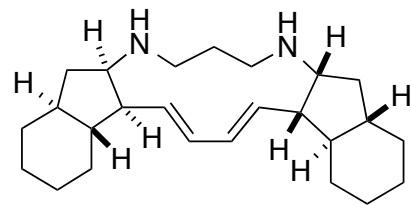
Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16.

Weinreb, S. M. *Acc. Chem. Res.* **2002**, *36*, 59.

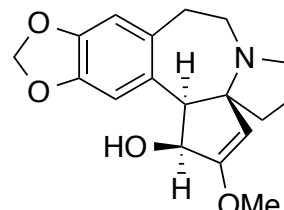
Short, P. *C&EN* **2005**, *83*, 65.

Weinreb, S. M. *Heterocycles* **2006**, *70*, 5.

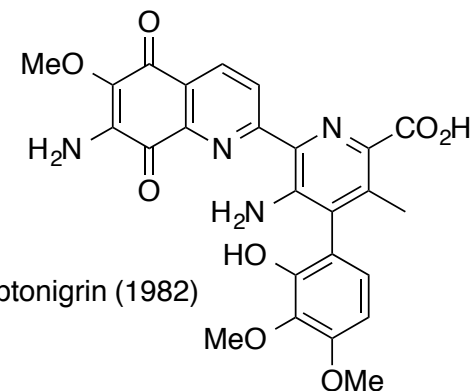
Early synthetic targets



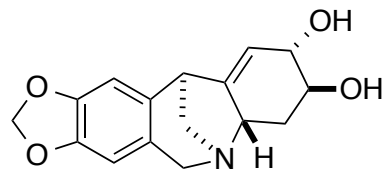
papuamine (1994)



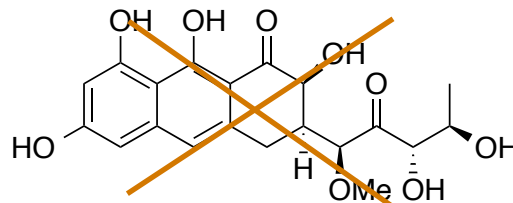
cephalotaxine (1972)



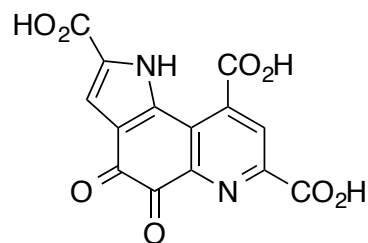
streptonigrin (1982)



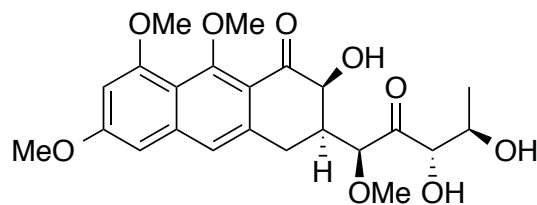
pancracine (1997)



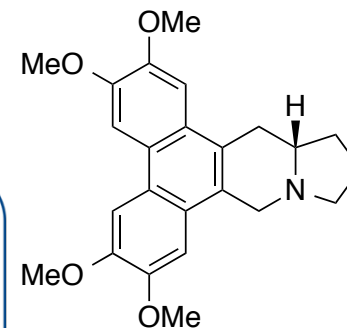
~~oliviv ("1984")~~



methoxatin (1981)



tri-O-methyloliviv (1984)



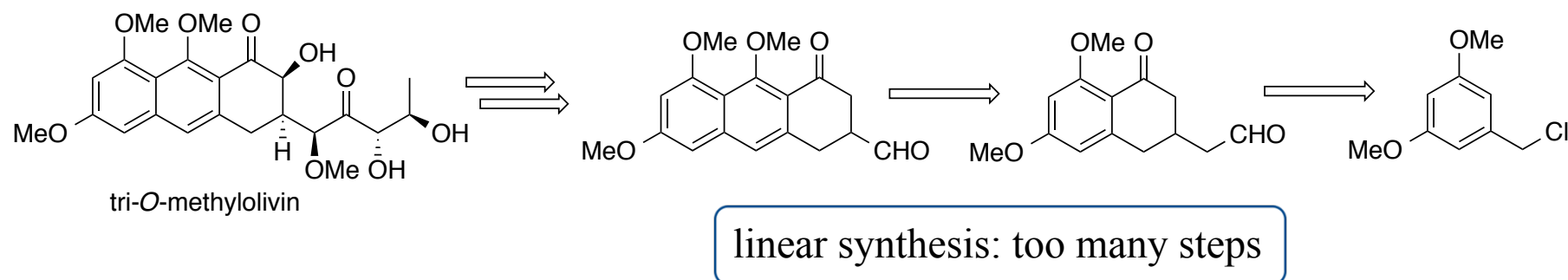
tylophorine (1979)



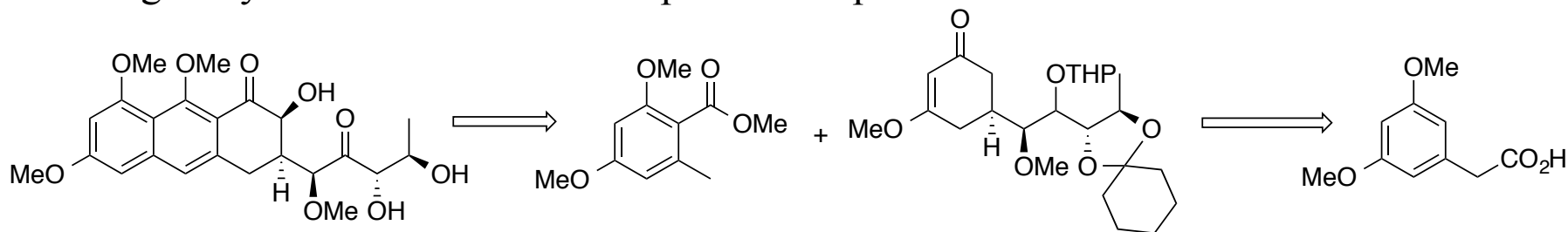
Steve Weinreb

Tri-O-methylolivin

Initial plan:

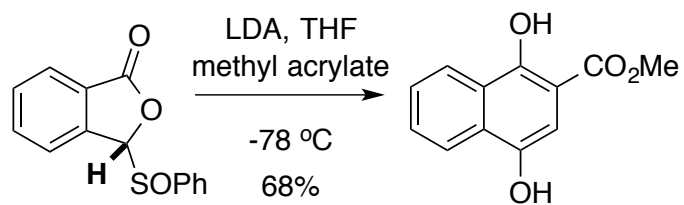


Convergent synthesis: let's take the naphthalene apart...

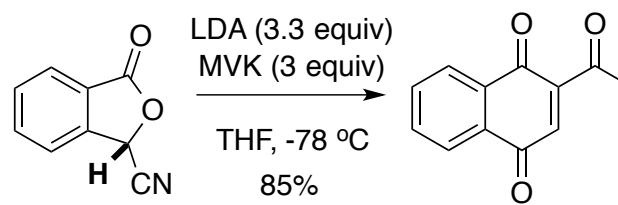


Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *JOC* **1978**, *43*, 4172.
Todd, J. H.; Starrett, J. E.; Weinreb, S. M. *JACS* **1984**, *106*, 1811.

Weinreb was inspired by four other people:



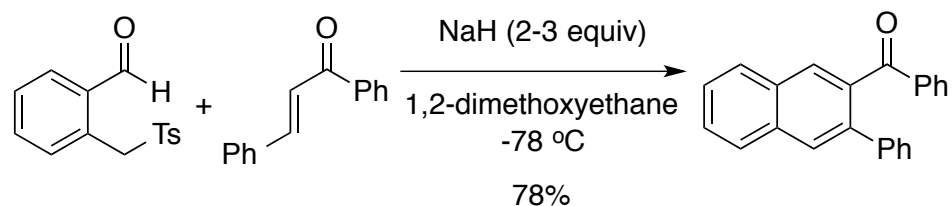
Hauser, 1978



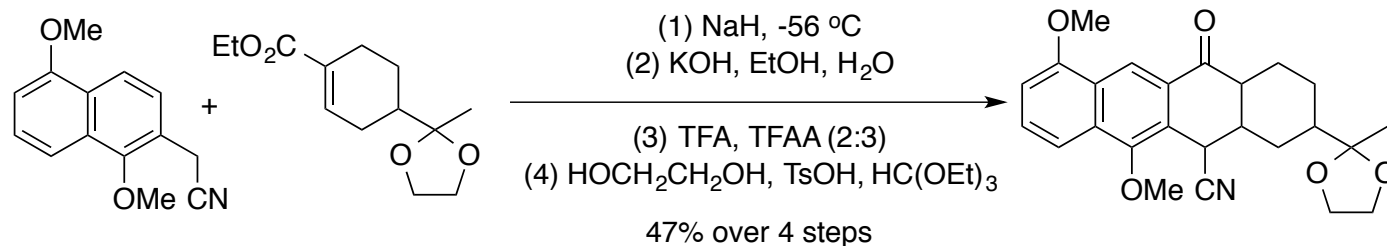
Kraus, 1978

1. R. Gompper, Chem. Ber., **93**, 187 (1960).
2. E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., **94**, 6190 (1972).
3. For some recent, conceptually similar "Michael type" approaches to polycyclic linear aromatics see: F. M. Hauser and R. P. Rhee, J. Org. Chem., **43**, 178 (1978); G. A. Kraus and H. Sugimoto, Tetrahedron Lett., 2263 (1978); J. Wildeman, P. C. Borgen, H. Pluim, P. H. F. M. Rouwette and A. M. van Leusen, ibid., 2213 (1978); K. A. Parker and

Dodd, J. H.; Weinreb, S. M. *Tetrahedron* **1979**, *20*, 3593.
Hauser, F. M.; Rhee, R. P. *JOC* **1978**, *43*, 178.
Kraus, G. A.; Sugimoto, H. *TL* **1978**, *19*, 2263.



van Leusen, 1978



Parker, 1979

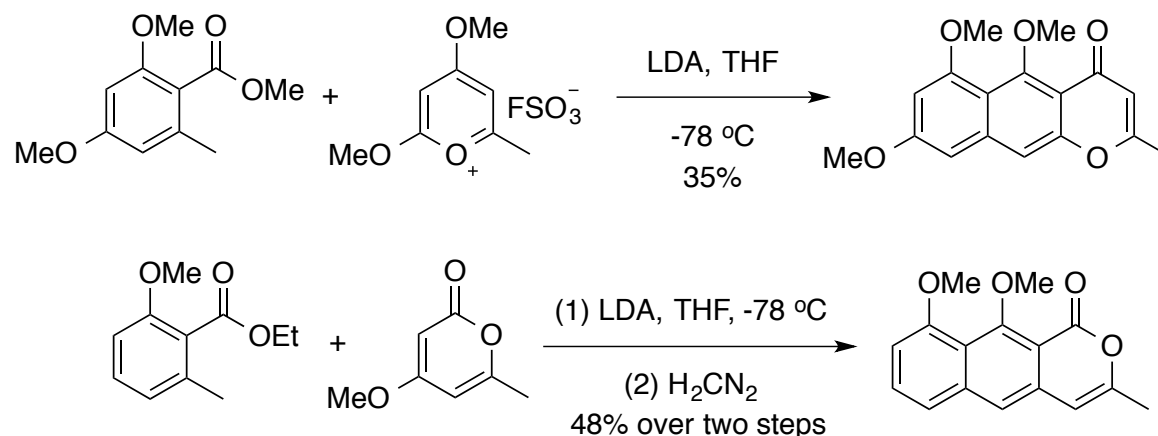
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2. E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., **94**, 6190 (1972).
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Dodd, J. H.; Weinreb, S. M. *Tetrahedron* **1979**, *20*, 3593.
 Wildeman, J.; Borgen, P. C.; Pluim, H.; Rouwette, P. H.F.M.; van Leusen, A. M. *TL* **1978**, *19*, 2213.
 Parker, K. A.; Kallmerten, J. L. *TL* **1979**, *20*, 1197.

14. After completion of the work described here, some analogous condensations of orsellinate anion appeared: G. E. Evans, F. J. Leeper, J. A. Murphy and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 205 (1979); F. J. Leeper and J. Staunton, *ibid.*, 206 (1979).



Jim Staunton

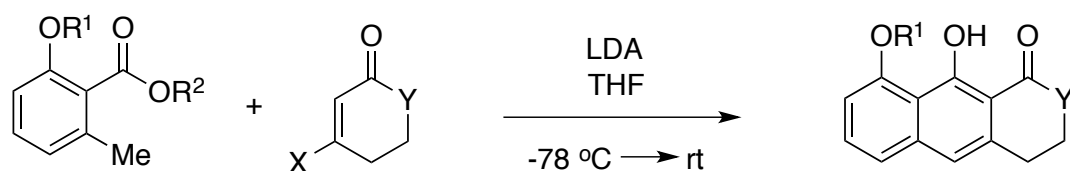


And this brings us to the Staunton-Weinreb annulation

Dodd, J. H.; Weinreb, S. M. *Tetrahedron* **1979**, 20, 3593.

Evans, G. E.; Leeper, F. J.; Murphy, J. A.; Staunton, J. *JCS Chem. Comm.* **1979**, 205 and 406.

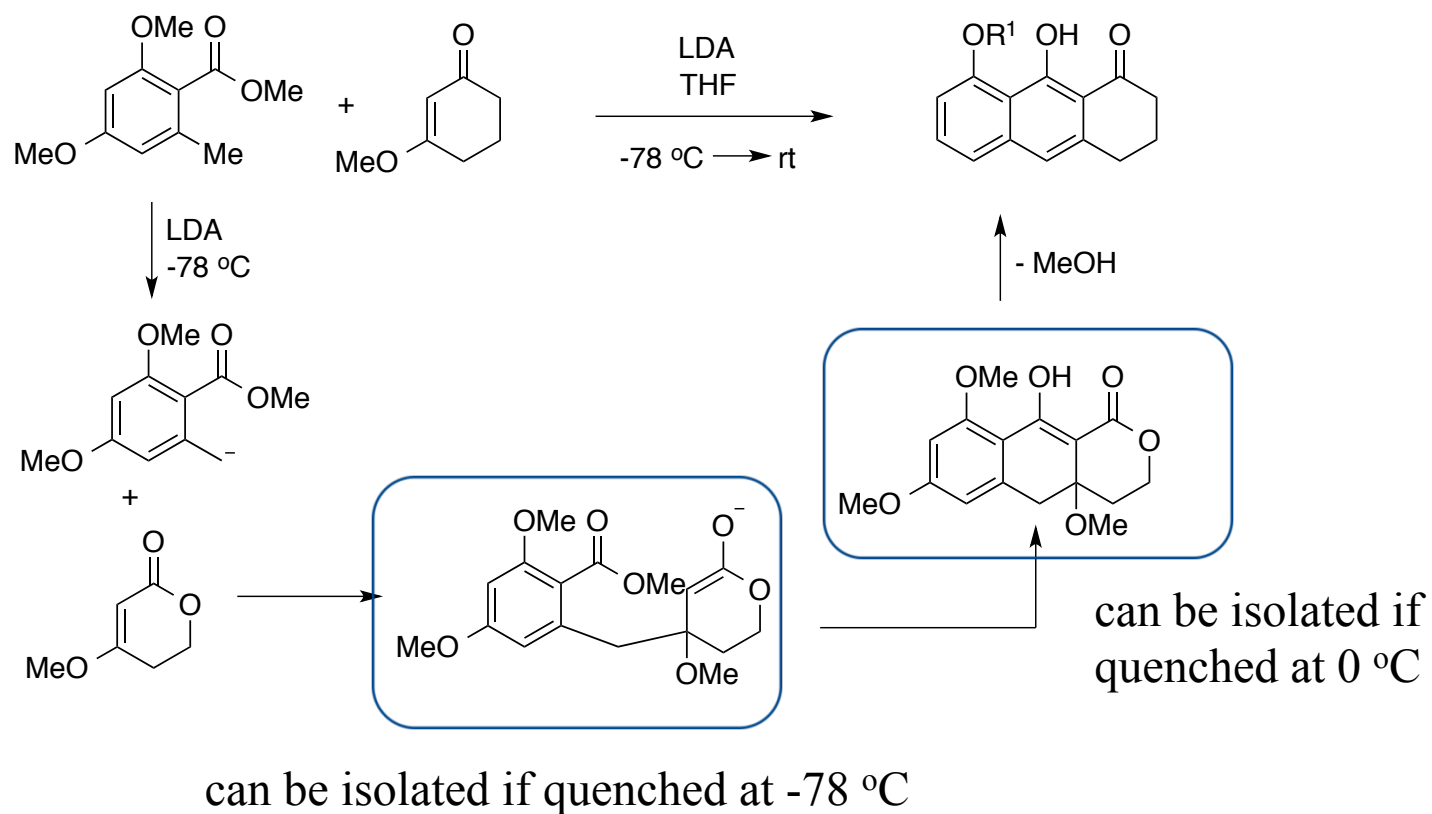
Staunton-Weinreb annulation general scheme



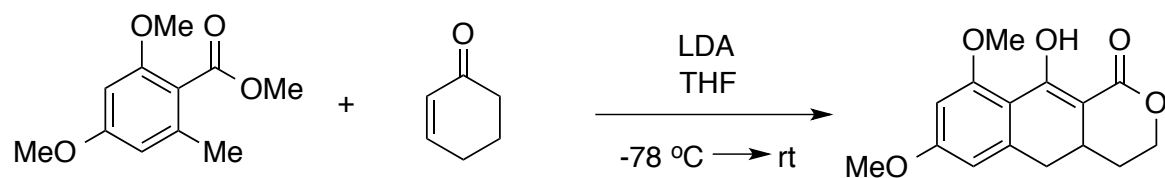
- $R^1 = R^2 =$ alkyl, Bn, MOM, MEM
- $X =$ usually H or OMe
- $Y = \text{CH}_2$ or O
- *o*-toluate is preformed with base
- *o*-toluate anion is bright yellow
- electrophile is added later
- Michael acceptor can be acyclic or cyclic, esters or ketones

It's a stepwise sequence involving Michael addition followed by Dieckmann condensation and subsequent aromatization

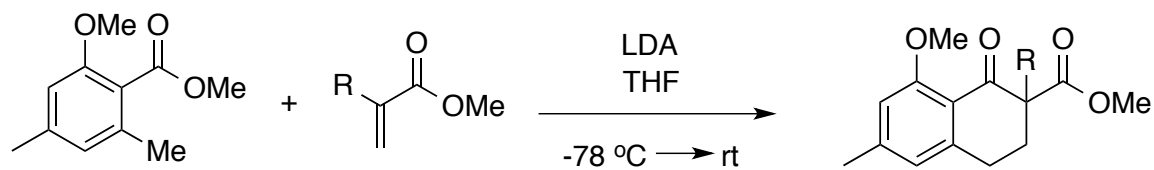
Staunton-Weinreb annulation general mechanism



Staunton-Weinreb annulation general mechanism



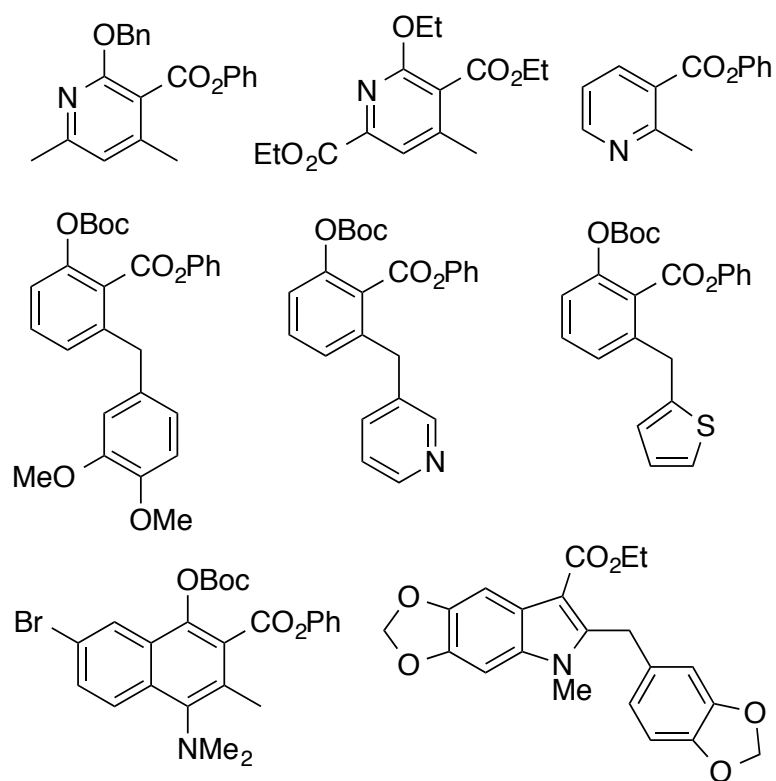
if a leaving substituent is absent, tetralones will be isolated



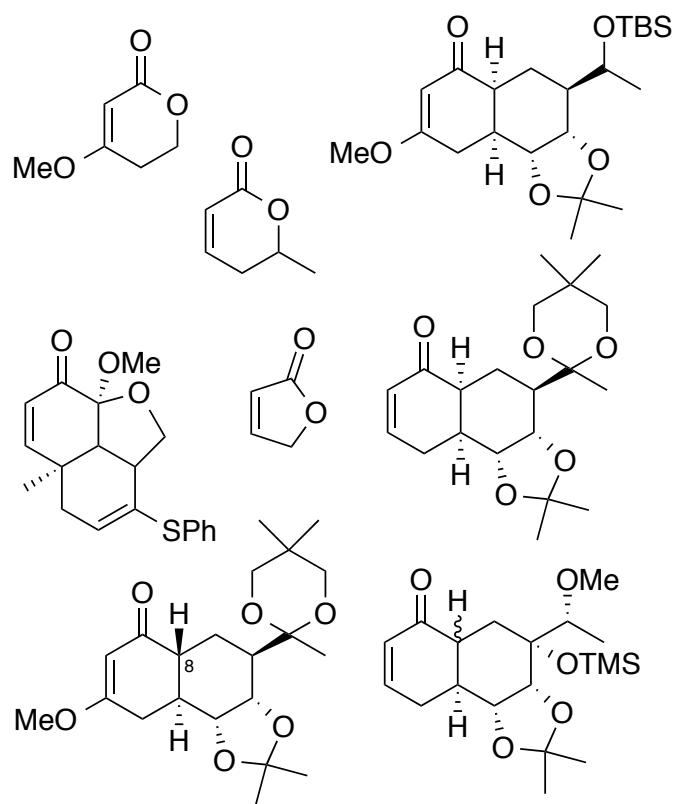
if the alpha position is saturated, decarboxylation can be done to aromatize

The reaction works great with...

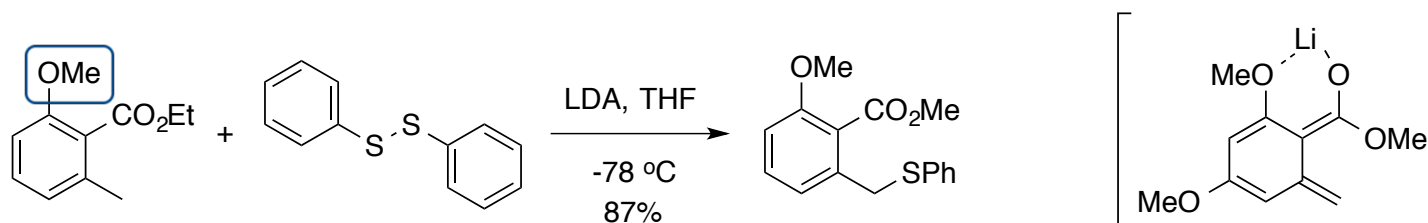
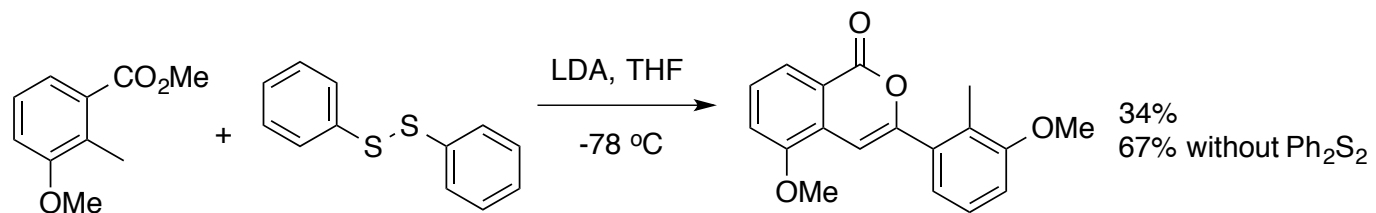
variety of *o*-toluates



α,β -unsaturated esters/ketones

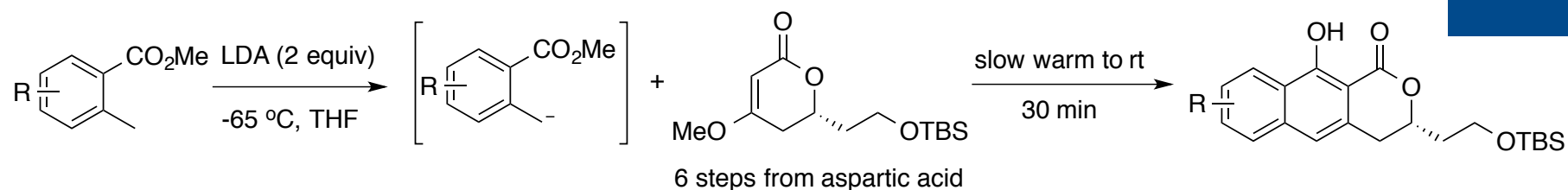


Essentials in the nucleophile



A methyl ether *ortho* to the ester group is necessary to stabilize the anion

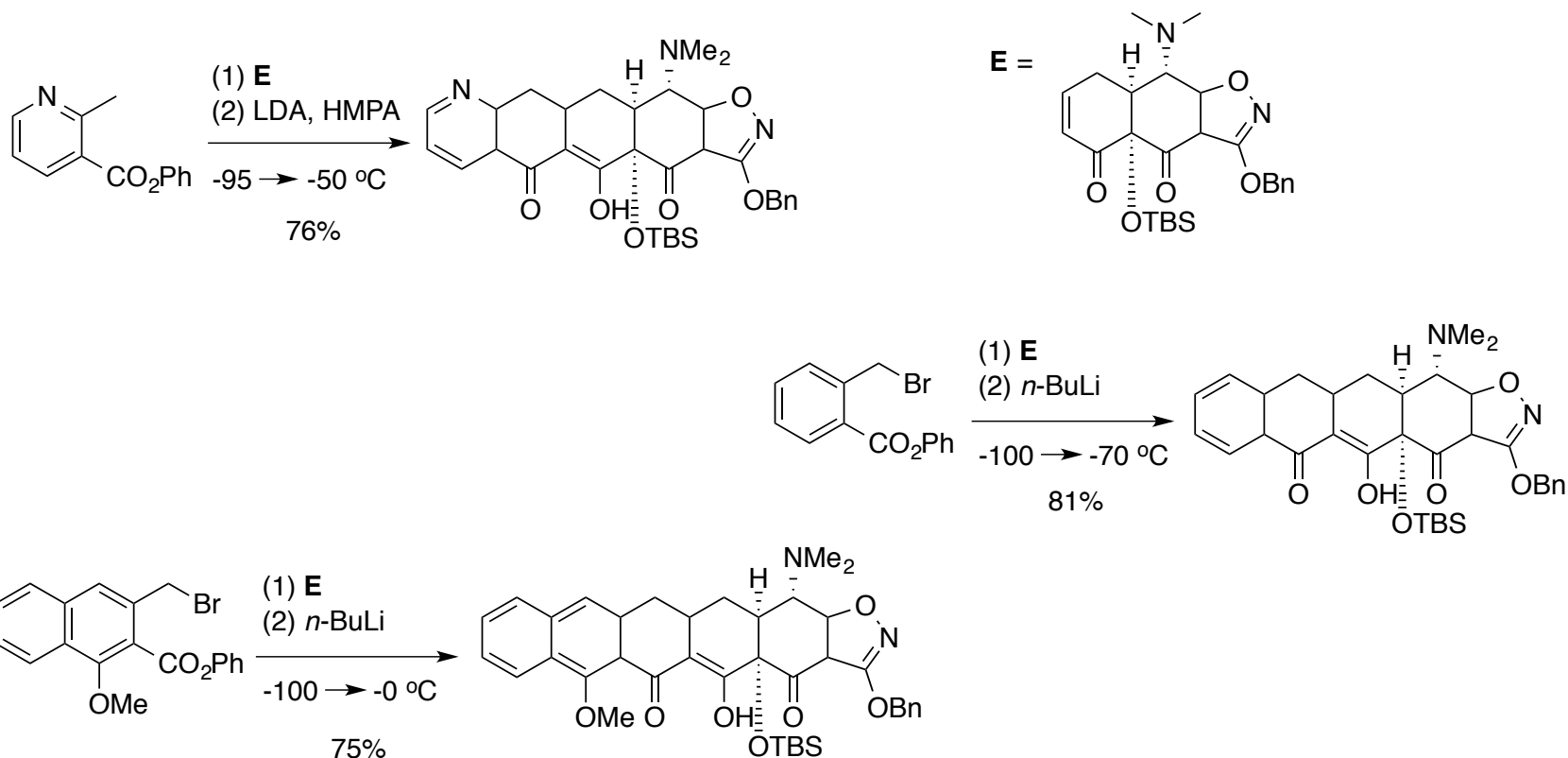
Aryl Substituent effects



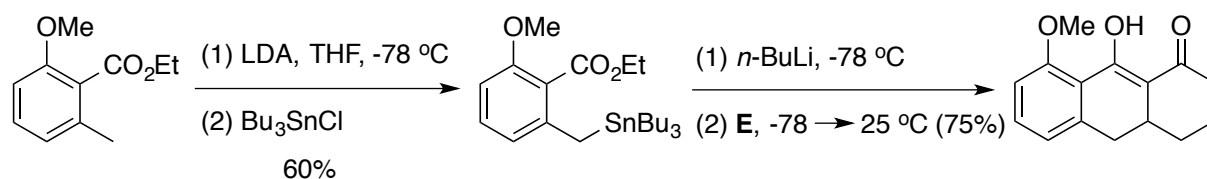
 0%	 0%	 41%	 20%
 46%	 0%	 49%	
 <5%	 0%	 0%	 "10%"

It's a three-way balance between steric interactions, electron density on the toluate and the stabilization offered by chelation

Skipping the *preformed* “enolate”

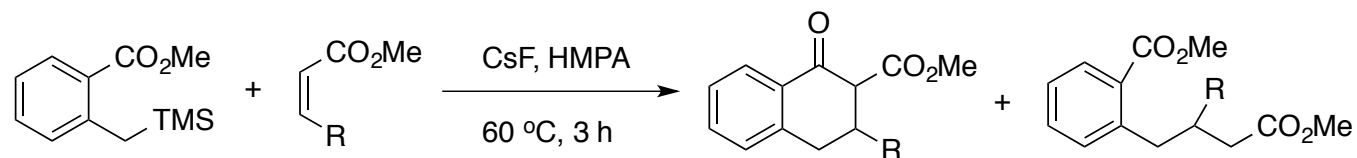


Two additional enolate generation methods...Sn



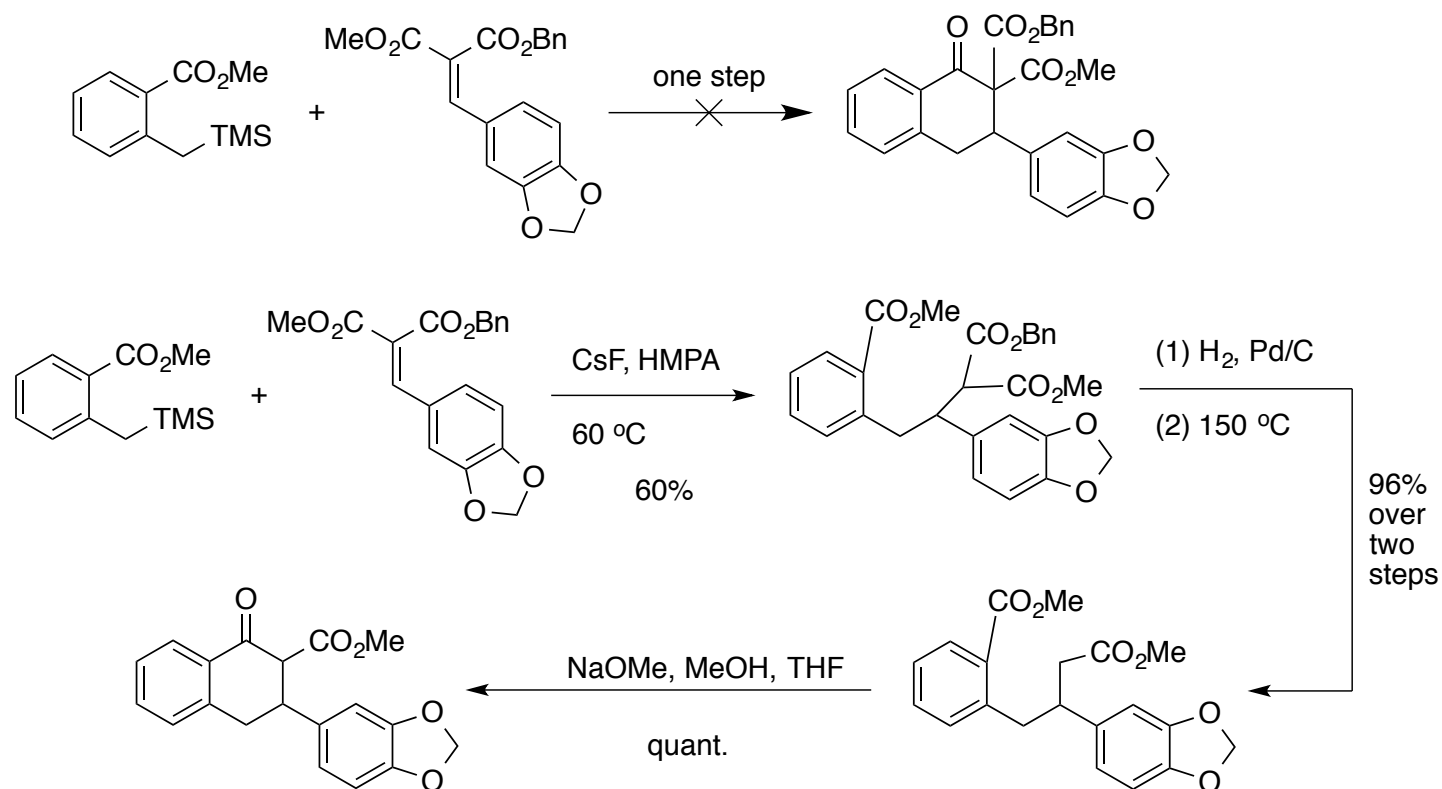
<p>75%</p>	<p>71%</p>	<p>51%</p>
<p>74%</p>	<p>62%</p>	<p>47%</p>
<p>83%</p>		

Two additional enolate generation methods...Si



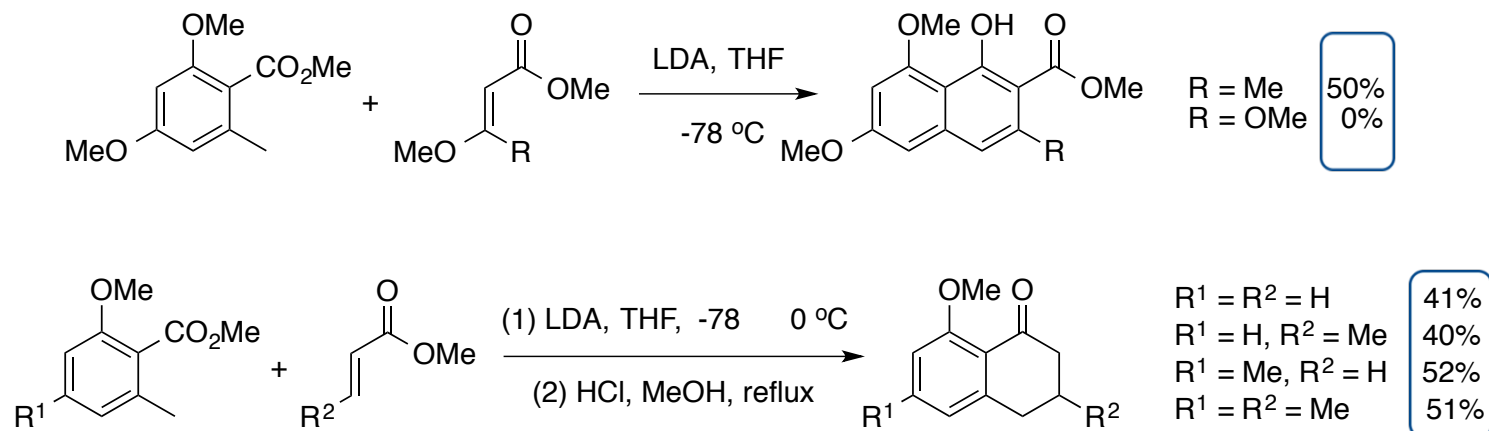
	 17%	 21%		 43%	 15%	
	 14%	 33%			 0%	 70%
	 41%	 28%			 0%	 26%
	 41%	 0%				

Two additional enolate generation methods...Si



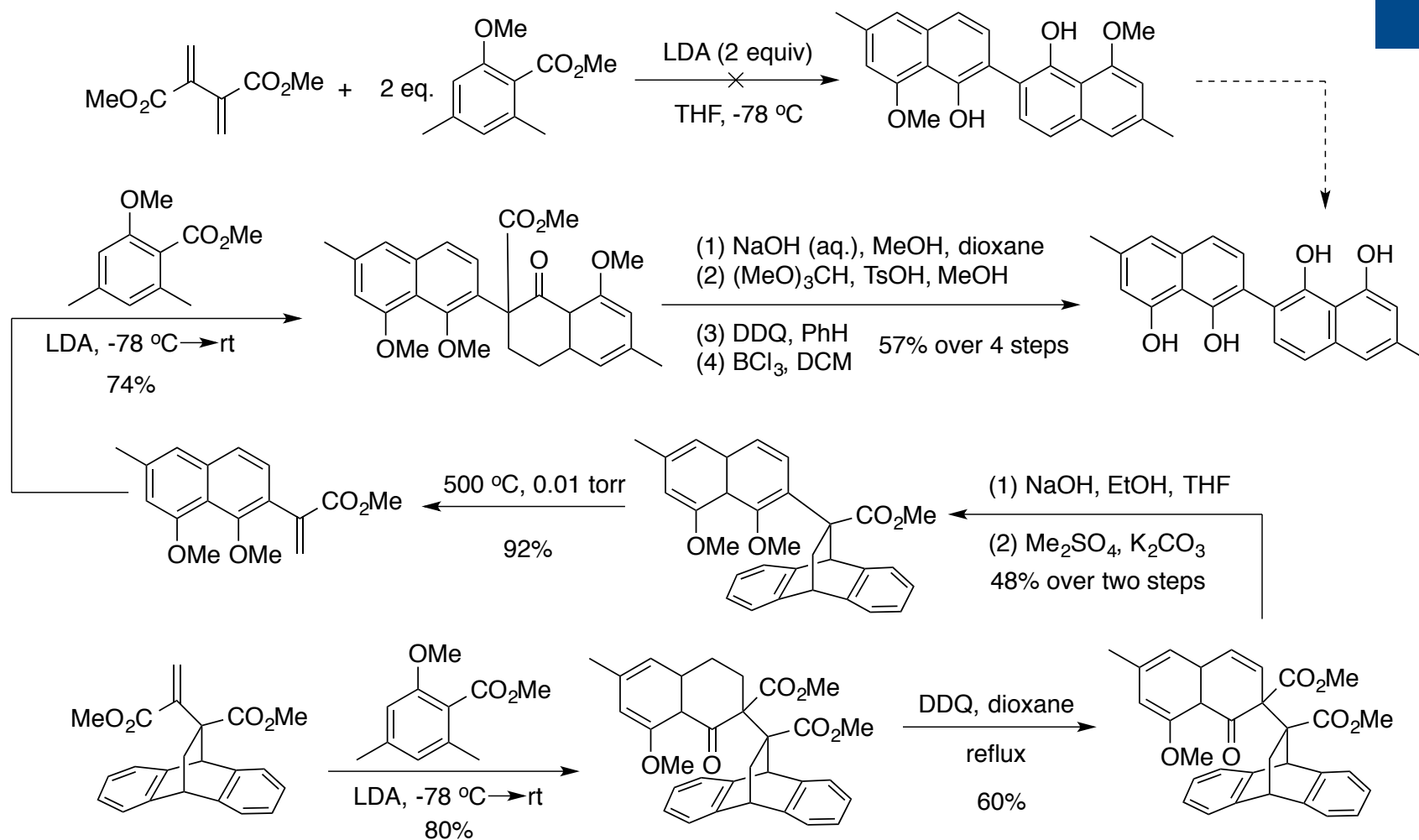
Characteristics of electrophiles

Acyclic Michael acceptor are hit/miss and generally don't work well

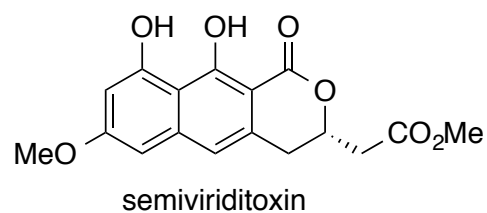


Yields aren't so great

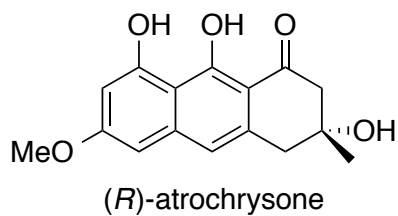
A "cyclic" Michael acceptor



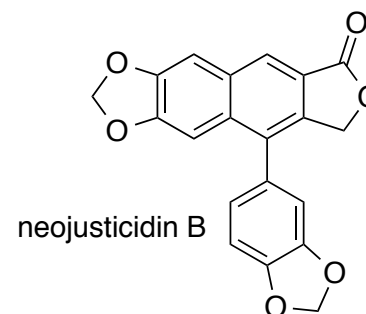
Applications of this annulation in natural product synthesis



FtsZ inhibitor; broad spectrum antibiotic activity against gram-positive pathogens

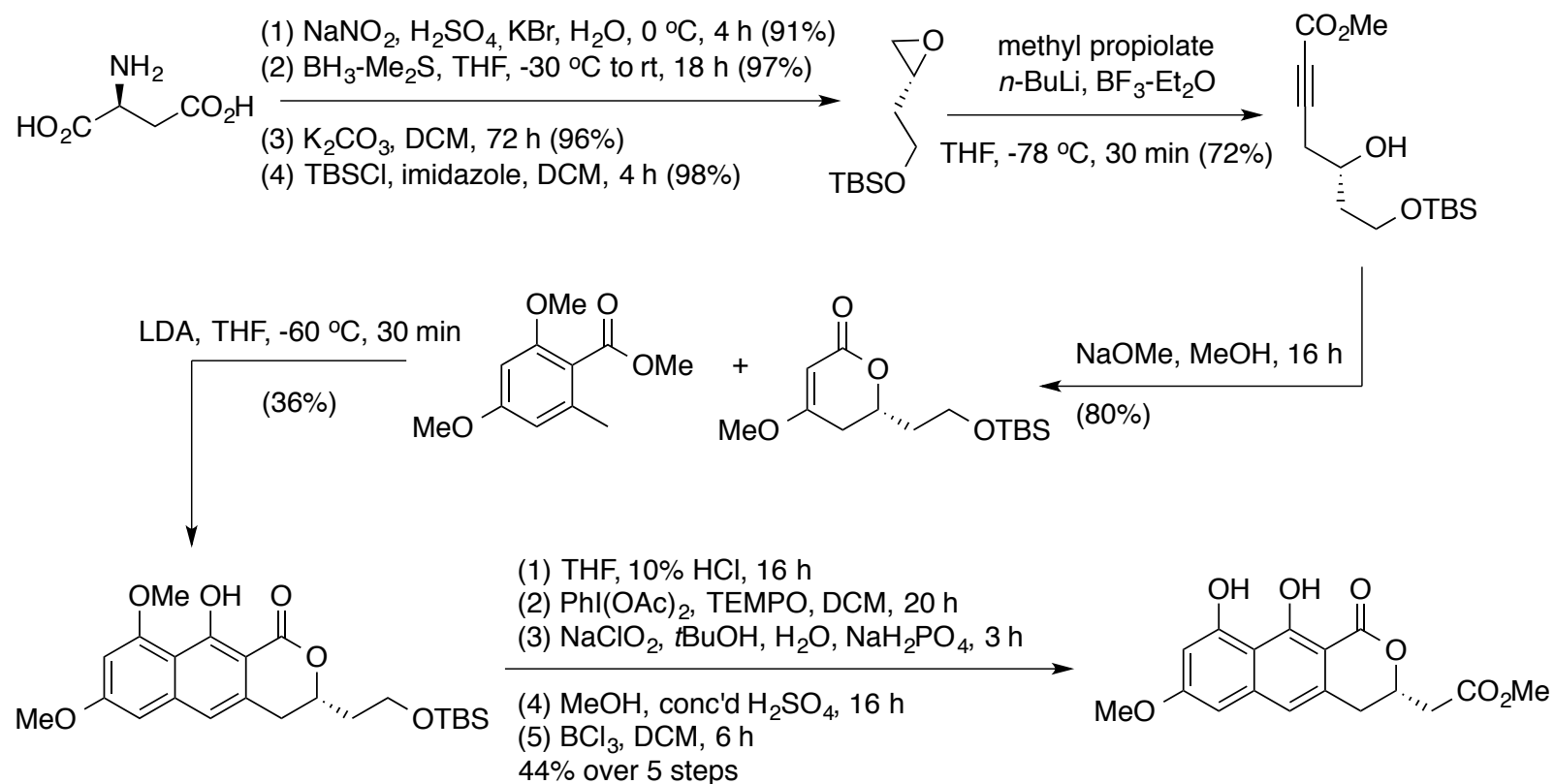


A family of anthranoids, which has displayed anti-bacterial, anti-malarial, and insect antifeedant activities

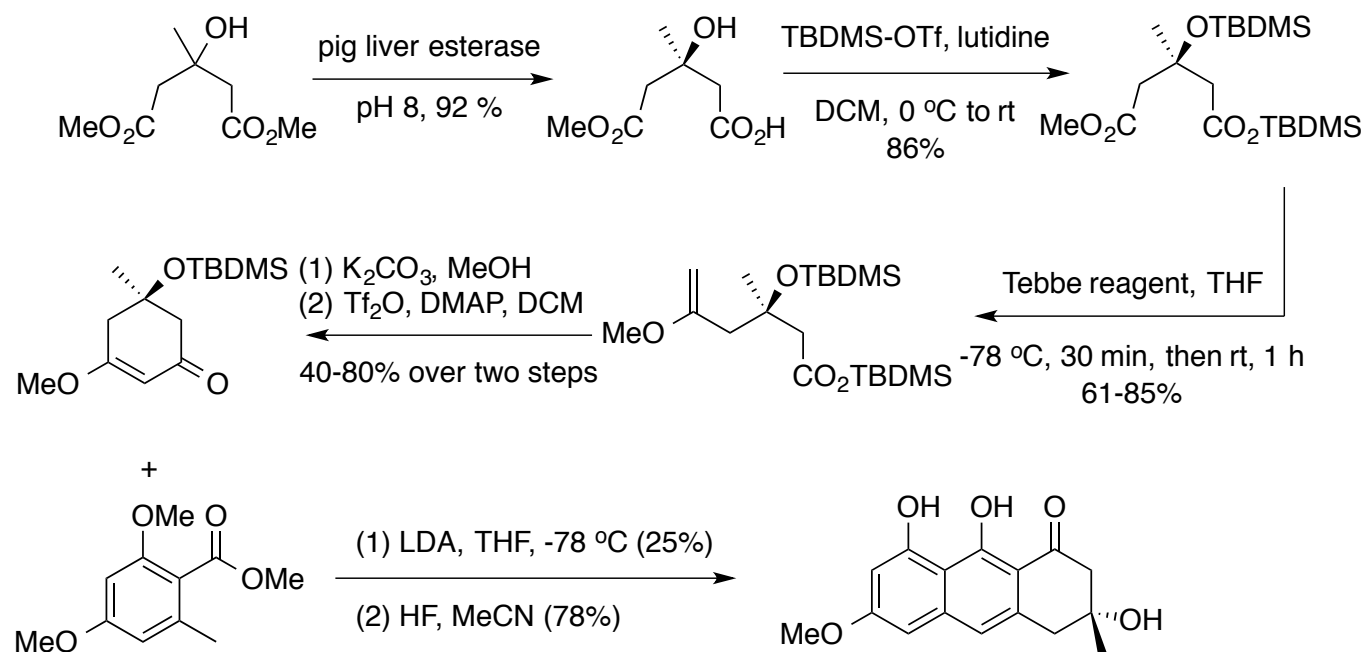


Interesting skeleton for organic synthesis

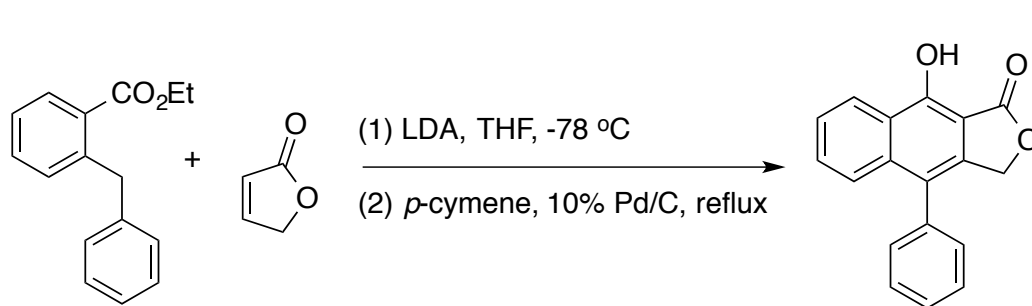
Synthesis of semiviriditoxin



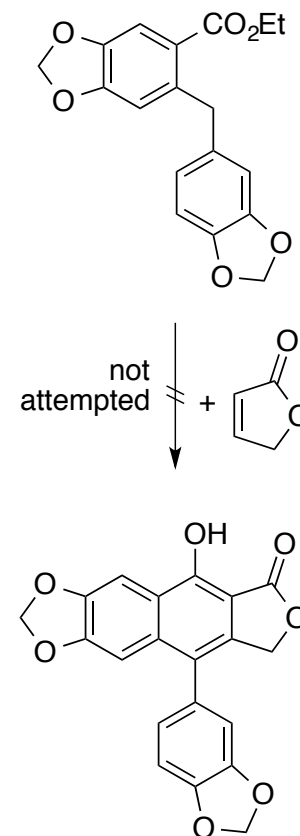
Synthesis of atrochryson



Synthesis of neojusticidin B

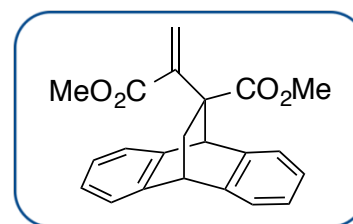
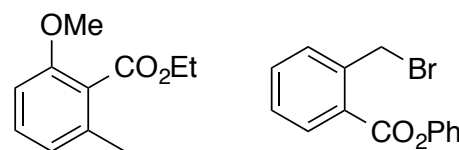
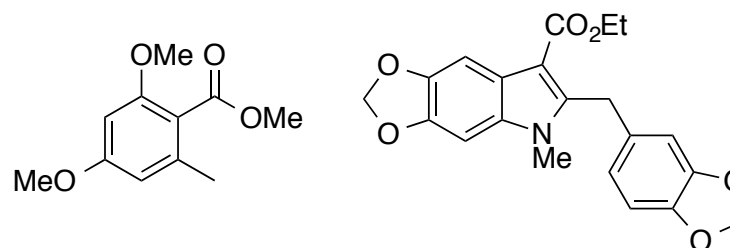
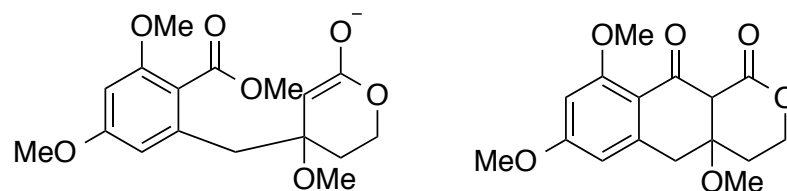
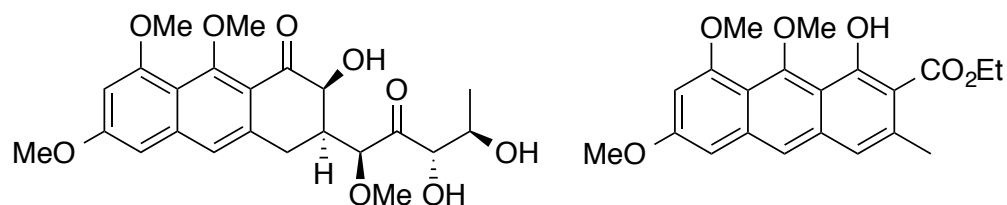


to room temperature to avoid the dihydronaphtholuranone adduct **2**. With 1 equivalent of LDA the sequence appeared to proceed not so cleanly as judged by TLC of the reaction mixture, and the product after dehydrogenation **3** (*vide infra*) was obtained only in a low yield. Every attempt to isolate this adduct in a pure form resulted in failure, because it was not only sparingly soluble in organic solvents, such as diethyl ether or dichloromethane, but also unstable under purification conditions. Therefore, after the production of compound **2** was briefly confirmed on the basis of its IR spectrum (3354, 1781, 1720 and 1671 cm^{-1}), which seemed to indicate that it was an equilibrium mixture of **2A** and **2B**, it was subjected to the next step without any purification. Dehydrogenation of **2** was suc-

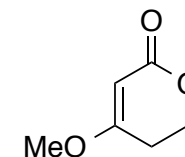


Staunton-Weinreb Annulation

- Discovered Independently by Staunton and Weinreb in 1979 for synthesizing linear polycycles
- Tandam Michael addition, Dieckmann condensation followed by optional aromatization
- *ortho*-toluates
- Generally requires an ether group *ortho* to ester for anion stabiliztion
- ...unless the Anion is generated in situ by lithium-halogen exchange
- cyclic esters and ketones are generally better electrophiles



still acyclic



One more thing...



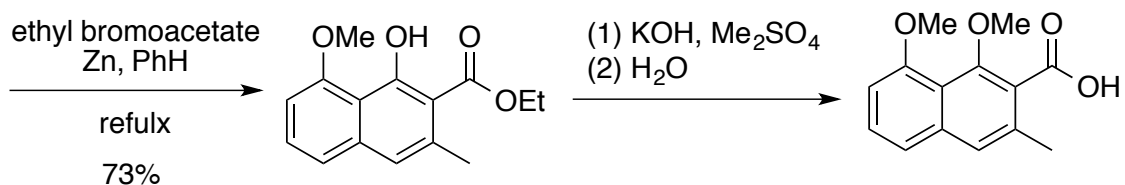
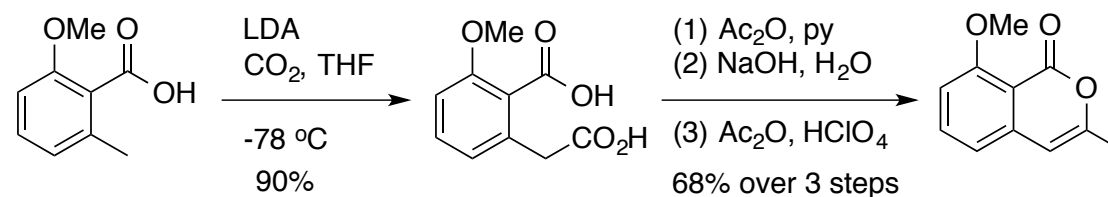
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What happened to Hauser, Kraus, van Leusen, and Parker?

Supposingly, this should be the beginning of this part of history

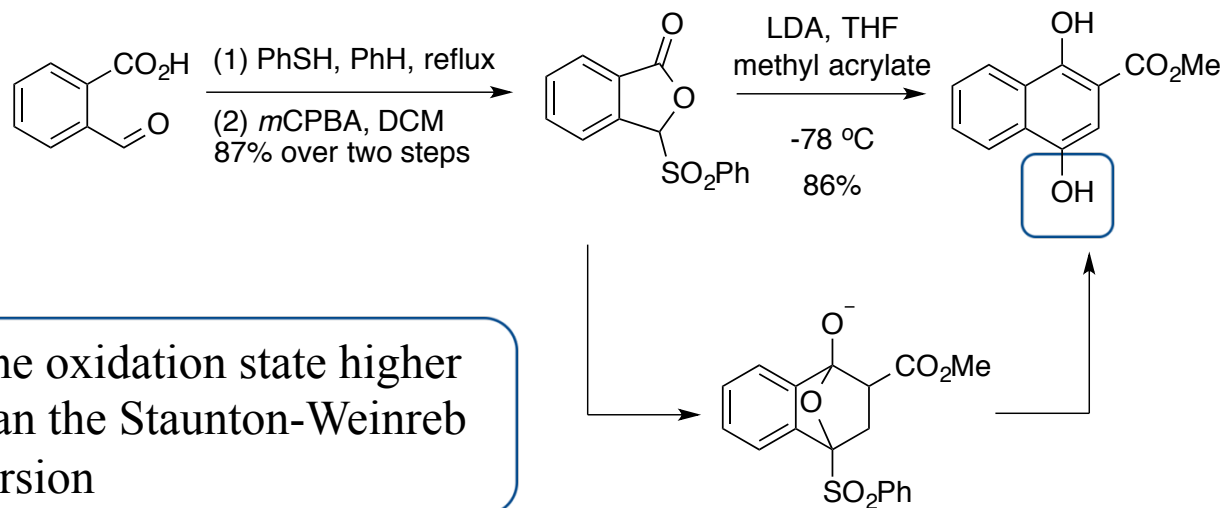
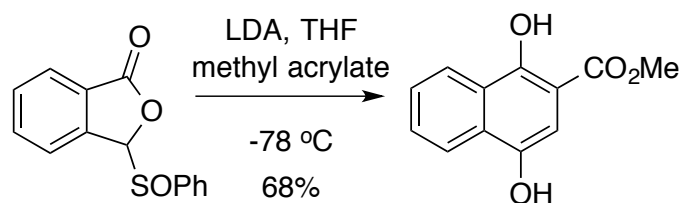


Frank Hauser



then on and on for longer polycyclic chains

(Stabilized) phthalide nucleophiles



One oxidation state higher than the Staunton-Weinreb version



Frank Hauser

Synthesis of neojusticidin B

