Reviews:

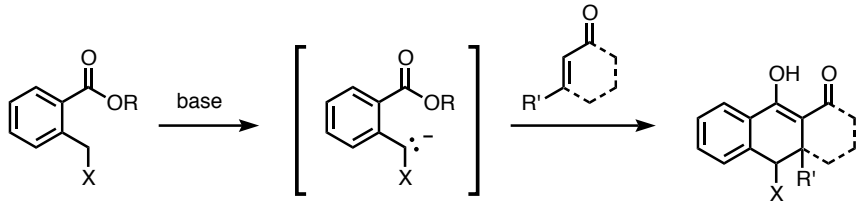
Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892–1918.

Rathwell, K.; Brimble, M. *Synthesis* **2007**, 643–662.

Mitchell, A. S.; Russell, R. A. *Tetrahedron* **1995**, *51*, 5207–5236.

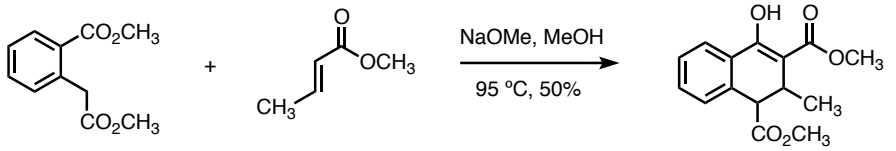
- Anionic Michael-Dieckmann condensation reactions provide a powerful method for the construction of six-membered rings.

Generalized Reaction Scheme



- X = H, CN, SO_2Ph, SPh, F, Br, SnR_3, $P(O)(OR)_2$, CO_2CH_3
- Base = LDA, LiHMDS, LiO*t*-Bu, KO*t*-Bu, NaHMDS, KHMDS, LiTMP, etc

- In a very early example, Schmid showed that esters of homophathalic acid undergo annulation reactions:

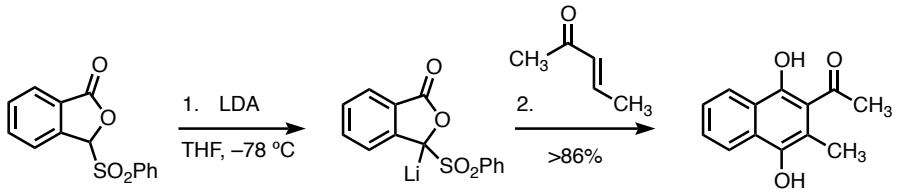


(relative stereochemistry not determined)

Eisenmuth, W.; Renfroe, H. B.; Schmid, H. *Helv. Chim. Acta.* **1965**, *48*, 375–379.

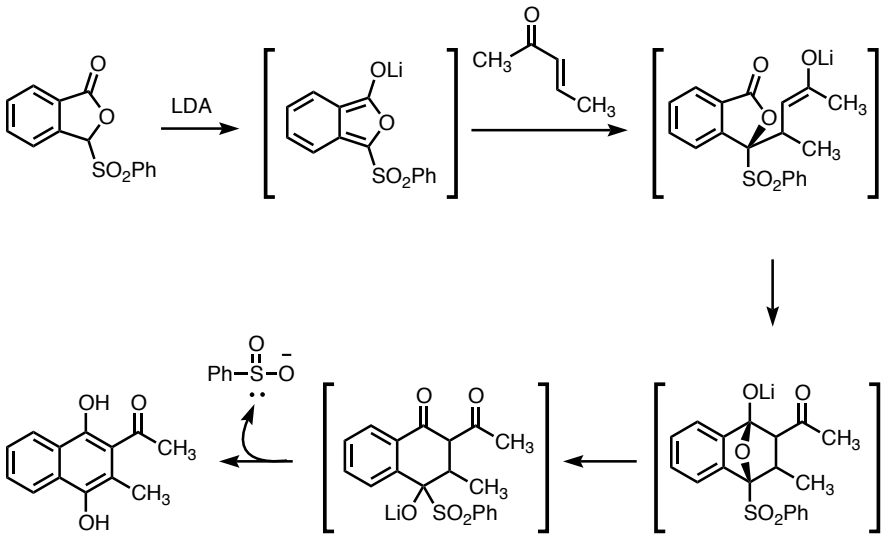
Hauser Annulation

- Annulation reactions of 3-phenylsulfonyl isobenzofuranones with Michael acceptors provide 1,4-dihydroxynaphthalenes:



Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178–180.

- It is generally accepted that the transformation proceeds by an initial Michael addition reaction followed by Claisen cyclization and elimination of phenylsulfinic acid:



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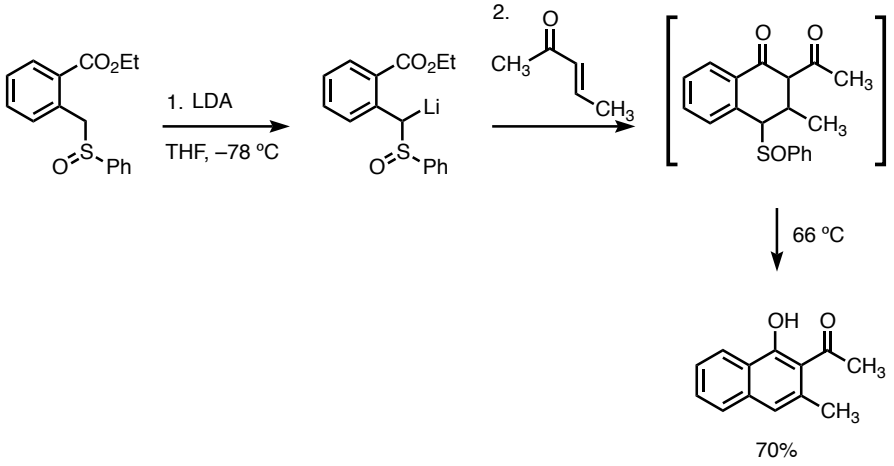
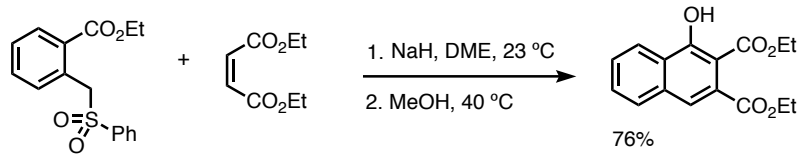
- Conjugate addition of a phenyl sulfoxide derivative followed by intramolecular condensation and thermal elimination of phenylsulfenic acid gives 1-hydroxynaphthalenes:



Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178–180

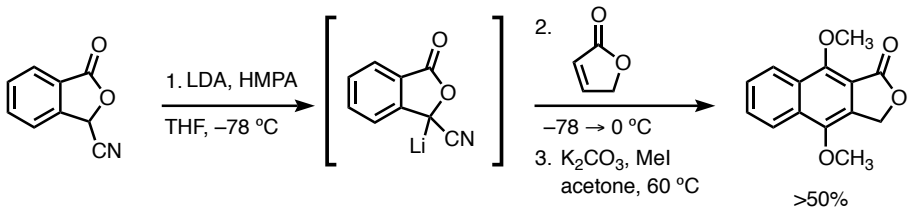
- A closely related method was reported by van Leusen, which involves thermal elimination of phenylsulfinic acid:



Wildeman, J.; Borgen, P. C.; Pluim, H.; Rouwette, P. H. F. M.; van Leusen, A. M. *Tetrahedron Lett.* **1978**, *25*, 2213–2216.

Kraus Annulation

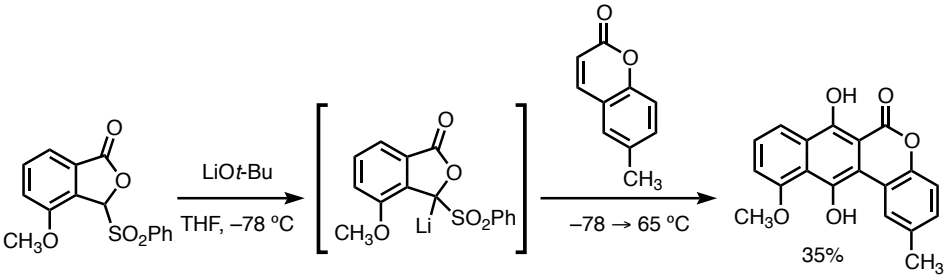
- 3-cyanoisobenzofuranones are effective substrates for anionic cyclizations:

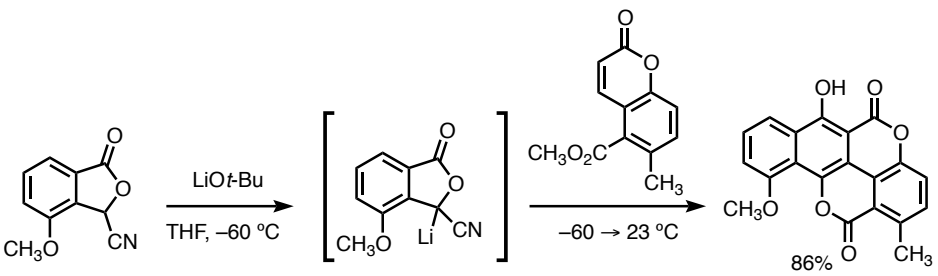


Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, *26*, 2263–2266.

Comparison of Hauser and Kraus Annulations

- While yields for the two methods can be similar in some cases, in other cases the Kraus annulation was found to be more effective, likely because the cyanoisobenzofuranone nucleophile is less hindered and more soluble in the reaction medium:





Hauser, F. M.; Combs, D. W. *J. Org. Chem.* **1980**, *45*, 4071–4073.
Mal, D.; Patra, A.; Roy, H. *Tetrahedron Lett.* **2004**, *45*, 7895–7898.

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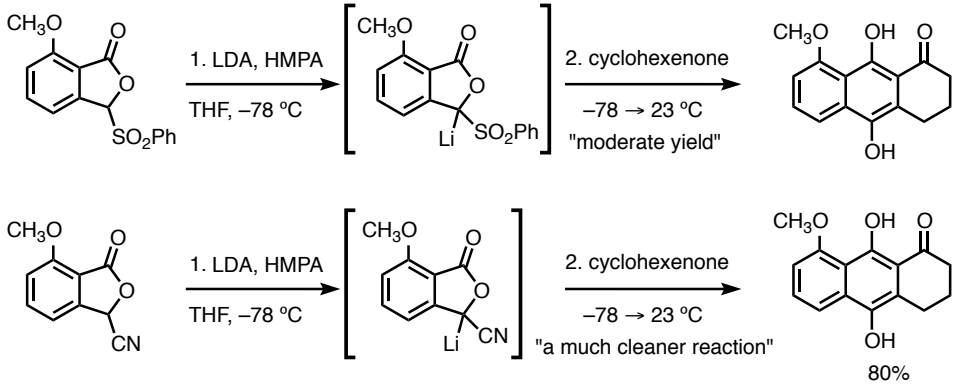
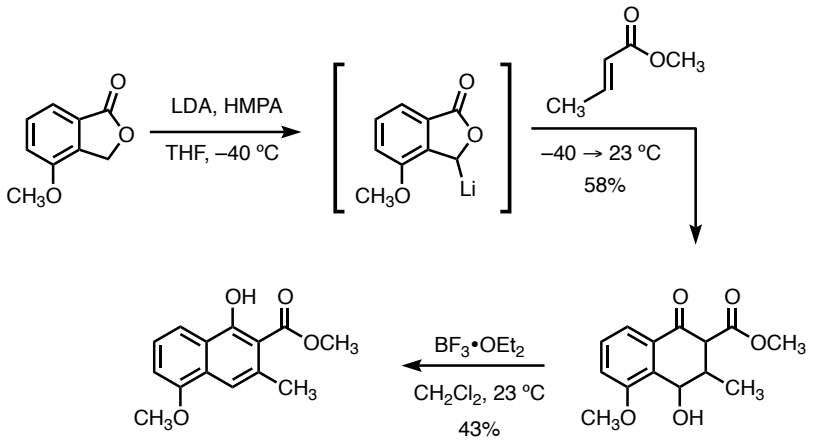
- In the following example, the Kraus annulation was reported to be a "much cleaner reaction":



Li, T.-T.; Walsgrove, T. C. *Tetrahedron Lett.* **1981**, *22*, 3741–3744.

- **Sammes Annulation**

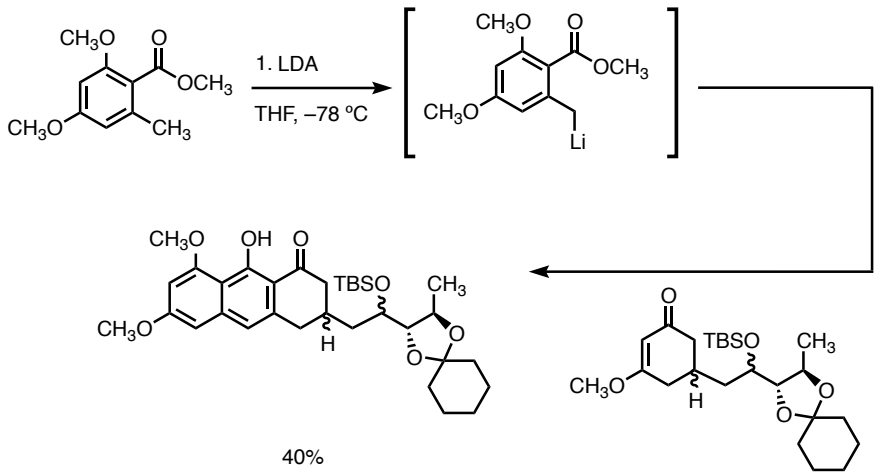
- It was shown that a phthalide anion is a suitable reaction partner en route to 1-hydroxynaphthalenes:



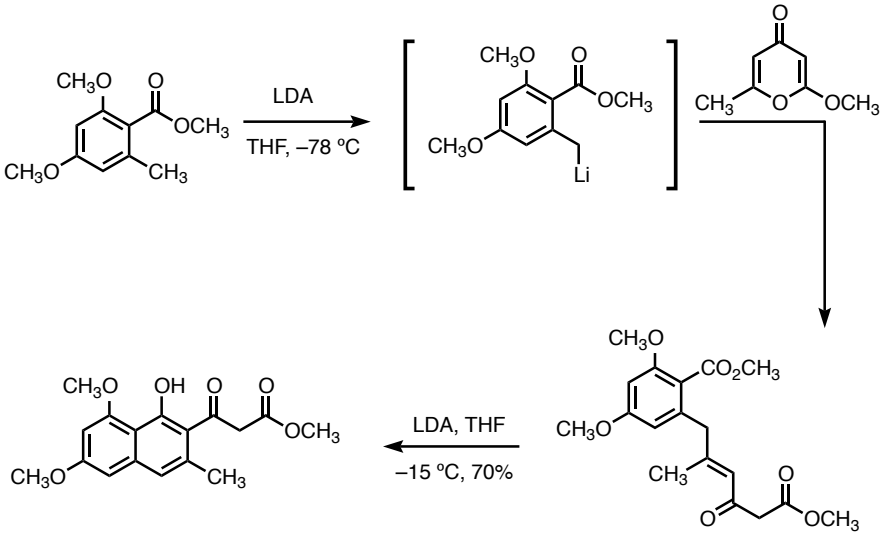
Broom, N. J. P.; Sammes, P. G. *J. Chem. Soc. Chem. Commun.* **1978**, 162–164.
Broom, N. J. P.; Sammes, P. G. *J. Chem. Soc. Perkin Trans. 1* **1981**, 465–470.

- **Staunton-Weinreb Annulations**

- Staunton and Weinreb showed independently in 1979 that *o*-toluates are suitable nucleophiles for anionic cyclization reactions.



Dodd, J. H.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, *38*, 3593–3596.



Evans, G.; Leeper, F. J.; Murphy, J. A.; Staunton, J. *J. Chem. Soc. Chem. Commun.* **1979**, 205–206.
Leeper, F. J.; Staunton, J. *J. Chem. Soc. Chem. Commun.* **1979**, *5*, 206–207.

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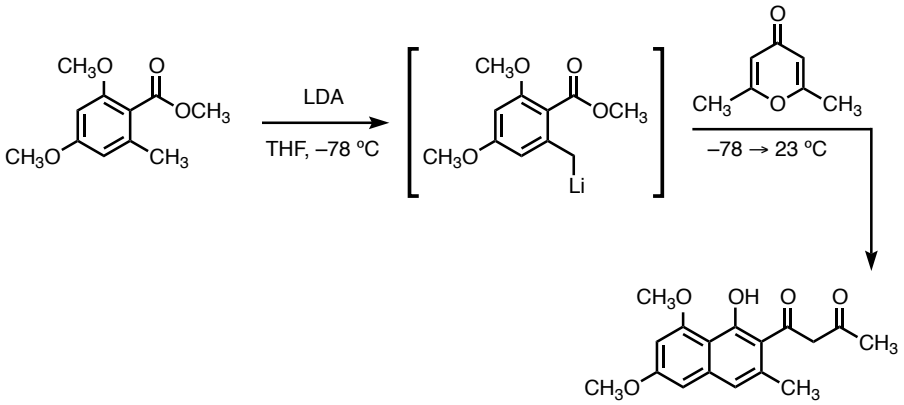
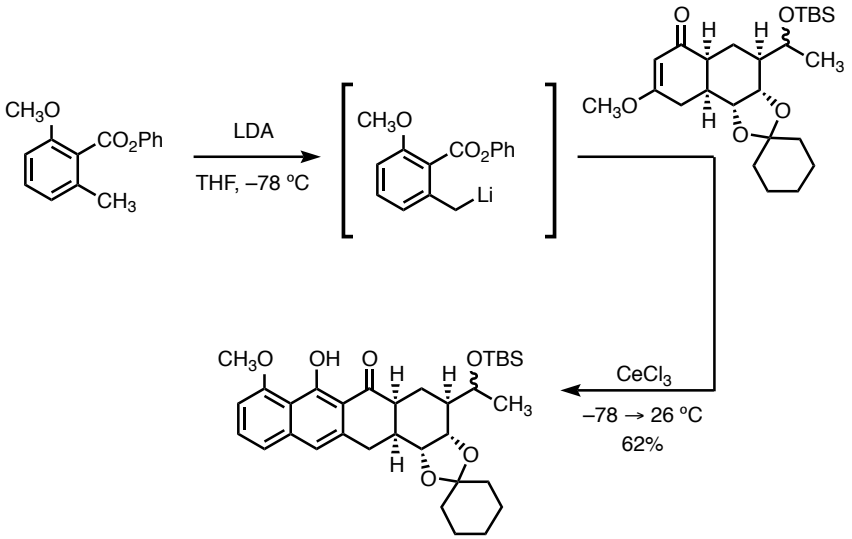
- This annulation reaction can also be done in a single step:



- A phenyl ester was employed in a synthetic approach to (+)-pillaromycinone:

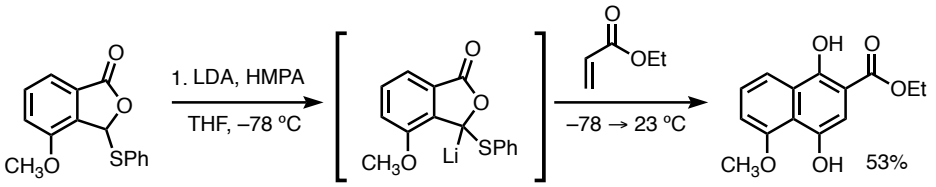


White, J. D.; Nolen, E. G.; Miller, C. H. *J. Org. Chem.* **1986**, *51*, 1152–1155.

- In the Stauton-Weinreb annulation reaction, it is imperative that an alkoxy group is present *ortho* to the ester group to prevent self-coupling of the nucleophile.

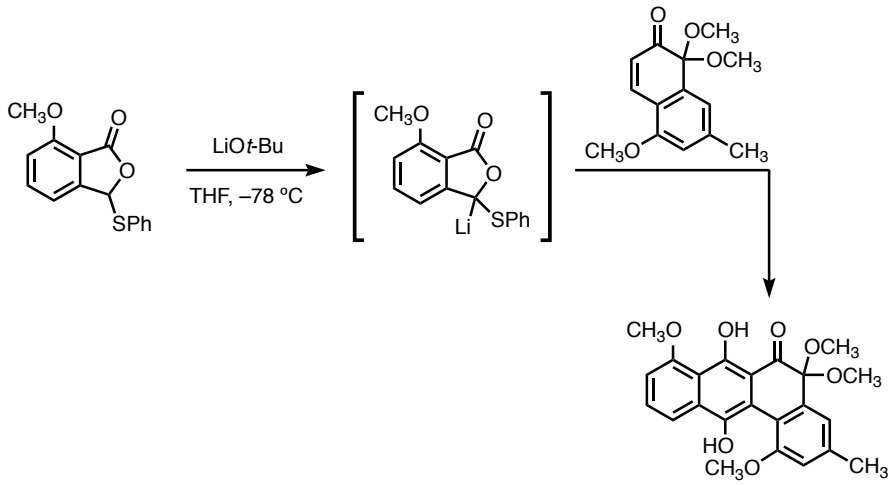
Other Nucleophiles

- Phenylsulfenylphthalide, originally reported by Kraus, was also found to be a competent annulation partner:



Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.* **1983**, *48*, 3439–3944.

- In the following example, use of the traditional Hauser cyclization substrate, 3-phenylsulfonyl isobenzofuranone, did not afford the desired product. Using phenylsulfenyl phthalide, however, provided the desired product in good yield:



Hauser, F. M.; Dorsch, W. A.; Mal, D. *Org. Lett.* **2002**, *4*, 2237–2239.

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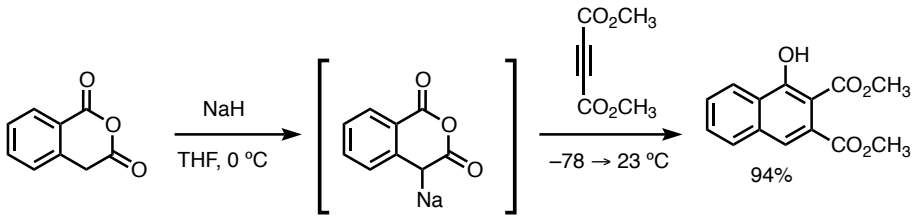
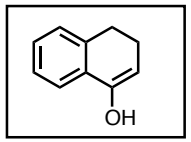
• Homophthalide anhydrides were also found to be good cyclization partners:



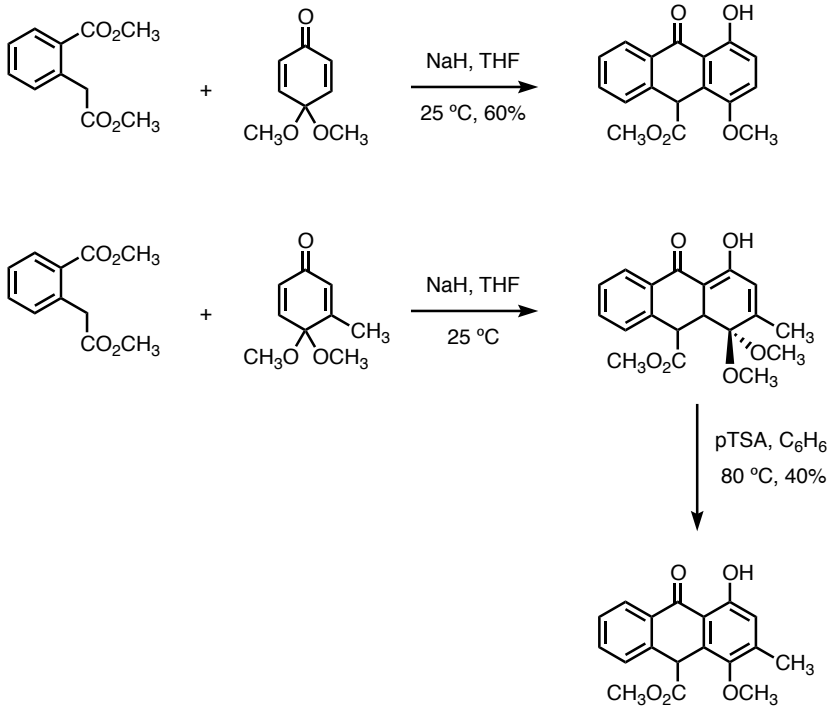
Tamura, Y.; Sasho, M.; Nakagawa, K.; Tsugoshi, T.; Kita, Y. *J. Org. Chem.* **1984**, *49*, 473–478.

• **Synthesis of Cyclohexanone Derivatives (Non-Aromatizing Cyclizations)**



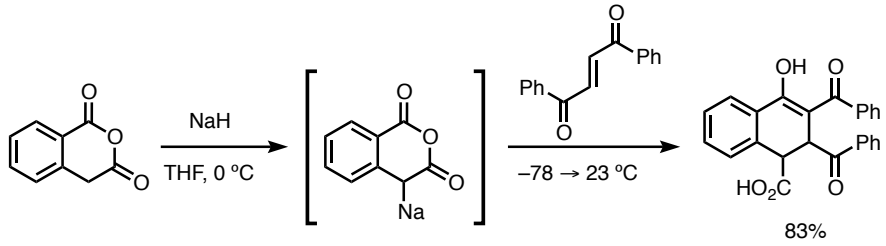
Swenton Annulation

• Swenton showed that Schmid's anionic cyclization nucleophile (shown on page 1) can be applied to quinone monoacetals under modified conditions:



Chenard, B. L.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc. Chem. Commun.* **1980**, 932–933.

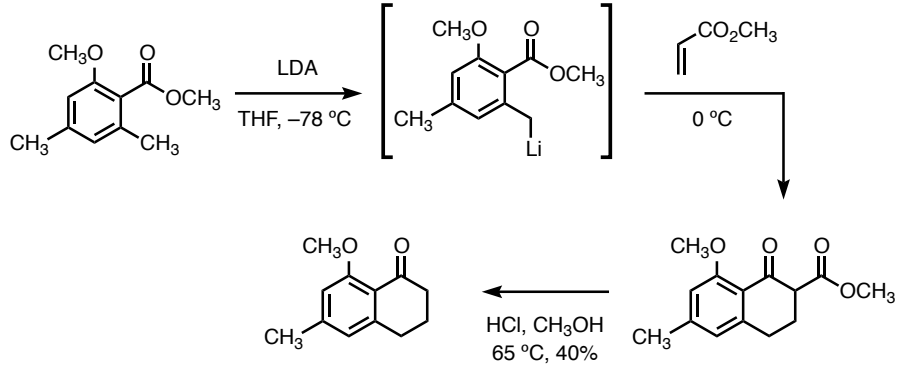
• Alternatively, homophthalide anhydrides can be used:



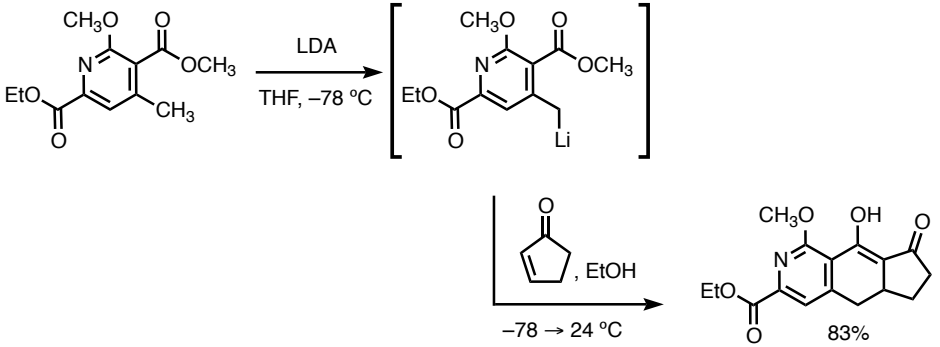
(relative stereochemistry not determined)

Tamura, Y.; Sasho, M.; Nakagawa, K.; Tsugoshi, T.; Kita, Y. *J. Org. Chem.* **1984**, *49*, 473–478.

• Michael-Dieckmann cyclization of *o*-toluate anions with Michael acceptors affords cyclohexanone derivatives:



Tarnchompoo, B.; Thebtaranonth, C.; Thebtaranonth, Y. *Synthesis* **1986**, 785–786.



Boger, D. L.; Zhang, M. *J. Org. Chem.* **1992**, *57*, 3974–3977.
Clive, D. L. J.; Sedgeworth, J. *J. Heterocyclic Chem.* **1987**, *24*, 509–511.

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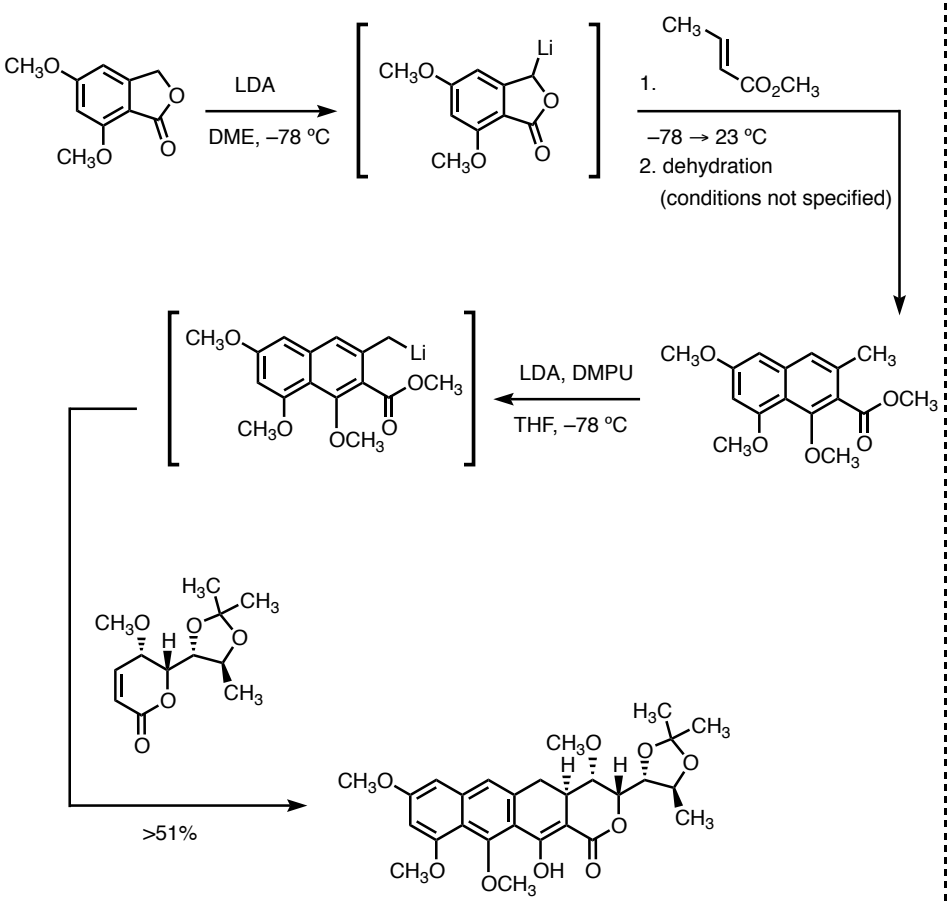
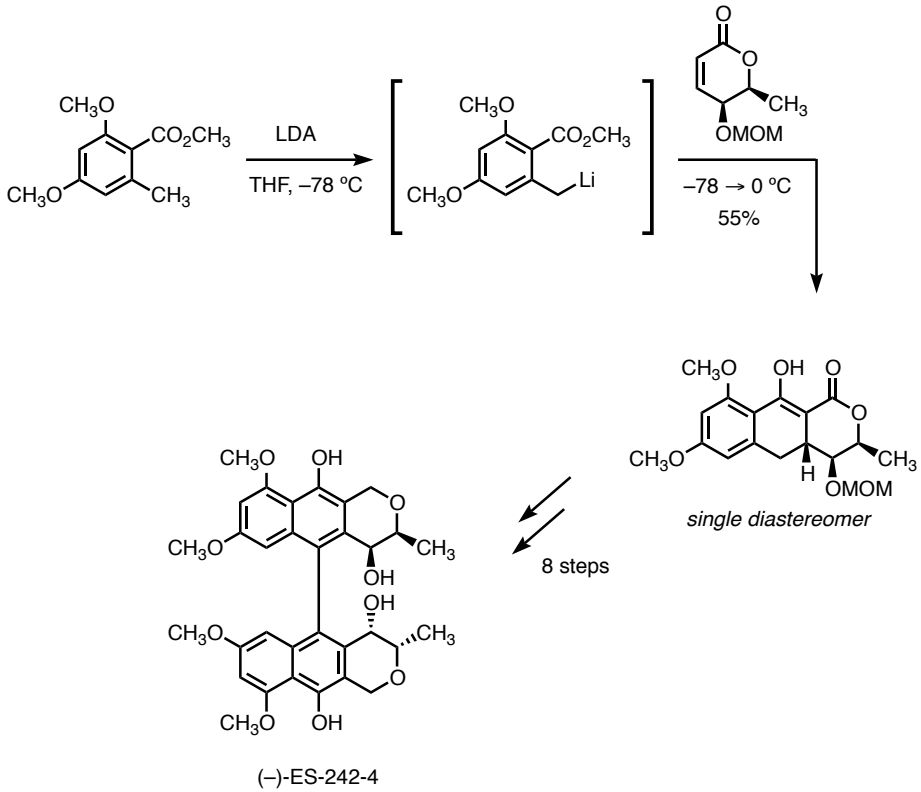
- **Stereoselective Synthesis of Cyclohexanone Derivatives**

- One of the first stereoselective anionic cyclization reactions was reported in 1986 in the synthesis of olivin trimethyl ether:



Franck, R. W.; Bhat, V.; Subramaniam, C. S. *J. Am. Chem. Soc.* **1986**, *108*, 2455–2457.

- Synthesis of bioxanthracene (–)-ES-242-4:



Tatsuta, K.; Yamazaki, T.; Mase, T.; Yoshimoto, T. *Tetrahedron Lett.* **1998**, *39*, 1771–1772.

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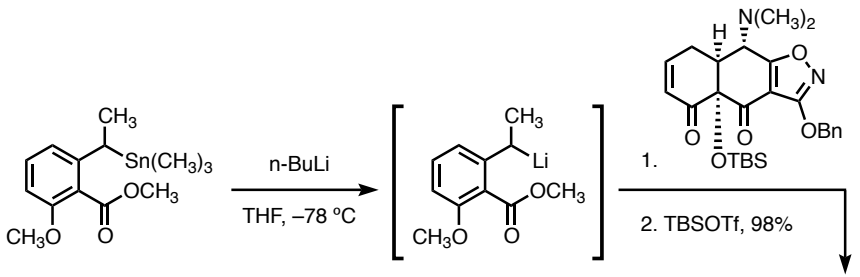
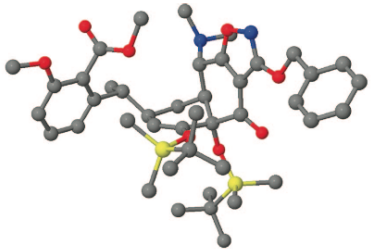
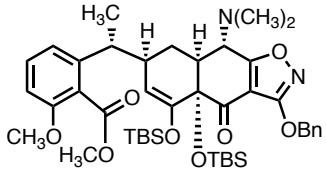
- Stereoselective anionic cyclizations were employed in the synthesis of tetracycline antibiotics. An initial experiment using an organostannane showed that Michael addition occurred with complete stereoselectivity:



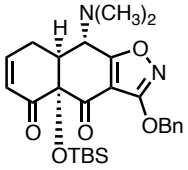


≡



single diastereomer

- The stereochemical outcome in the addition step is consistent with a pseudoaxial addition to the enone, from the π-face opposite the bulky *tert*-butyldimethylsilyloxy substituent:



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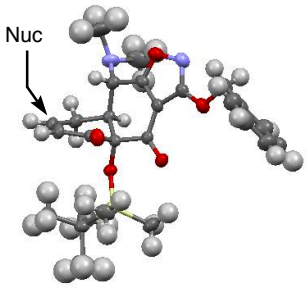
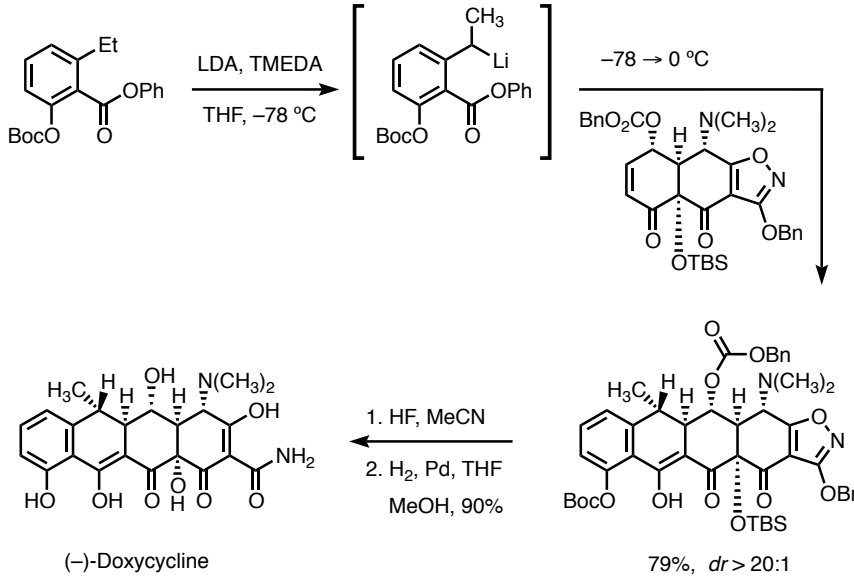
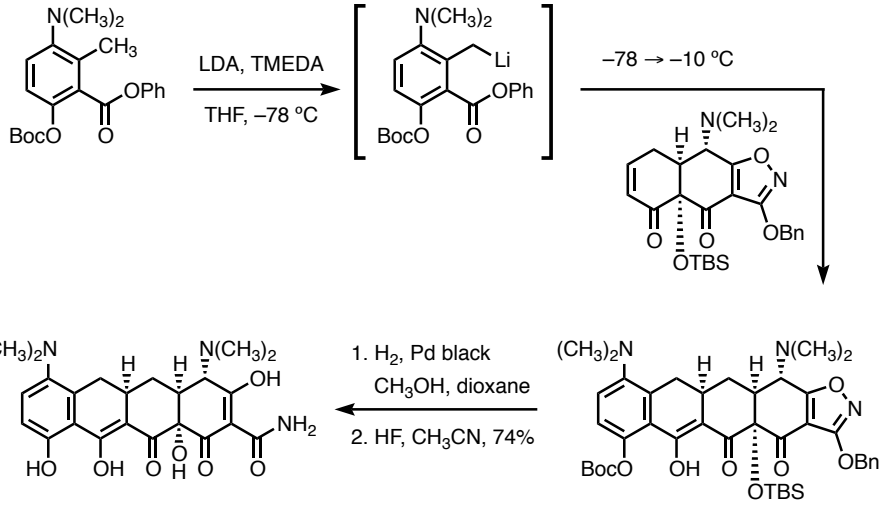


Sun, C.; Wang, Q.; Brubaker, J. D.; Wright, P.; Lerner, C. D.; Noson, K.; Charest, M.; Siegel, D. R.; Wang, Y.-M.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 17913–1717927.
Carpenter, T. A.; Evans, G. E.; Leeper, F. J.; Staunton, J.; Wilkinson, M. R. *J. Chem. Soc. Perkin Trans. 1* **1984**, *1043–1051*.

- By using a phenyl ester and LDA for anion formation, Michael-Claisen cyclization occurred in high yields and with excellent diastereoselectivities:





Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D.; Myers, A. G. *Science* **2005**, *308*, 395–398.
Sun, C.; Wang, Q.; Brubaker, J. D.; Wright, P.; Lerner, C. D.; Noson, K.; Charest, M.; Siegel, D. R.; Wang, Y.-M.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 17913–1717927.

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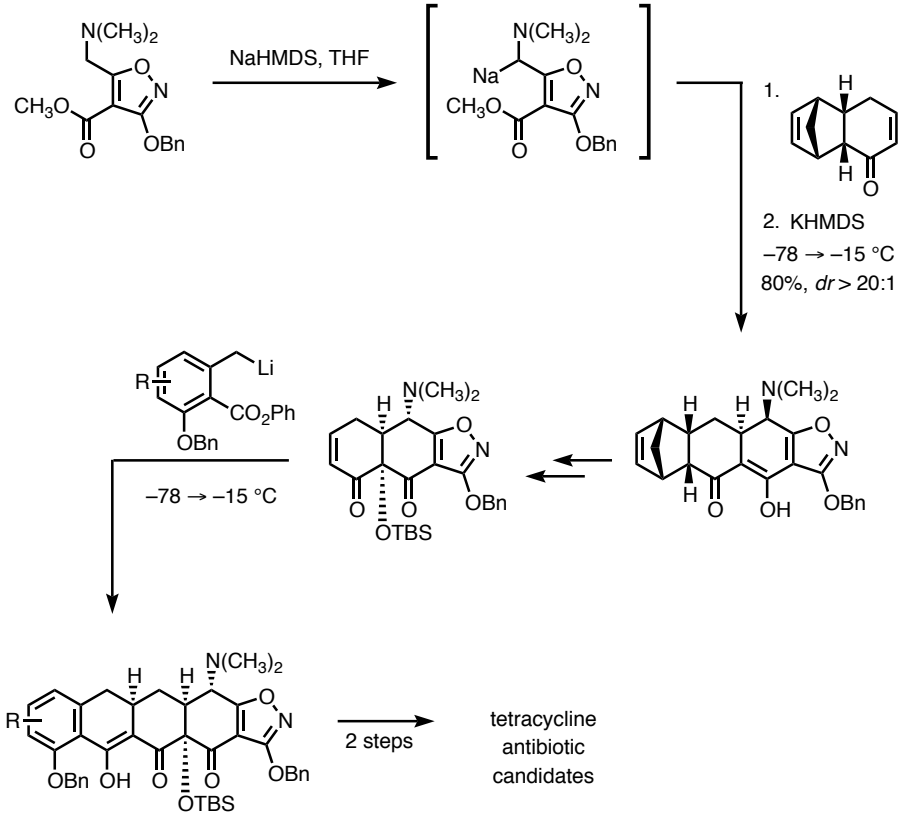
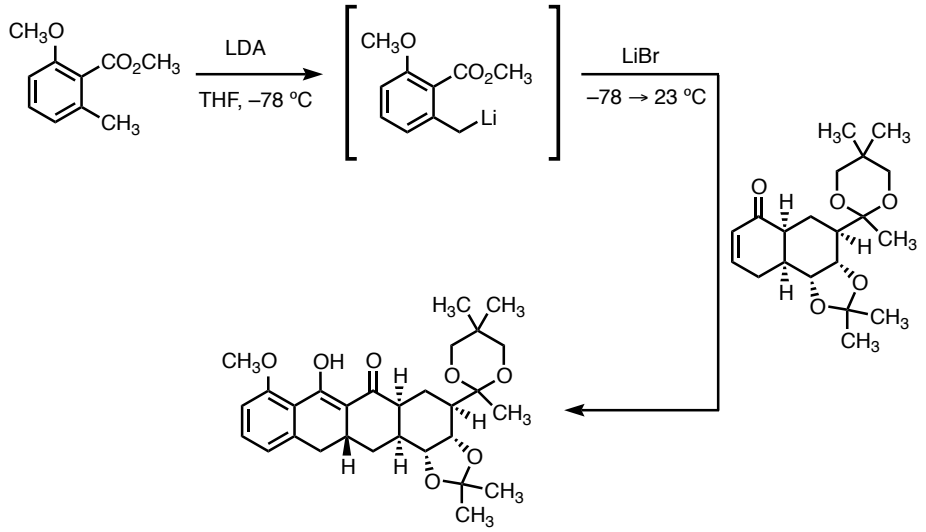
- In the most recently reported route, two consecutive stereoselective anionic cyclization reactions were used to construct tetracycline antibiotics. In the first cyclization, addition of KHMDS to deprotonate the final Claisen product was crucial to prevent quenching of the enolate intermediate by proton transfer from the product or methanol:



- More than 3000 fully synthetic novel tetracycline antibiotic candidates have been prepared using stereoselective anionic cyclization reactions.

Kummer, D. A.; Li, D.; Dion, A.; Myers, A. G. *Chem. Sci.* **2011**, *2*, 1710–1718.
Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D.; Myers, A. G. *Science* **2005**, *308*, 395–398.
Sun, C.; Wang, Q.; Brubaker, J. D.; Wright, P.; Lerner, C. D.; Noson, K.; Charest, M.; Siegel, D. R.; Wang, Y.-M.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 17913–1717927.

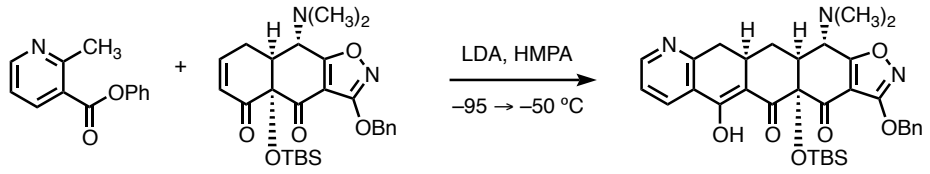


99%, *single diastereomer*

White, J. D.; Demnitz, F. W. J.; Xu, Q.; Martin, W. H. C. *Org. Lett.* **2008**, *10*, 2833–2836.

- In the examples above, an alkoxy substituent must be present *ortho* to the ester functionality to prevent dimerization of the nucleophile.

- This limitation was overcome in tetracycline synthesis by deprotonating the substrate in the presence of the Michael acceptor:



76%, *dr* > 20:1

Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D.; Myers, A. G. *Science* **2005**, *308*, 395–398.

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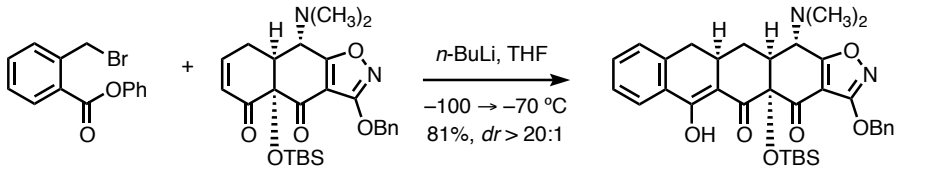
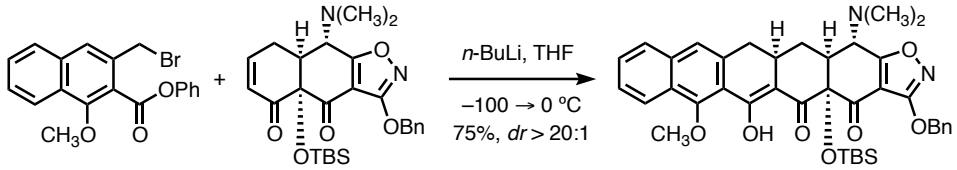
- Another strategy permitting cyclization of aromatic ester substrates lacking ortho substituents involved *in situ* anion formation by lithium-halogen exchange, in the presence of the Michael acceptor:

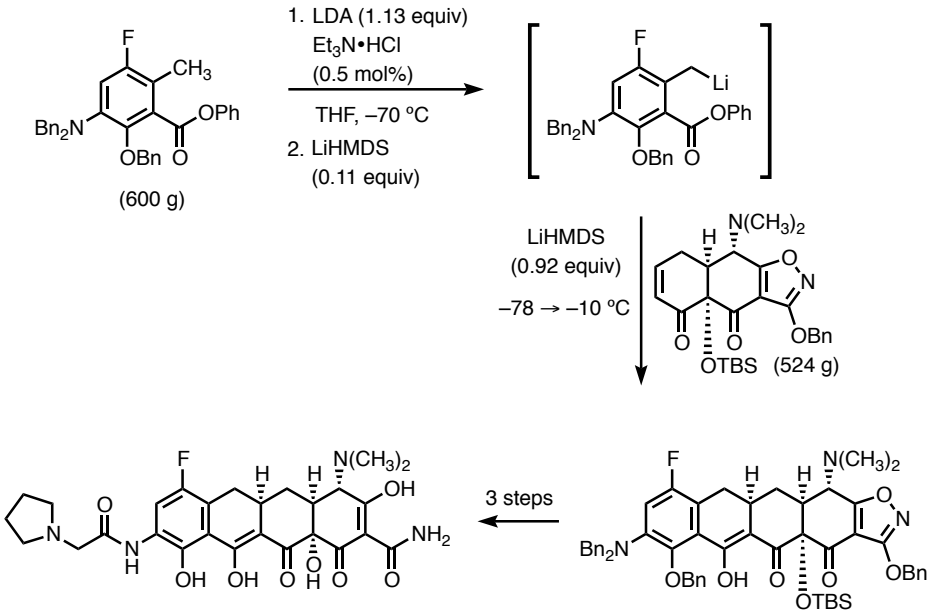




- In the example above, attempted cyclization by direct deprotonation of the corresponding *o*-methylnaphthalene was not successful.

Charest, M. G.; Lerner, C. D.; Brubaker, J. D.; Siegel, D.; Myers, A. G. *Science* **2005**, *308*, 395–398.
Sun, C.; Wang, Q.; Brubaker, J. D.; Wright, P.; Lerner, C. D.; Noson, K.; Charest, M.; Siegel, D. R.; Wang, Y.-M.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 17913–1717927.

- A stereoselective anionic cyclization reaction is used in the industrial synthesis of a novel tetracycline antibiotic candidate:



- The use of a small amount of Et_3N•HCl in the deprotonation step, which provides a source of LiCl, was found to be crucial in providing consistent and clean cyclization results on a manufacturing scale.

- Because the presence of excess LDA appeared to promote the formation of byproducts, a weaker base, LiHMDS, was used as a substitute to deprotonate the acidic proton in the final product and drive the Claisen reaction to completion.

Ronn, M.; Zhu, Z.; Hogan, P. C.; Zhang, W.-Y.; Niu, J.; Katz, C. E.; Dunwoody, N.; Gilicky, O.; Deng, Y.; Hunt, D. K.; He, M.; Chen, C.-L.; Sun, C.; Clark, R. B.; Xiao, X.-Y. *Org. Process Res. Dev.* **2013**, *17*, 838–845.

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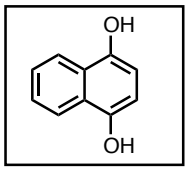
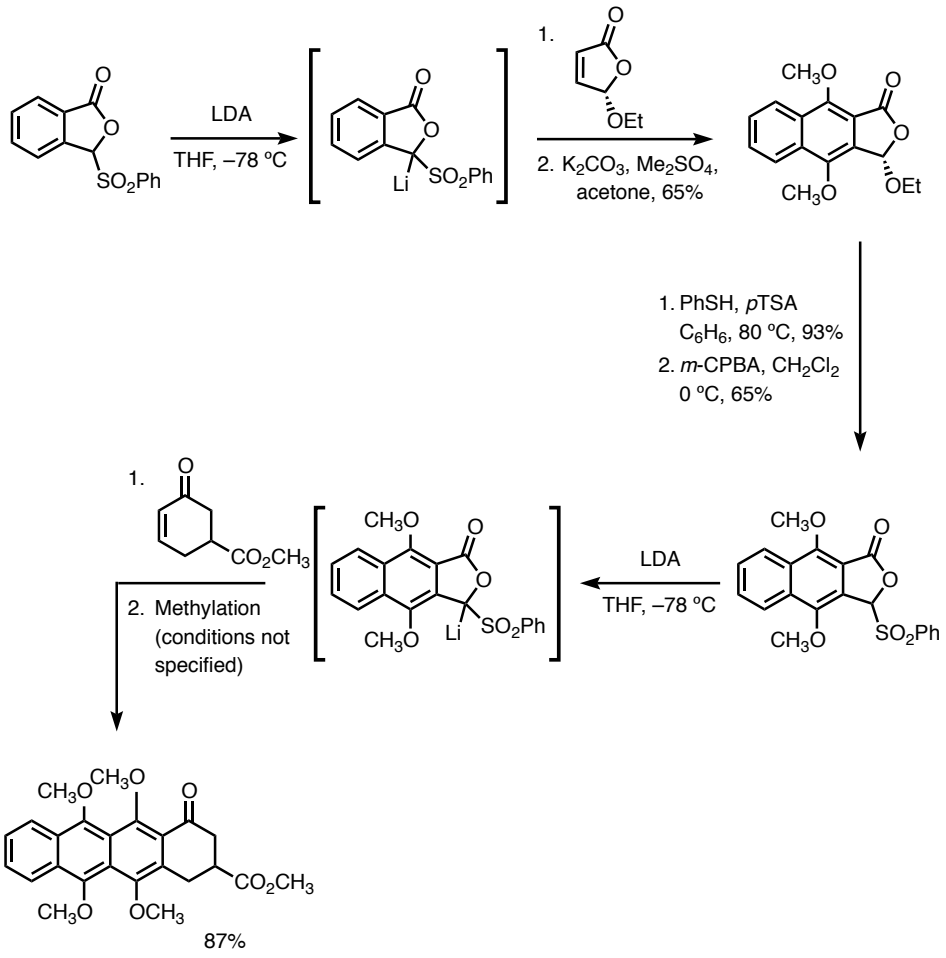
Examples in Synthesis

- **Synthesis of 1,4-Dihydroxynaphthalene Derivatives**

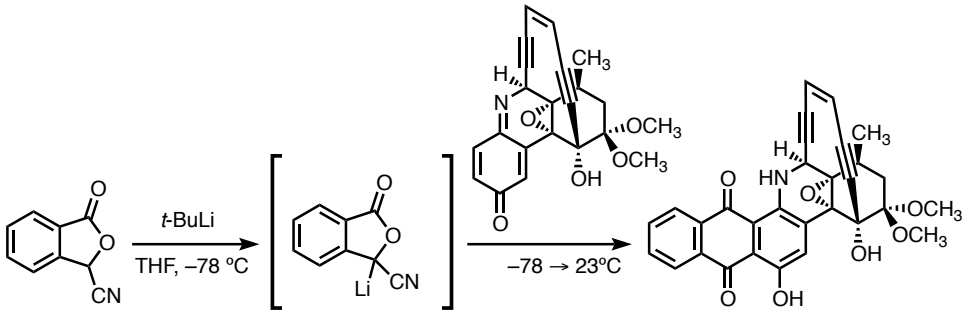


- Two consecutive anionic annulation reactions were employed for the synthesis of the core structure of anthracyclines:

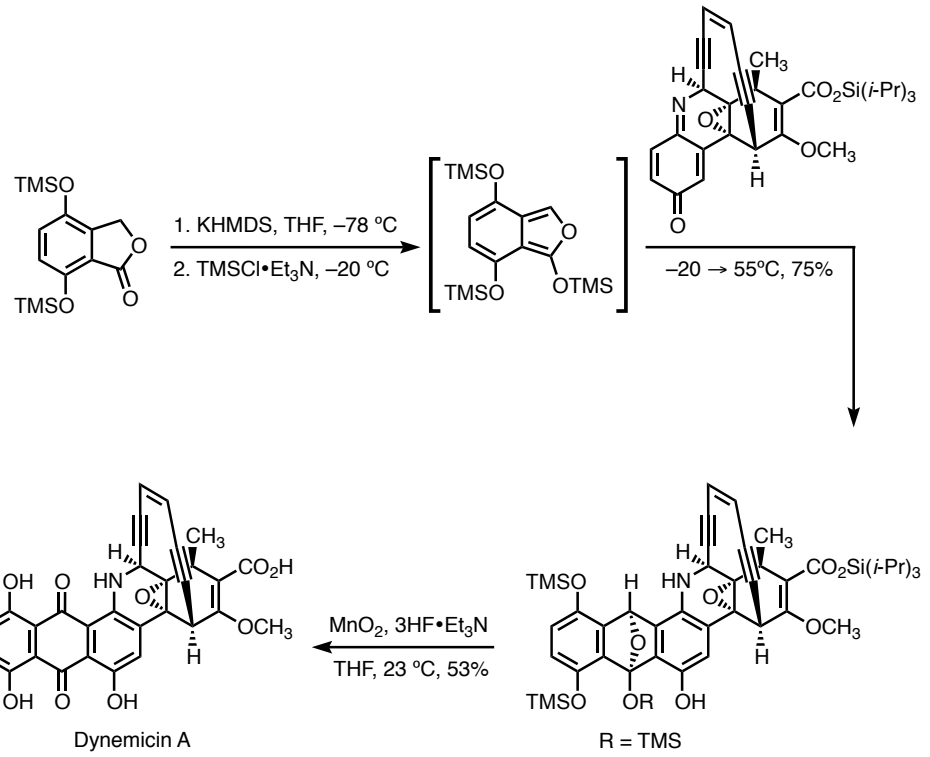


Hauser, F. M.; Prasanna, S. *J. Org. Chem.* **1979**, *44*, 2596–2598.

- Synthesis of a dideoxydynemicin analog:



- Kraus annulation proved to be ineffective for the synthesis of dynemicin A itself. Instead, a Diels-Alder cycloaddition was employed:



Myers, A. G.; Fraley, M. E.; Tom, N. J. *J. Am. Chem. Soc.* **1994**, *116*, 11556–11557.
Myers, A. G.; Fraley, M. E.; Tom, N. J.; Cohen, S. B.; Madar, D. J. *Chem. Biol.* **1995**, *2*, 33–43.
Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072–6094.

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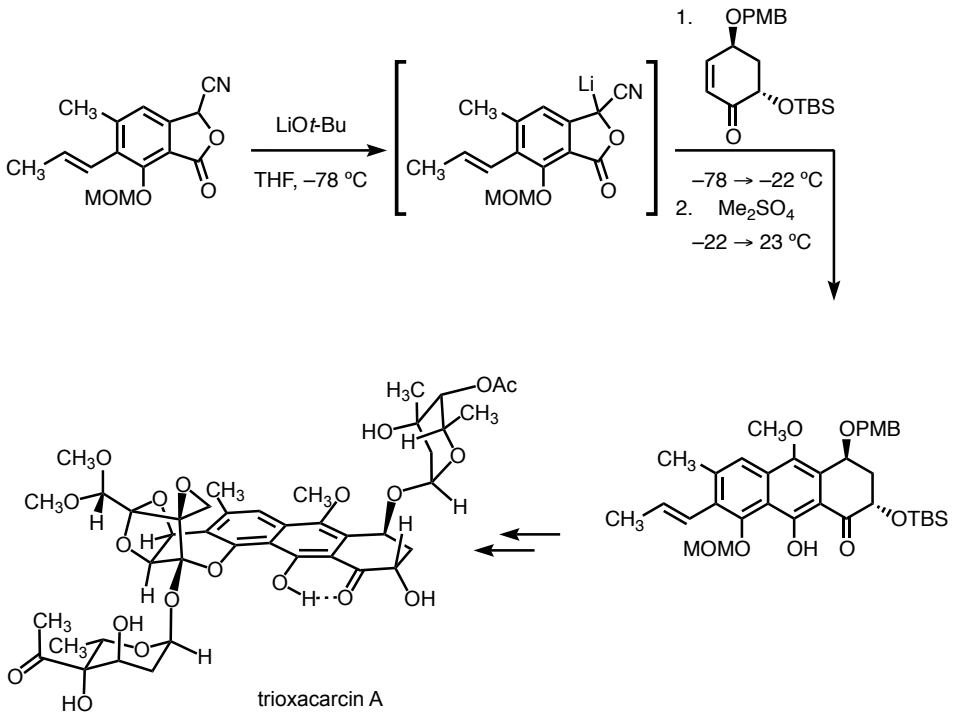
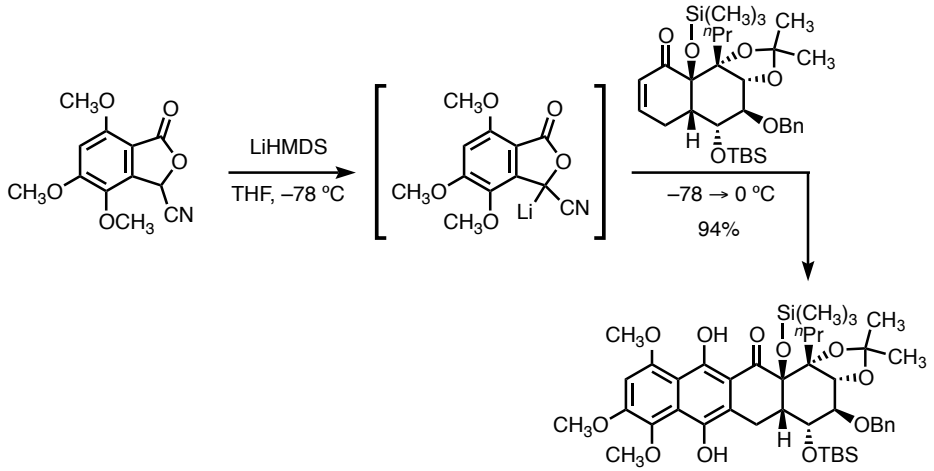
• Synthesis of Trioxacarcin A:

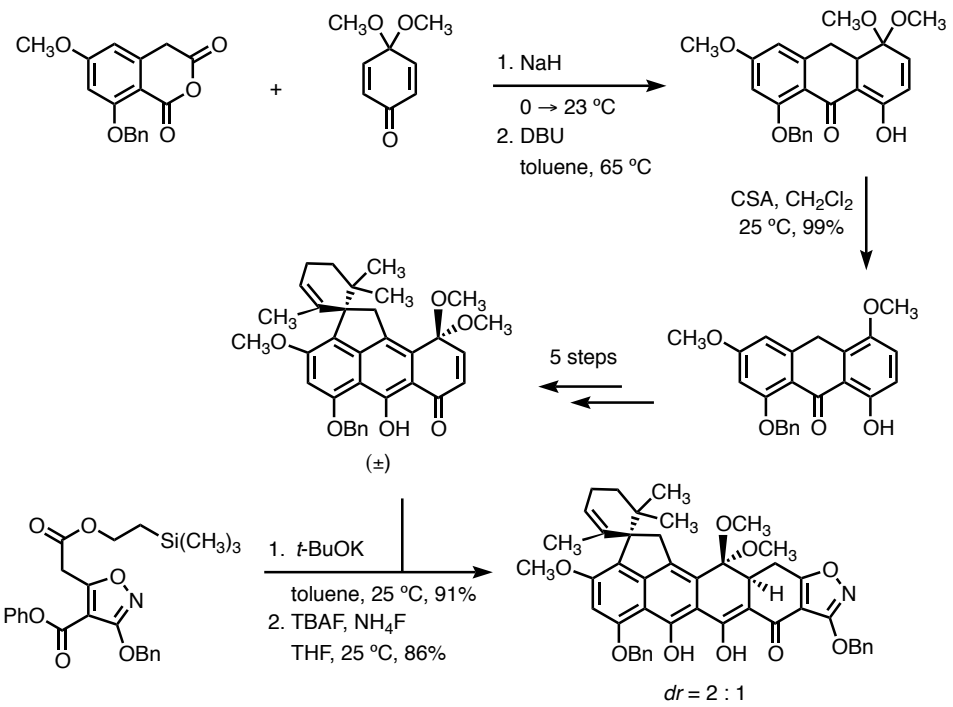


Svenda, J.; Hill, N.; Myers, A. G. *Proc. Natl. Acad. Sci.* **2011**, *108*, 6709–6714.
Magauer, T.; Smaltz, D. J.; Myers, A. G. *Nat. Chem.* **2013**, *5*, 886–893.



Liau, B. B.; Milgram, B. C.; Shair, M. D. *J. Am. Chem. Soc.* **2012**, *134*, 16765–16772.

• Synthesis of viridicatumtoxin B:



Nicolaou, K. C.; Nielewski, C.; Hale, C. R. H.; Ioannidou, H. A.; ElMarrouni, A.; Koch, L. G. *Angew. Chem. Int. Ed.* **2013**, *52*, 8736–8741.

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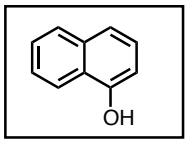
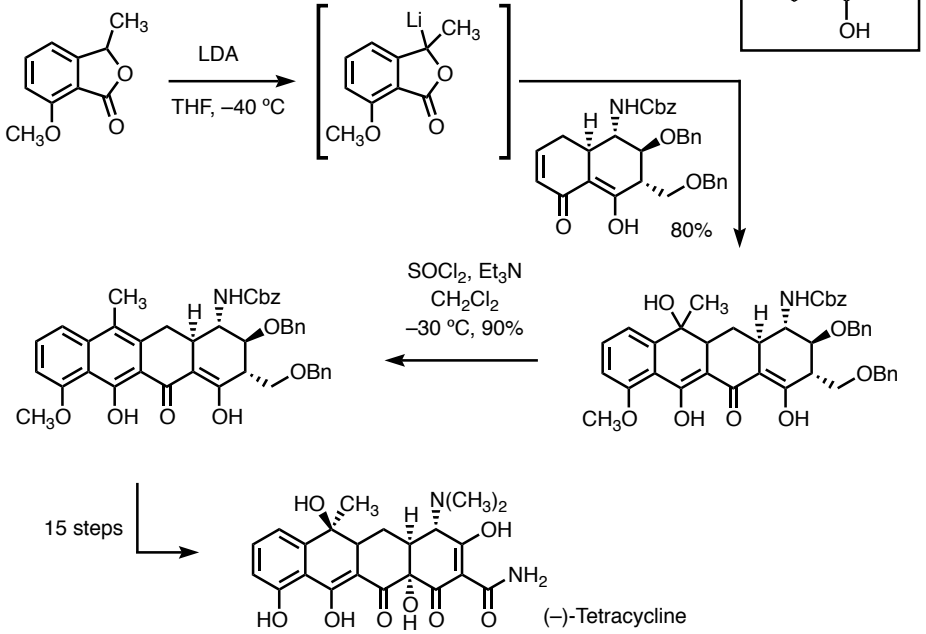
- **Synthesis of 1-Hydroxynaphthalene Derivatives**

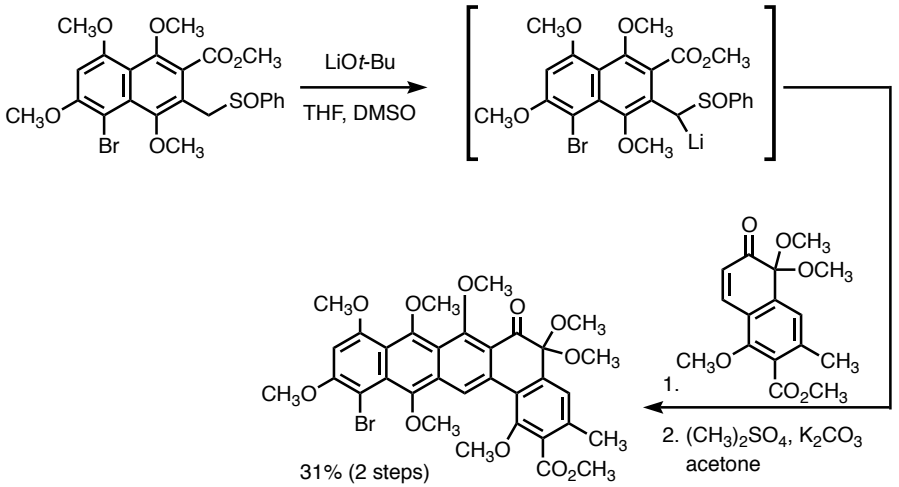


- Synthesis of tetracycline:



Tatsuta, K.; Yoshimoto, T.; Gunji, H.; Okado, Y.; Takahashi, M. *Chem. Lett.* **2000**, 646–647.

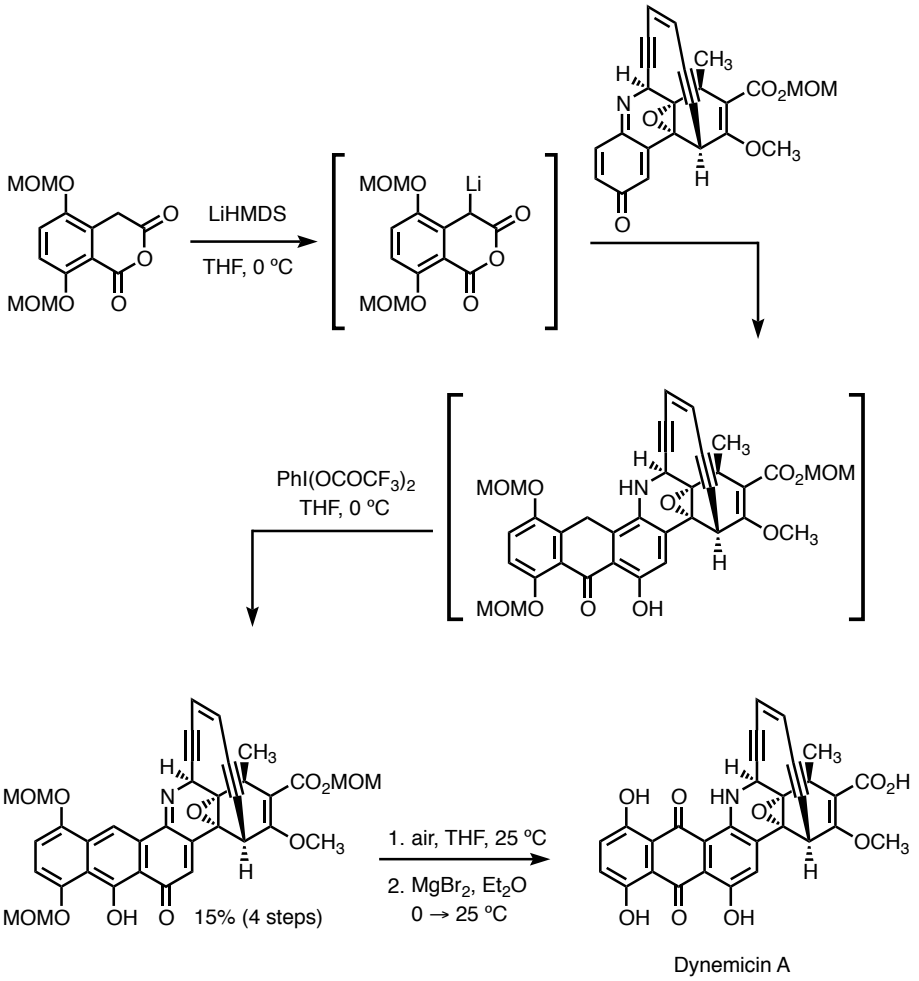
- Synthesis of a benanomicinone analogue:



Hauser, F. M.; Liao, H.; Sun, Y. *Org. Lett.* **2002**, *4*, 2241–2243.

- In Danishefsky's synthesis of dynemicin, a homophthalide anhydride substrate was found to be a superior cyclization partner, whereas the Kraus annulation failed to provide the desired product.

- In this synthesis, a series of oxidation reactions provided the anthraquinone of dynemicin A:



Shair, M. D.; Yoon, T.-Y.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1995**, *34*, 1721–1723.
Shair, M. D.; Yoon, T.-Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509–9525.

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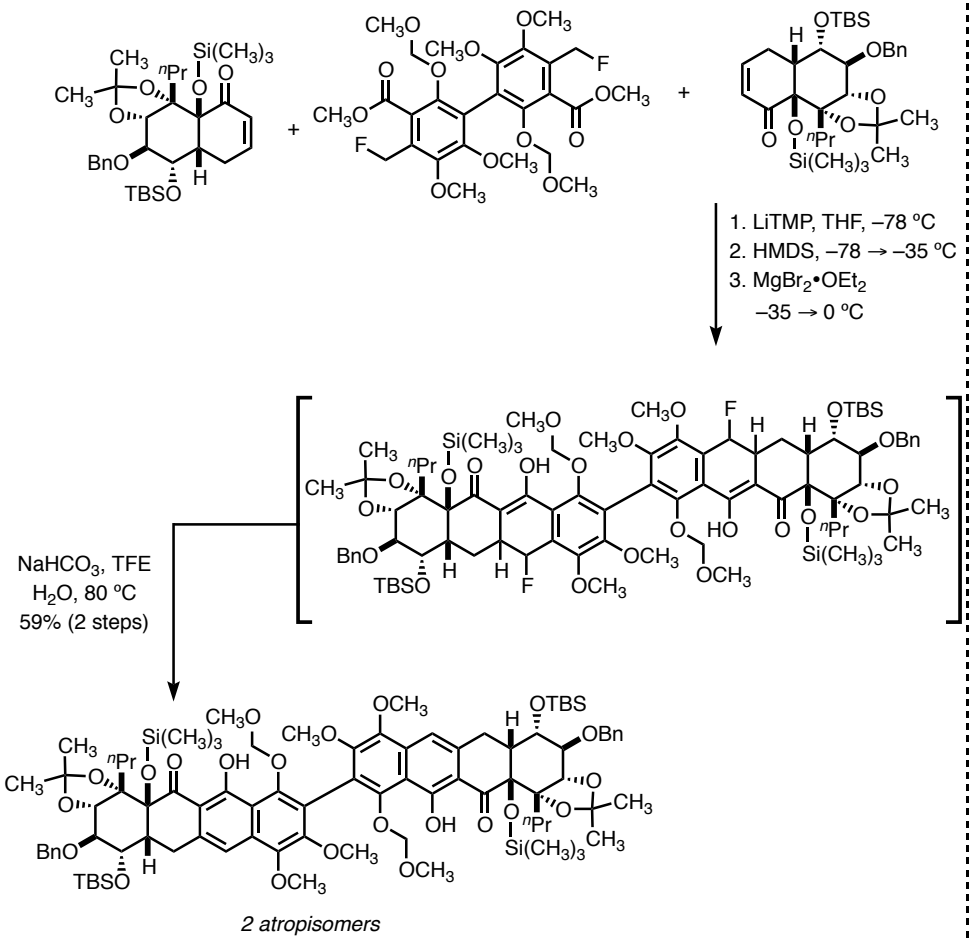
- The Shair group found that a particularly difficult annulation reaction was best carried out using a benzyl fluoride as the nucleophile:

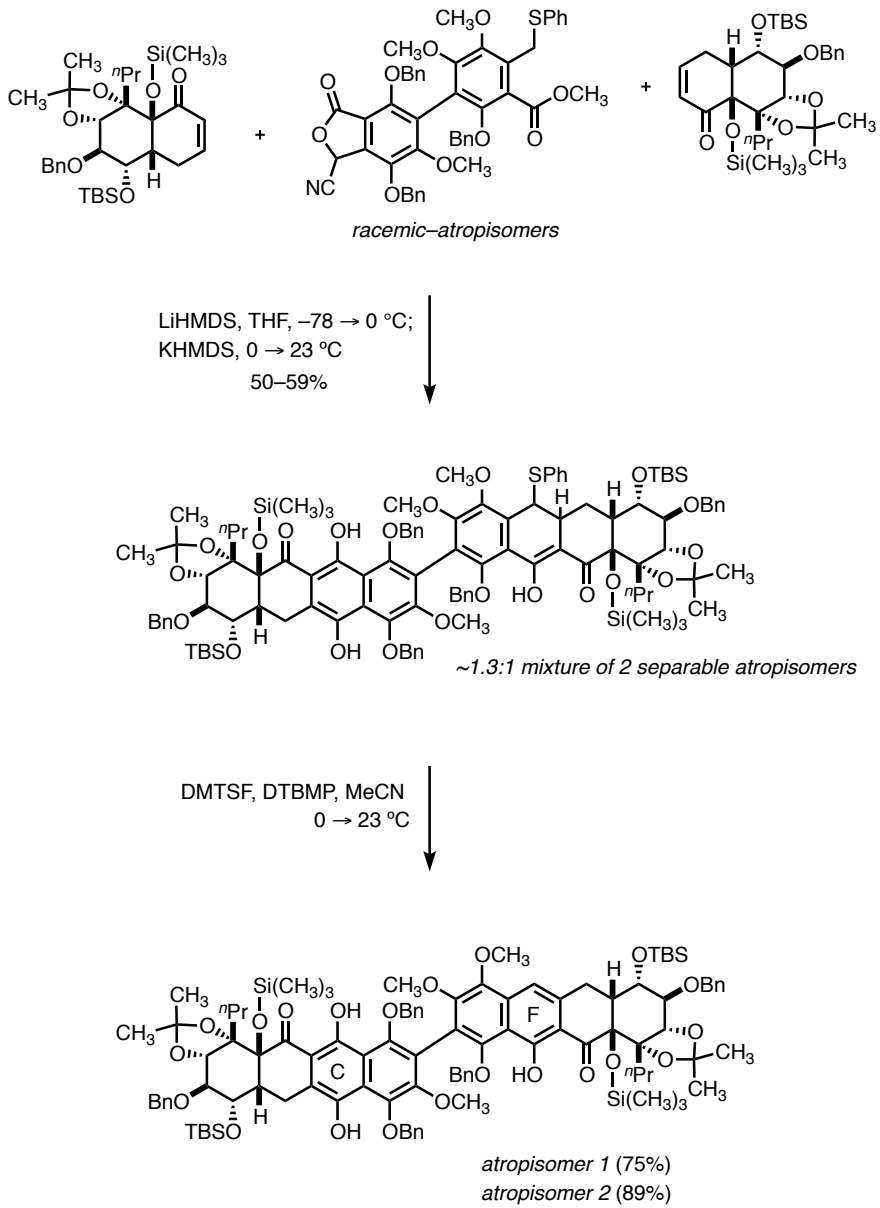


2 atropisomers

- The electronegative fluorine atom stabilizes the anion and is sterically unencumbered.
- In the absence of the fluorine atom, Michael addition occurred at –78 °C but the subsequent Claisen cyclization could never be driven to completion. The alternative Hauser and van Leusen substrates did not afford the desired product.
- Addition of HMDS prior to warming quenches excess LiTMP, which prevents substrate decomposition in the subsequent Claisen condensation step.

Liau, B. B.; Milgram, B. C.; Shair, M. D. *J. Am. Chem. Soc.* **2012**, *134*, 16765–16772.

- A bidirectional approach to hibarimicinone: note the use of two different nucleophiles to form the C and F rings:



racemic–atropisomers

~1.3:1 mixture of 2 separable atropisomers

atropisomer 1 (75%)
atropisomer 2 (89%)

Liau, B. B.; Milgram, B. C.; Shair, M. D. *J. Am. Chem. Soc.* **2012**, *134*, 16765–16772.

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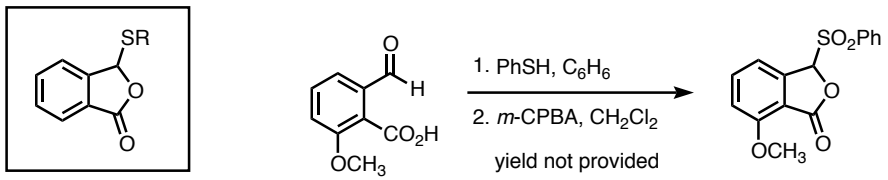
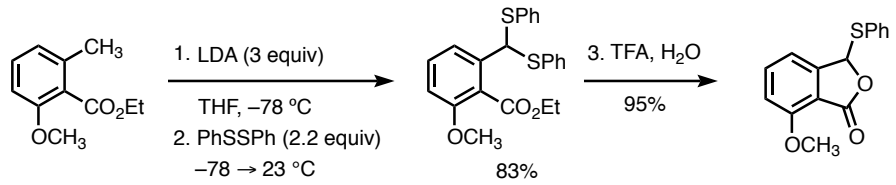
Synthesis of Annulation Substrates

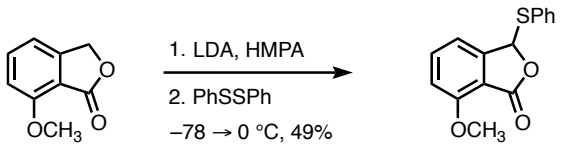
- Hauser Annulation Substrates



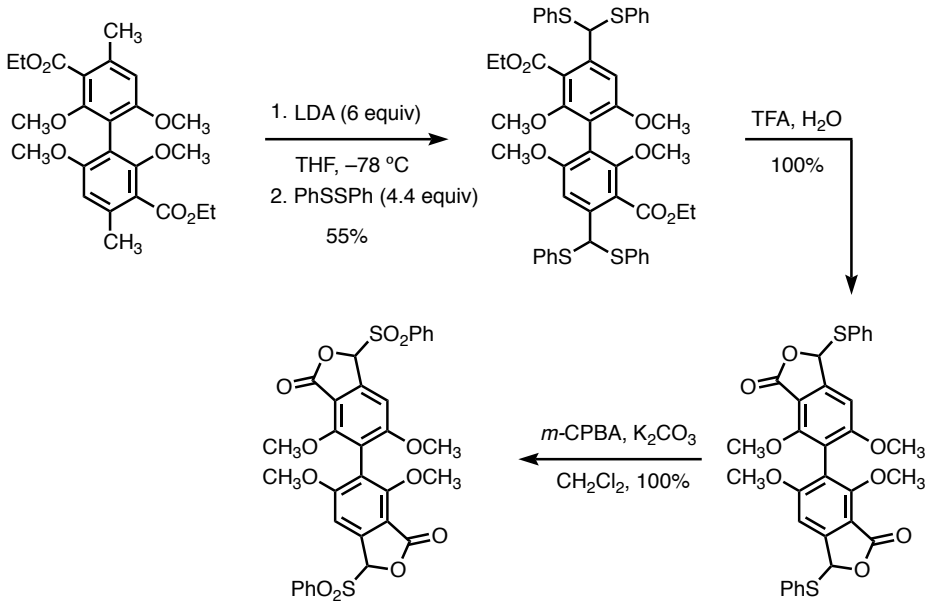
Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178–180



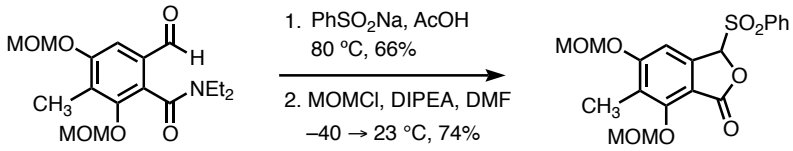
Hauser, F. M.; Rhee, R. P.; Prasanna, S. *Synthesis* **1980**, 72–74.



Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.* **1983**, *48*, 3439–3444.

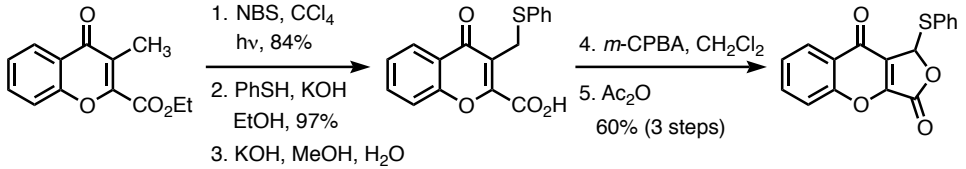


Hauser, F. M.; Gauuan, P. J. F. *Org. Lett.* **1999**, *1*, 671–672.



Tatsuka, K.; Inukai, T.; Itoh, S.; Kawarasaki, M.; Nakano, Y. *J. Antibiot.* **2002**, *55*, 1076–1080.

- In the following example, the sulfoxide intermediate underwent Pummerer rearrangement and the resulting sulfonium ion was trapped by the carboxylic acid:



Hauser, F. M.; Dorsch, W. A. *Org. Lett.* **2003**, *5*, 3753–3754.

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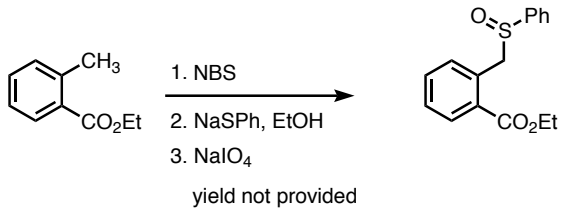
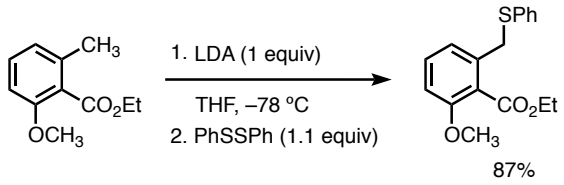
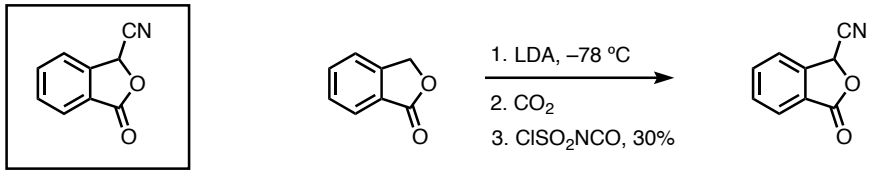


Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178–180

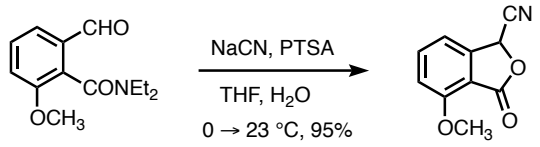


Hauser, F. M.; Rhee, R. P.; Prasanna, S. *Synthesis* **1980**, 72–74.

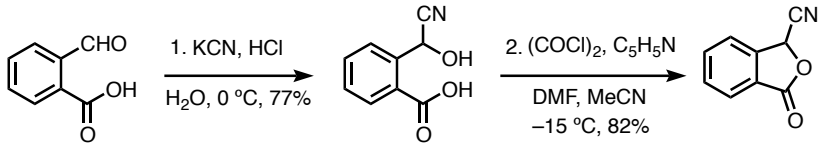
• Kraus Annulation Substrates



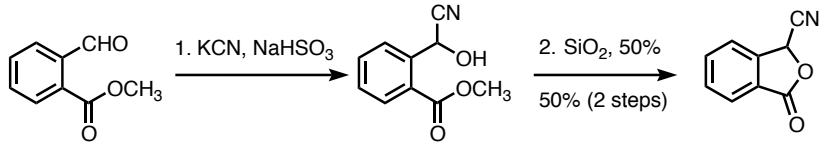
Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, *26*, 2263–2266.

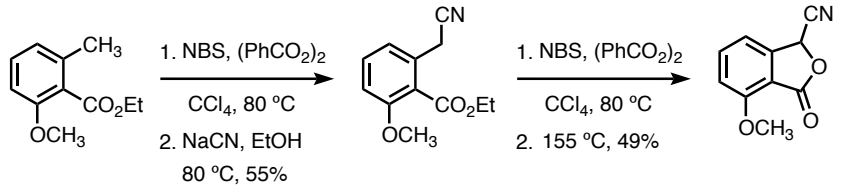


Li, T.-T.; Wu, Y. L. *J. Am. Chem. Soc.* **1981**, *103*, 7007–7009.

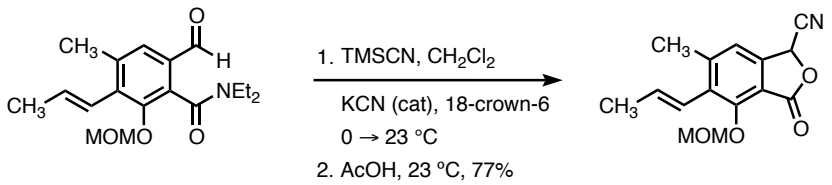


Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805–810.
Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, *26*, 2263–2266.





Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.* **1983**, *48*, 3439–3444.



Svenda, J.; Hill, N. ; Myers, A. G. *Proc. Natl. Acad. Sci.* **2011**, *108*, 6709–6714.
Magauer, T.; Smaltz, D. J.; Myers, A. G. *Nat. Chem.* **2013**, *5*, 886–893.

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