Applications of Deuterium-Labelled Compounds in Total Synthesis and Drug Development

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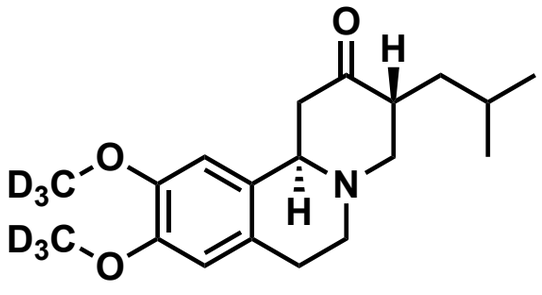
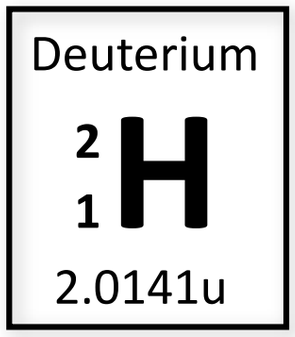
10/18/2018

From First Approved Deuterated Drug Back to Deuterium



deutetrabenazine (Austedo)

- First deuterated drug from Teva Pharmaceuticals
- Approved by FDA in 2017
- The treatment of chorea associated with Huntington's disease
- Beneficial deuterium effect: reduce rate of active metabolite demethylation driven by CYP2D6
- Higher efficacy at a lower doses and with a longer duration of action



- One of two stable isotopes of hydrogen
- Natural abundance: 0.0115% (earth)
- First discovered specterscopically and named by Harold Urey in 1931
- Deuterium won Urey the Nobel Prize in Chemistry in 1934.
- Famous by heavy water and "hydrogen bomb"

Application of Deuterated Compounds

Total synthesis: modify reaction selectivity

Drug development: enhance metabolic stability

Mass spectrometry internal standards

Clarification of organic reaction mechanisms

Elucidation of biosynthetic routes

Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid M. *Angew. Chem. Int. Ed.* ***2018***, *57*, 1758-1784.

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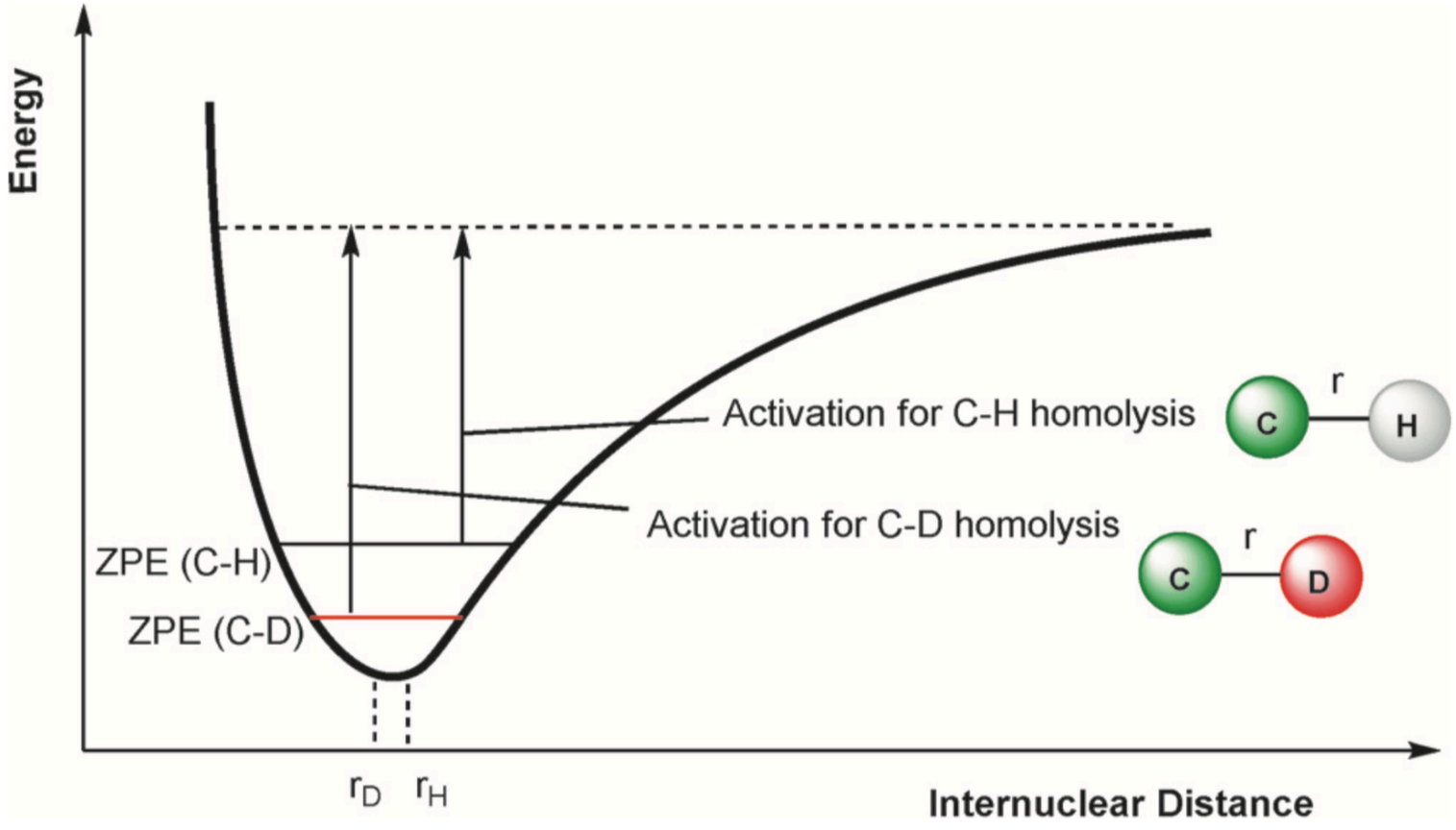
The Kinetic Isotope Effect

- Kinetic isotope effect (KIE) is observed in between the isoptopically labelled molecules showing different reaction rates.
- Primary KIE is attributed to a bond breaking event at the C-H/C-D bond.
- Vibrational frequency is relative to reduced mass μ.
- For C-D, lower vibrational frequency and lower zero-point energy (ZPE)



$$E_n = (n + 1)h\nu$$

$$\nu = \frac{1}{2\pi c}\sqrt{\frac{k}{\mu}}$$

$$\mu = \frac{m1 \bullet m2}{m1 + m2}$$

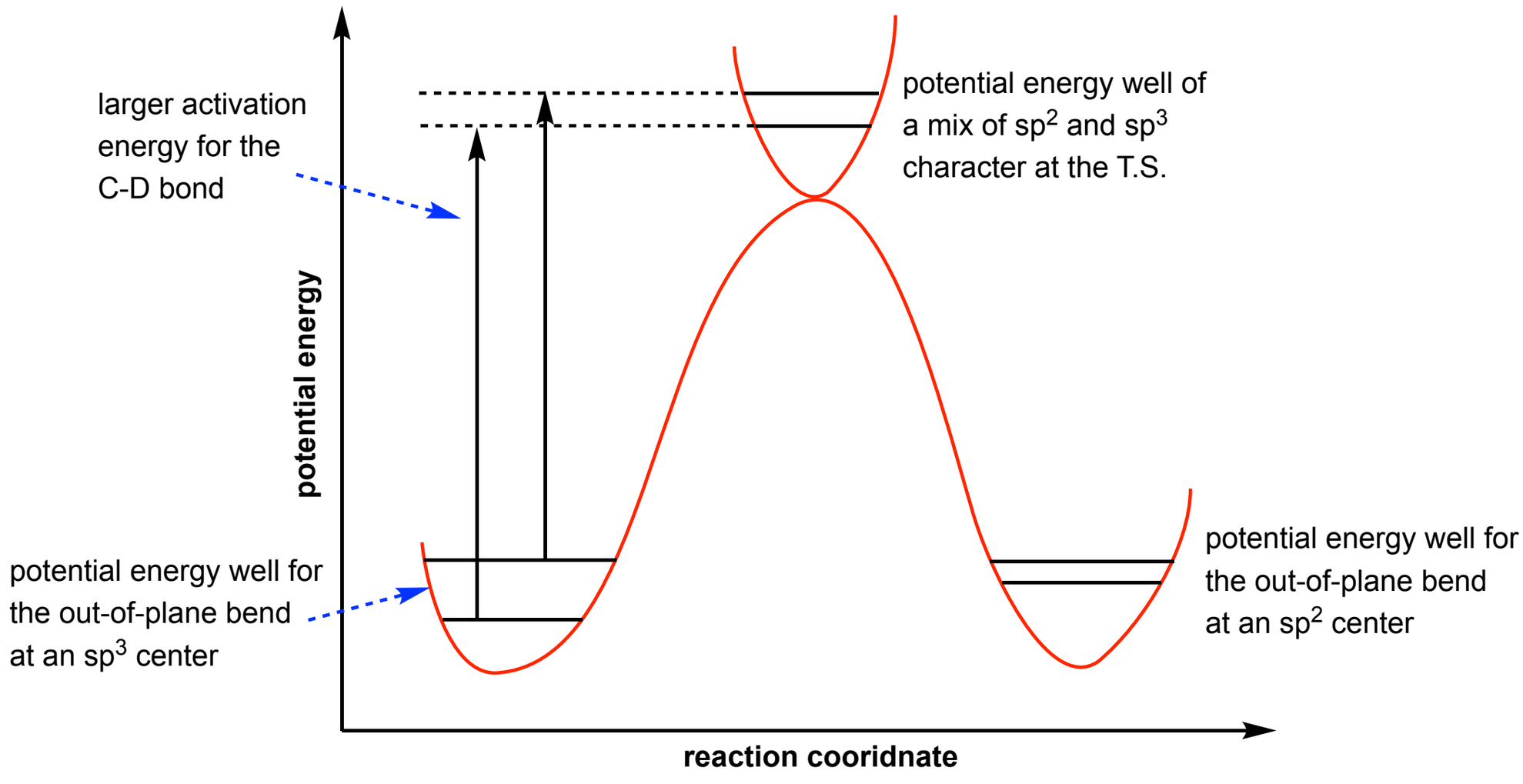
$\mu_{C\text{-}H} = 0.92$

$\mu_{C\text{-}D} = 1.71$

Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid M. *Angew. Chem. Int. Ed.* ***2018***, *57*, 1758-1784.

The Kinetic Isotope Effect

- Secondary KIE is the effect attributed to a rehybridization or arises from isotopic substitution remote from the bonds undergoing reaction.
- The large difference in force constant for the out-of-plane bend of an sp^3 hybrid versus and sp^2 hybrid means that there will be a significant difference in ZPE differences between C-H and C-D bonds.
- Similarly, a large difference in the frequency of the in-plane bend exists between sp^2 and sp hybrids



- $k_H/k_D > 1$
- usually at 1.1~1.2
- normal KIE

Anslyn, E. V.; Doughery, D. A. *Modrn Physical Organic Chemistry*; University Science Books, 2006

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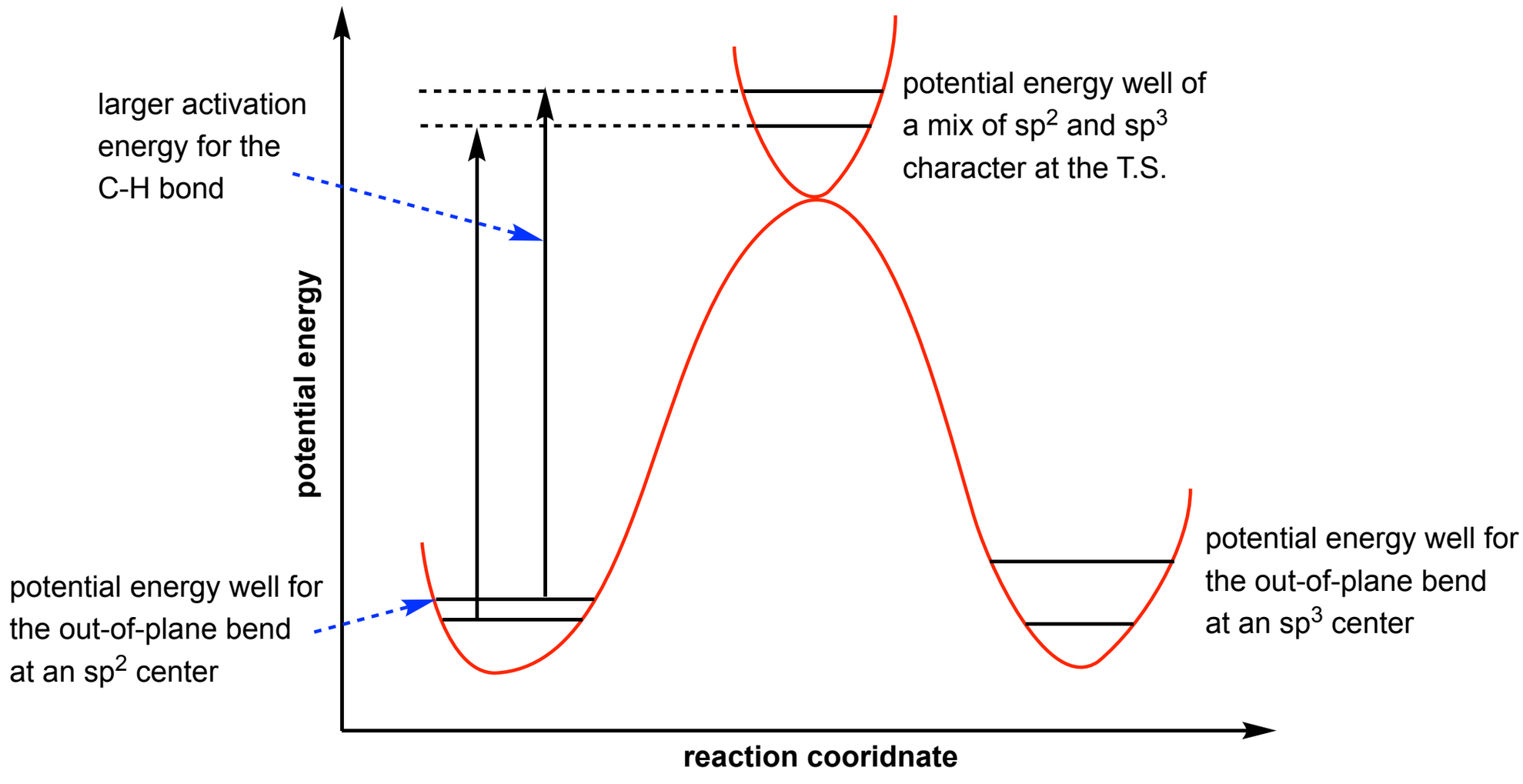

- $k_H/k_D < 1$
- usually at 0.8~0.9
- inverse KIE

Anslyn, E. V.; Doughery, D. A. *Modrn Physical Organic Chemistry*; University Science Books, 2006

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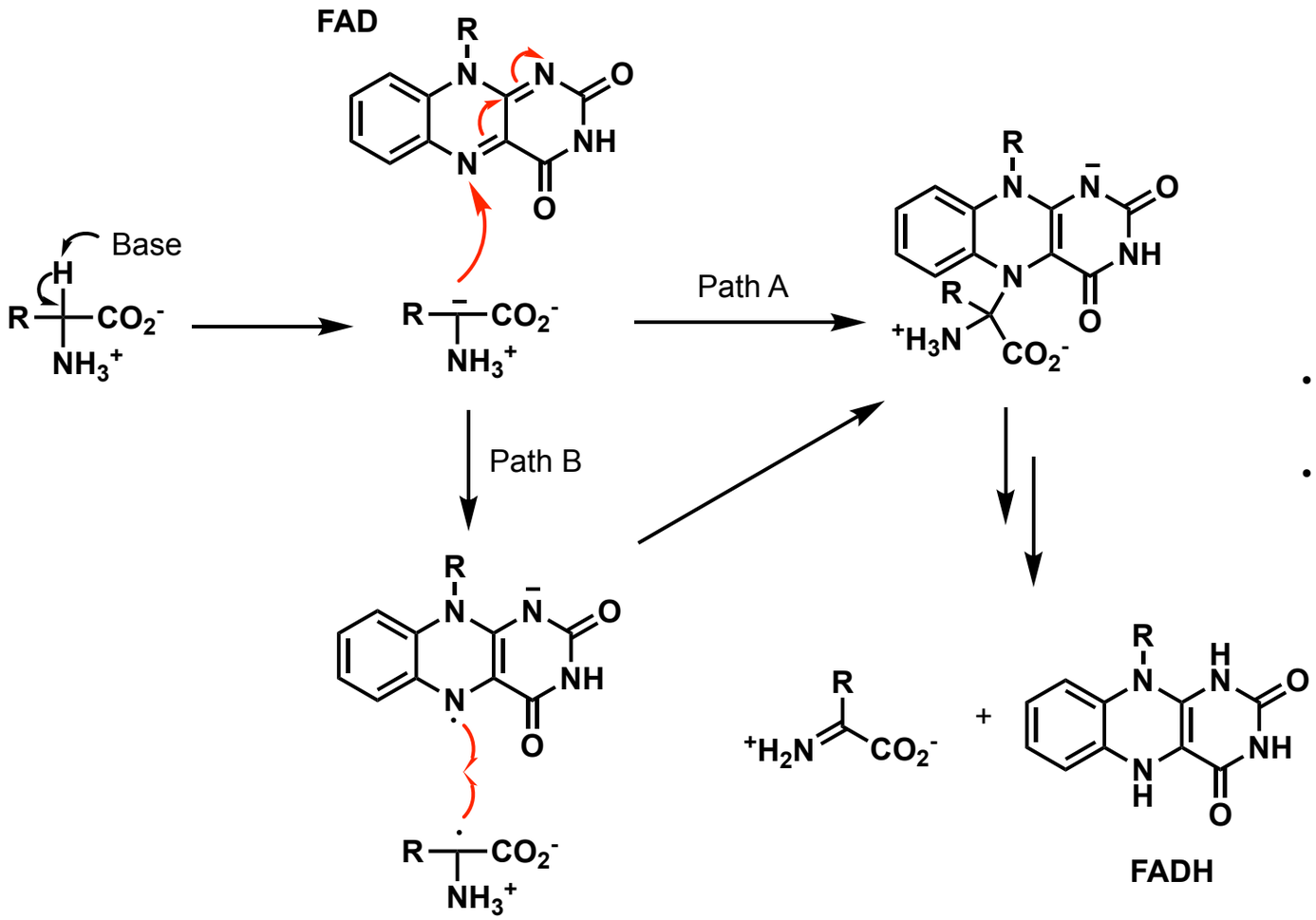

- Path A: nucleophilic addition to the flavin
- Path B: single electron transfer to the flavin followed by the coupling between two radicals.

Kurtz, K. A.; Fitzpatrick, P. F. *J. Am. Chem. Soc.* **1997**, 119, 1155.
Anslyn, E. V.; Doughery, D. A. *Modrn Physical Organic Chemistry*; University Science Books, 2006

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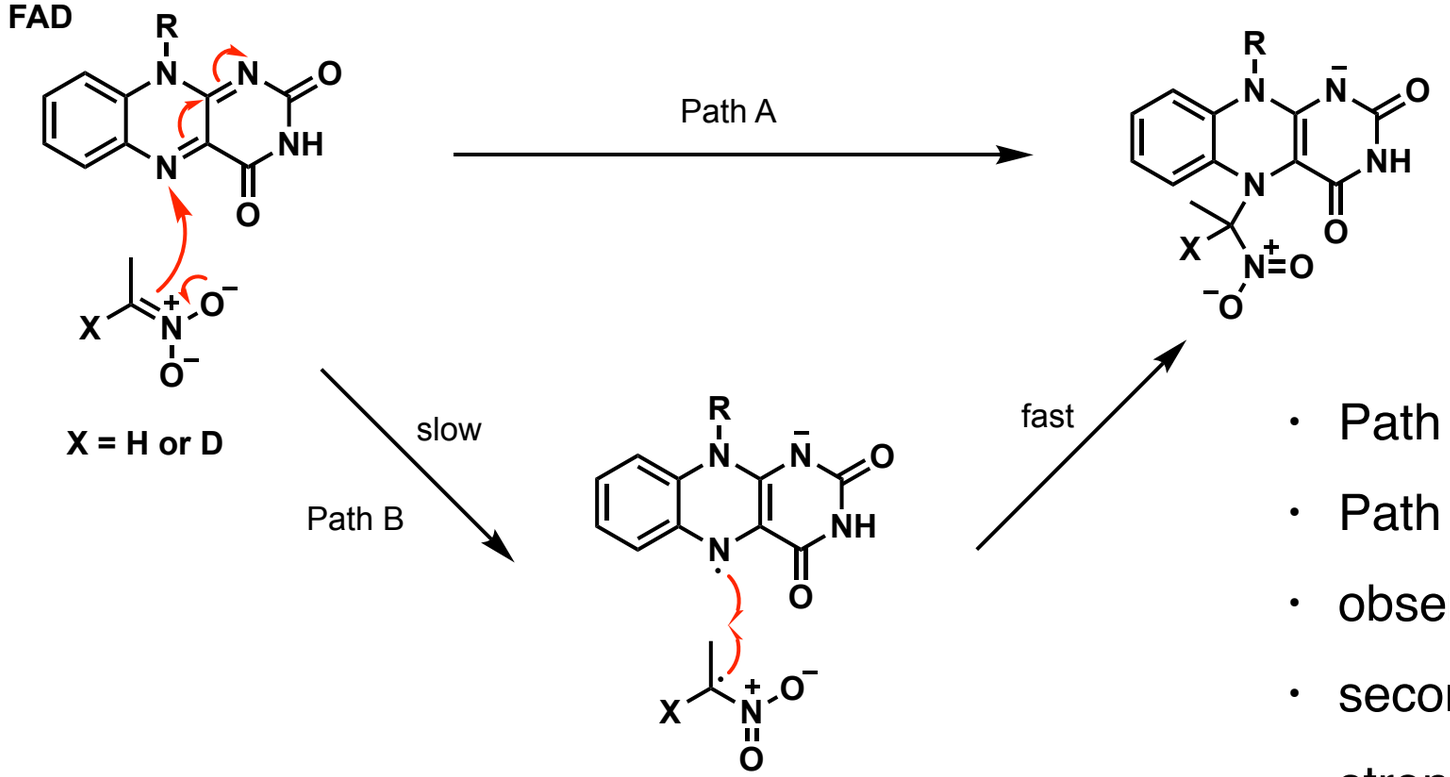
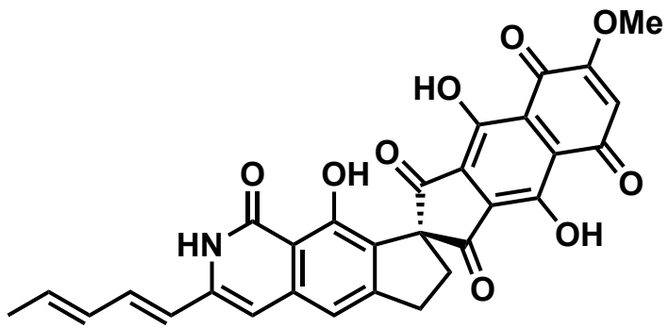


- Path A rds: sp^2 to sp^3
- Path B rds: sp^2 retained
- observed KIE = 0.84
- secondary inverse KIE
- strongly supported the nucleophilic mechanism

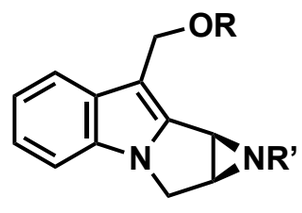
Kurtz, K. A.; Fitzpatrick, P. F. *J. Am. Chem. Soc.* **1997**, 119, 1155.
Anslyn, E. V.; Doughery, D. A. *Modrn Physical Organic Chemistry*; University Science Books, 2006

Applying Deuterium KIE in Total Synthesis

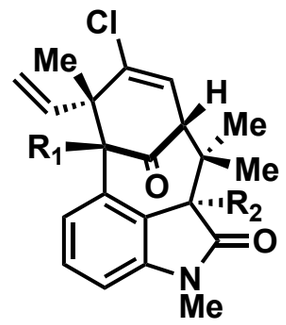
Total synthesis: modify reaction selectivity



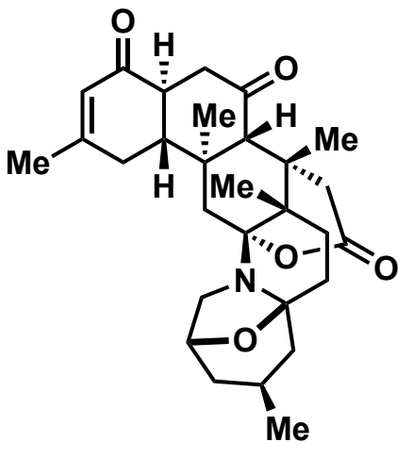
fredericamycin A



aziridinomitosenes



N-methylwelwitndolinone C



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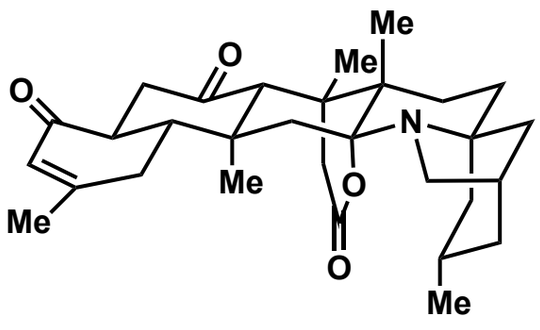
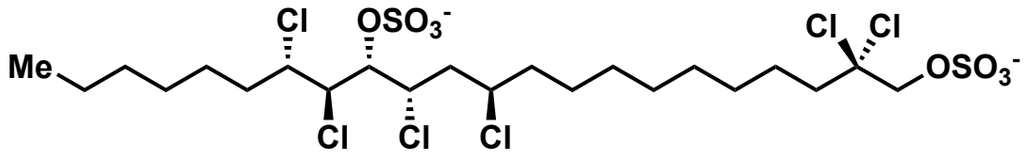
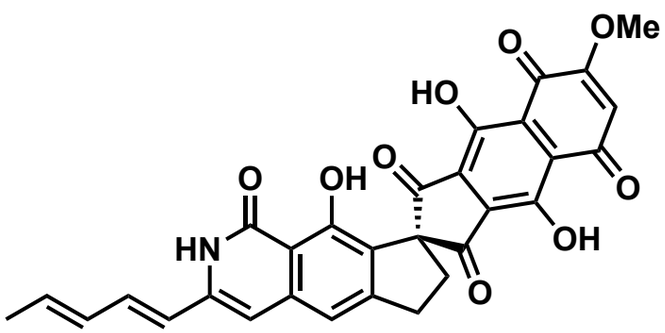


norzoanthmine

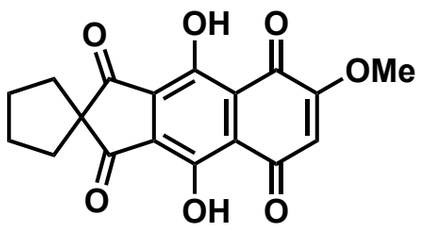


danicalipin A

Fredericamycin A



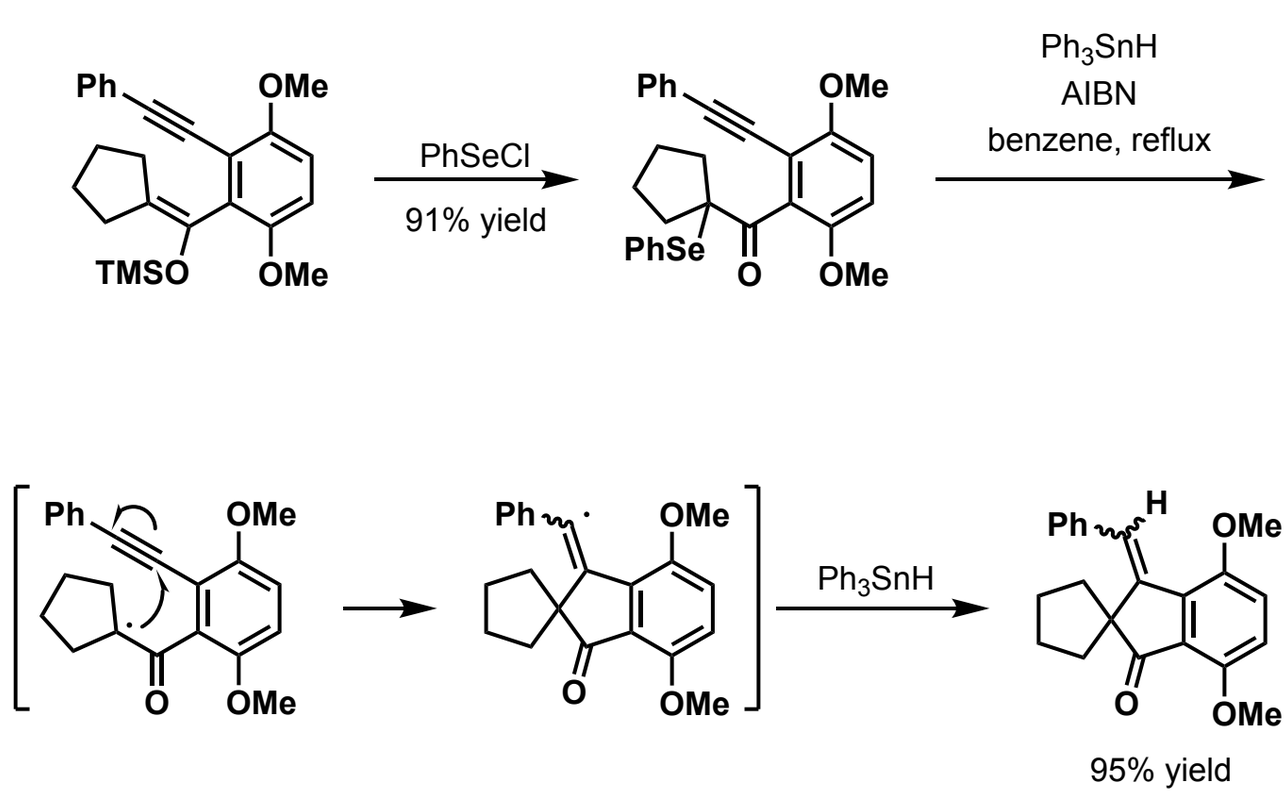
fredericamycin A



quinone system of fredericamycin A

- Antitumor antibiotic agent isolated from *Steptomyces griseus*
- Vitro cytotoxic acitivity and efficacious antitumor acitvity
- Procaryotic RNA/protein synthesis are inhibited
- Synthesized by Derrick L. J. Clive *et al.* in 1994.
- Key step — 5-exo-digonal radical spirocyclization
- Possibly the first application of deuterium KIE in total synthesis

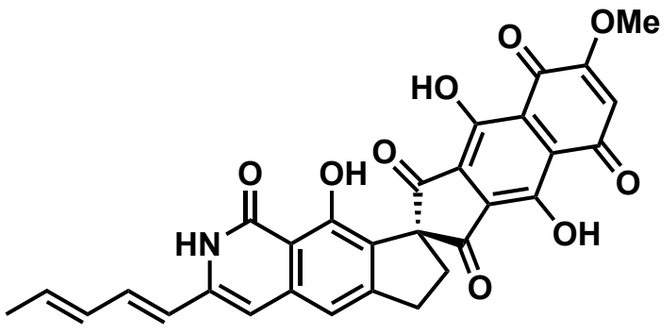
Model study



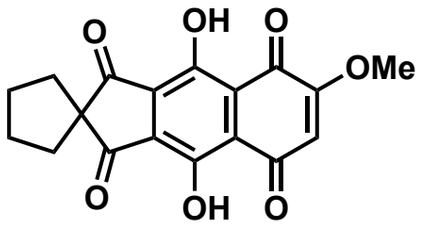
95% yield

Clive, D. L. J. *Tetrahedron* **1993**, *49*, 7917-7930.
Clive, D. L. J. *J. Am. Chem. Soc.* **1994**, *116*, 11275-11286.

Fredericamycin A

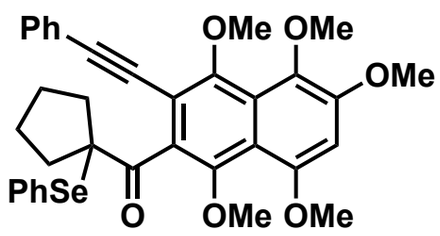


fredericamycin A

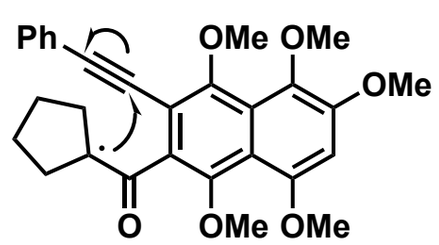


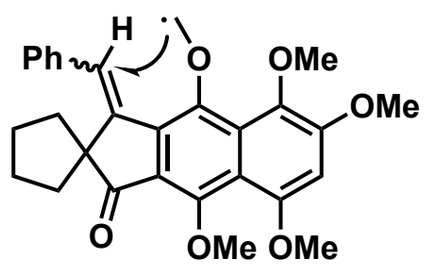
quinone system of fredericamycin A

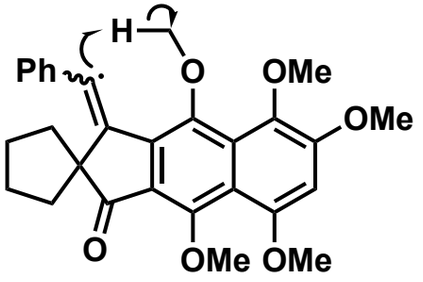
Unexpected intramolecular hydrogen abstraction



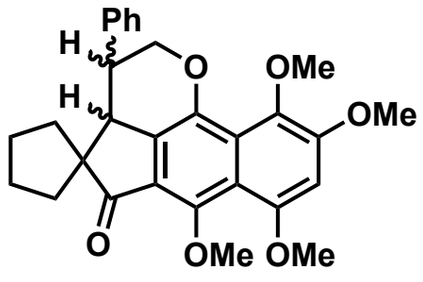
Ph_3SnH, AIBN
benzene, reflux





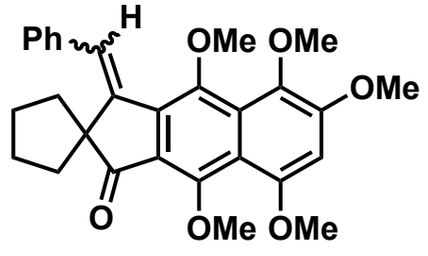


Ph_3SnH



40% yield

Ph_3SnH



48% yield

Clive, D. L. J. *Tetrahedron* **1993**, *49*, 7917-7930.
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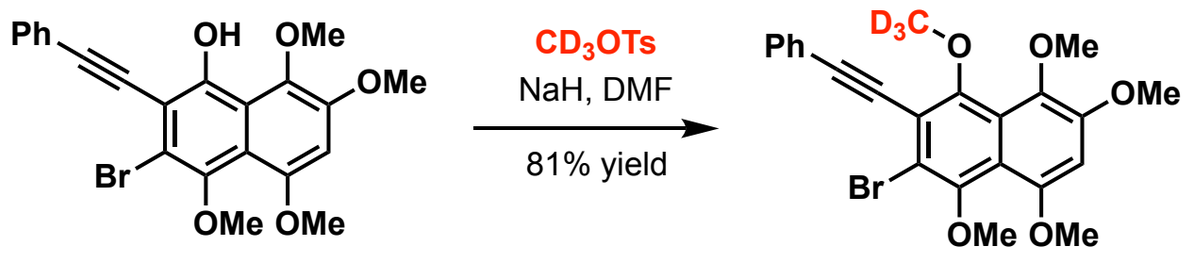
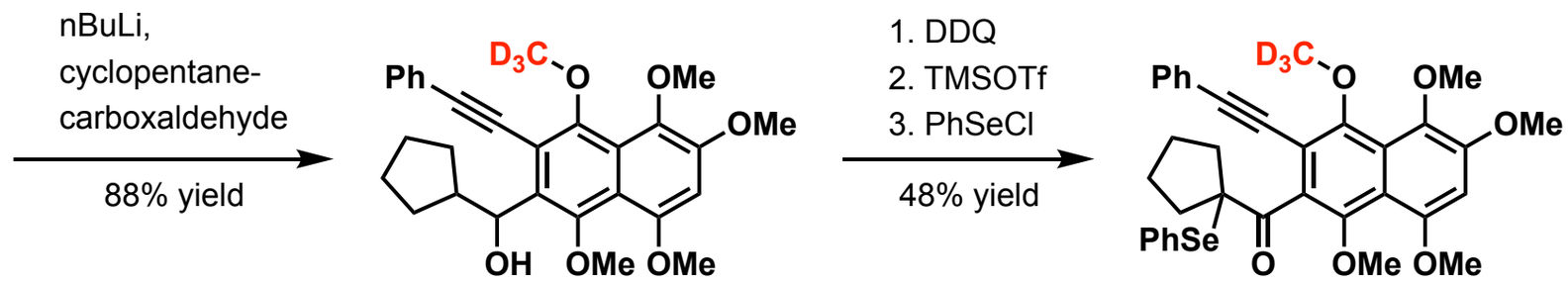
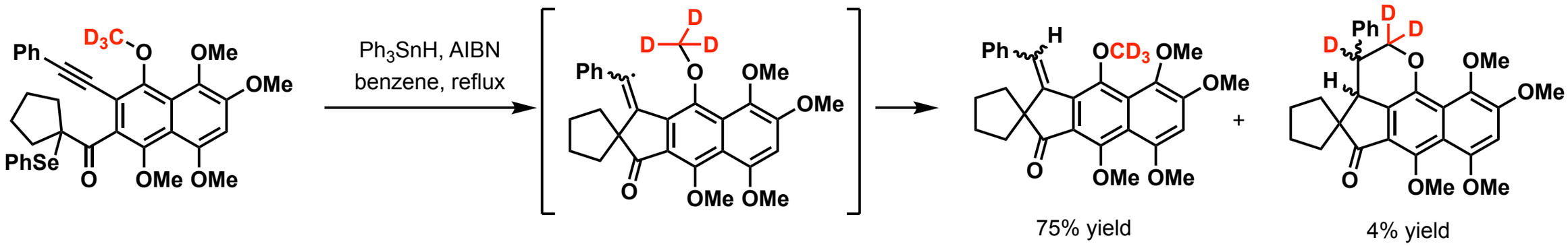
Fredericamycin A: Deuterium KIE suppress the hydrogen migration

Enhancing the stability of *peri*-methoxy group







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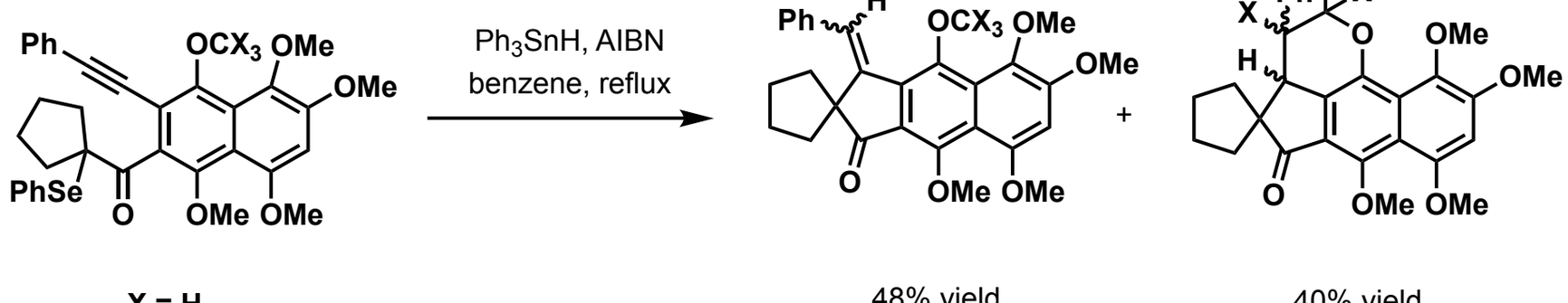
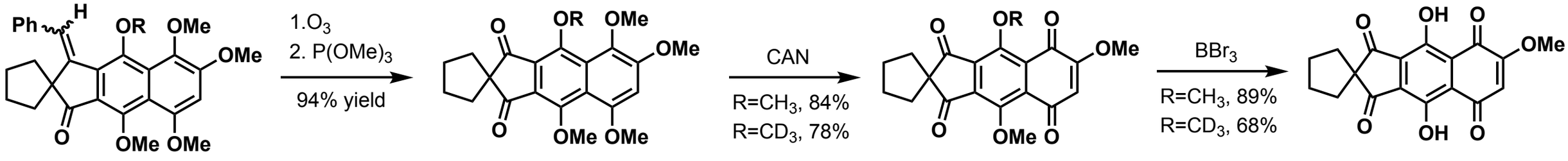
Fredericamycin A: Deuterium KIE suppress the hydrogen migration

Kenetic Isotopic effect



k_H/k_D = 15.6

Later revomal of deuterated unit



Clive, D. L. J. *Tetrahedron* **1993**, *49*, 7917-7930.
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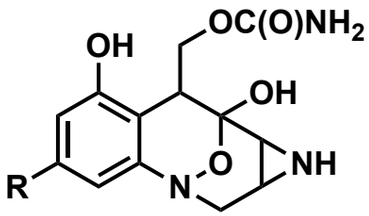
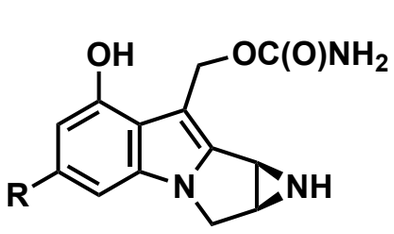
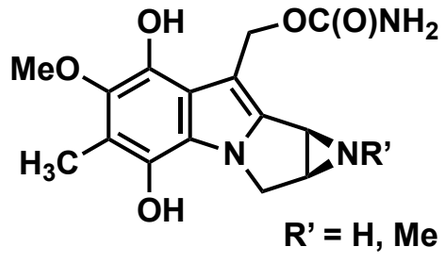
Aziridinomitosenes



FR66979 R = CH_2OH
FR900482 R = CHO

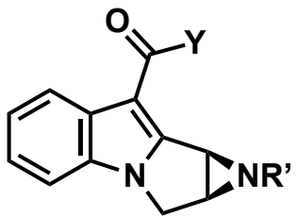


A

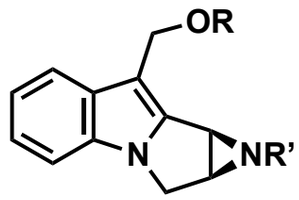


R' = H, Me

B



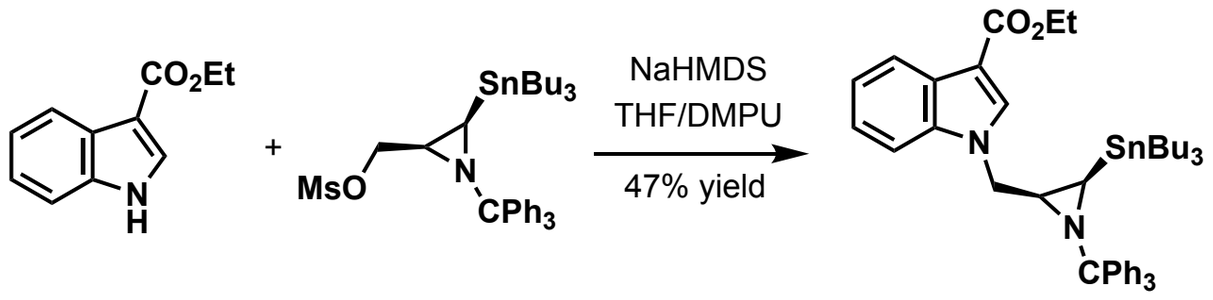
C

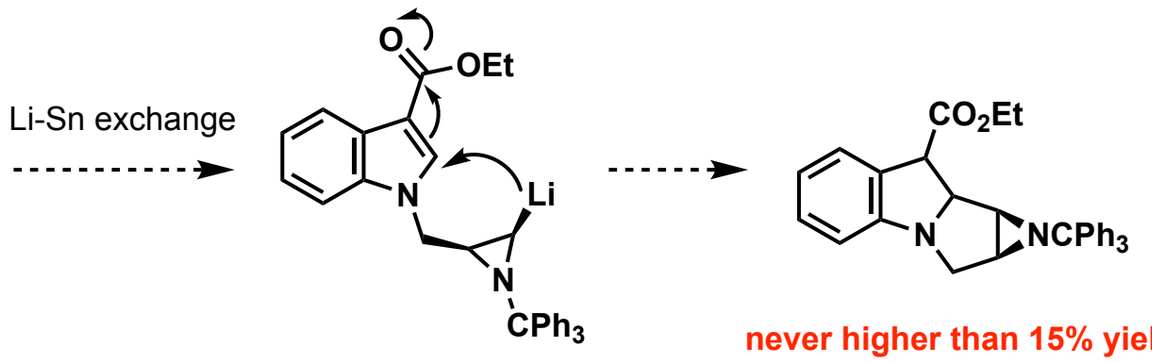


D

aziridinomitosenes

- Metabolic activation of FR66979 and FR900482 generates intermediate **A** having an ability to cross-link DNA.
- Leucoaziridinomitosenes **B** are responsible for the antitumor activity of the mitomycin antibiotics.
- Delocalization helps to stabilize carbonyl derivatives **C**, which had been synthesized.
- Nonstabilized core structure **D** was synthesized for the first time by Edwin Vedejs *et al*.

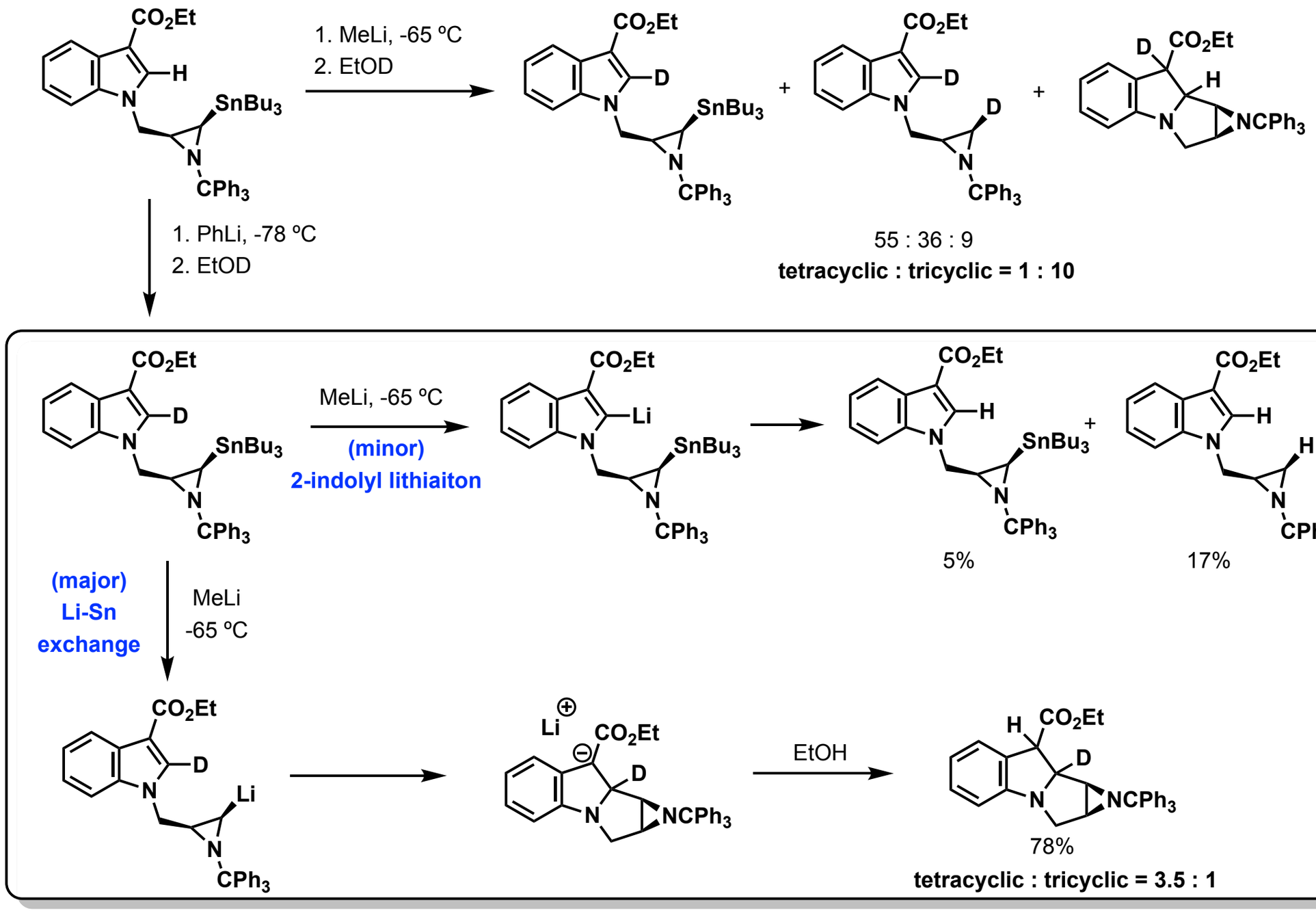




never higher than 15% yield

Vedejs, E. *J. Am. Chem. Soc.* **2002**, *124*, 748-749.

Aziridinomitosenes: Deuterium as a removable blocking group



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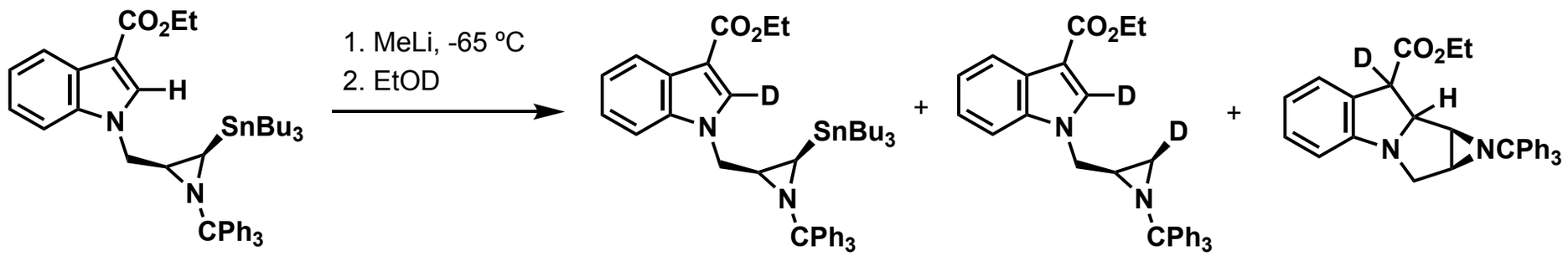
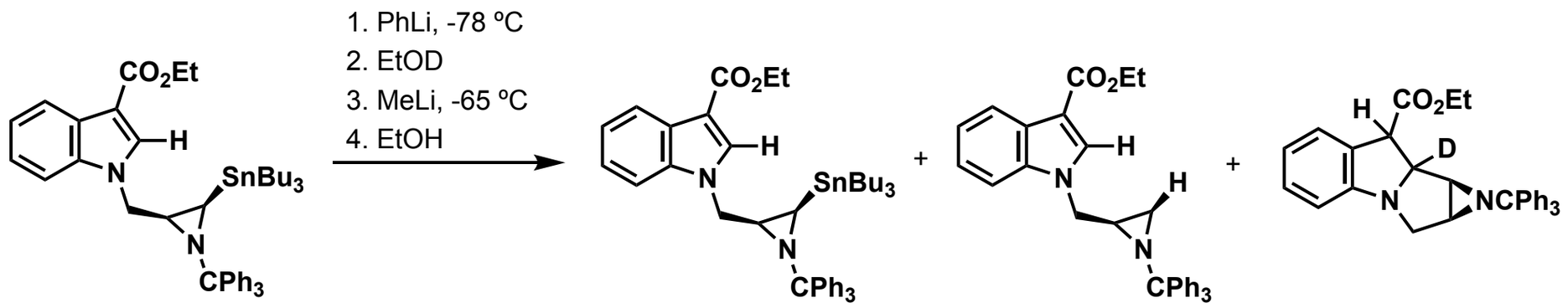
Aziridinomitosenes: Deuterium as a removable blocking group



55 : 36 : 9

$$\frac{\text{Li-Sn exchange}}{\text{2-indolyl lithiation}} = \frac{0.49}{1}$$



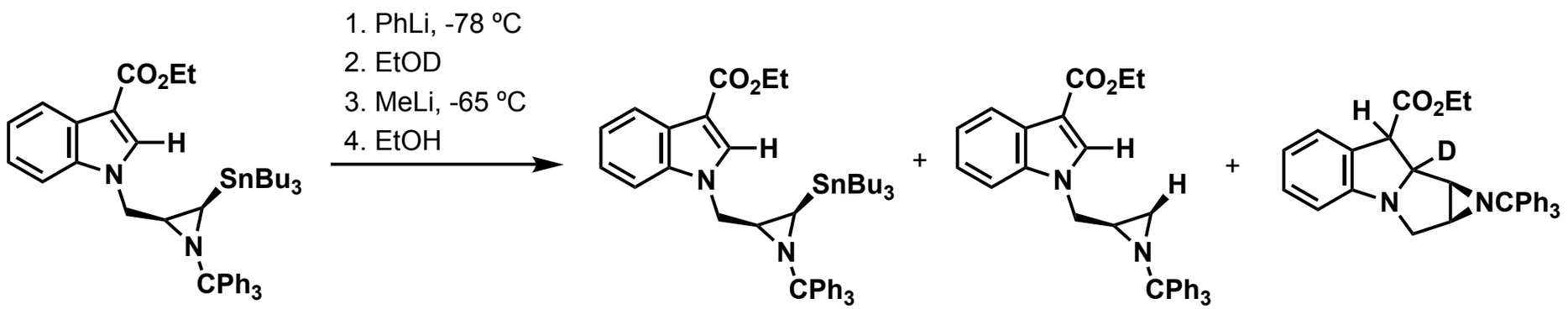
5 : 17 : 78

$$\frac{\text{Li-Sn exchange}}{\text{2-indolyl lithiation}} = \frac{4.3}{1}$$

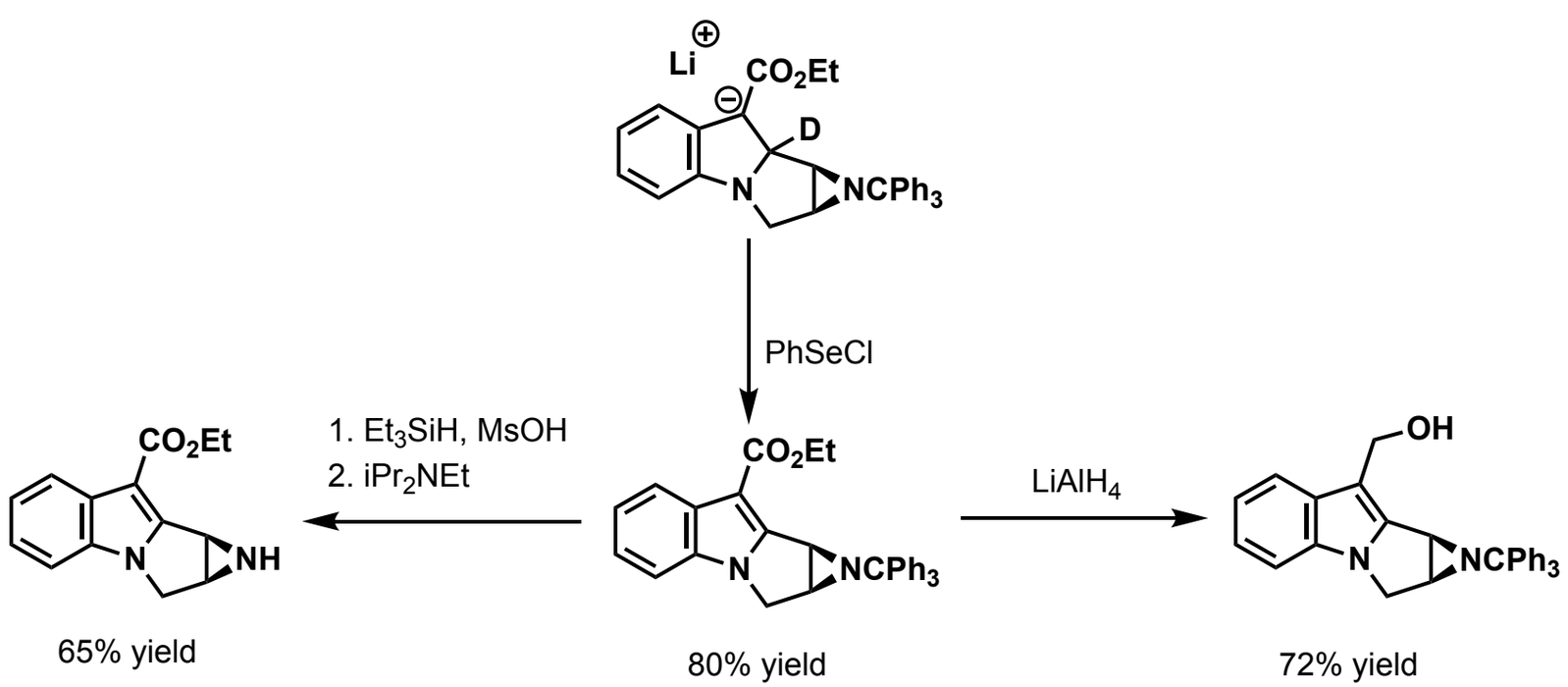
$k_H/k_D = 8.8$

Vedejs, E. *J. Am. Chem. Soc.* **2002**, *124*, 748-749.

Aziridinomitosenes: Deuterium as a removable blocking group

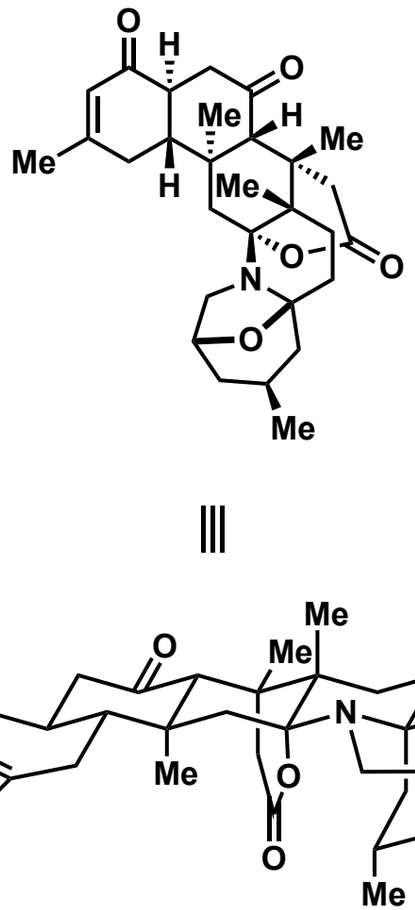


Removing the deuterium



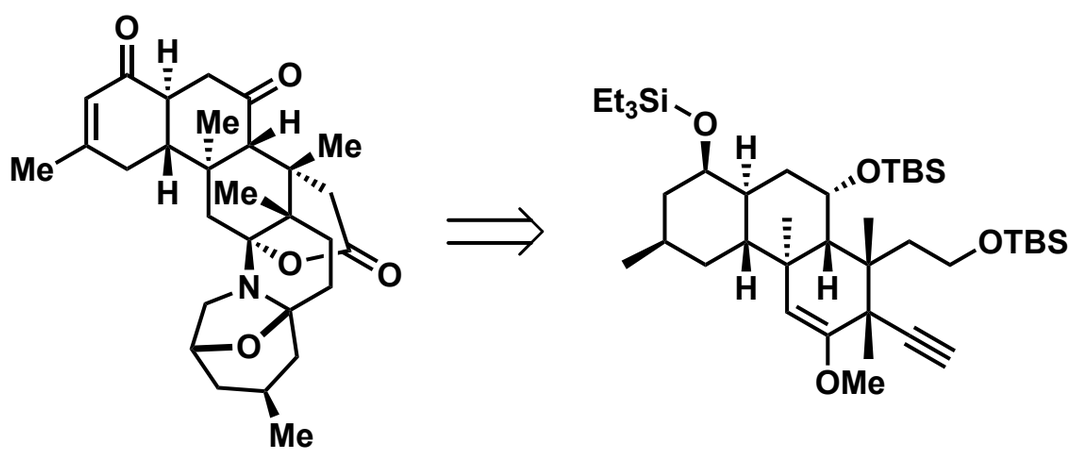
Vedejs, E. *J. Am. Chem. Soc.* **2002**, *124*, 748-749.

Norzoanthamine



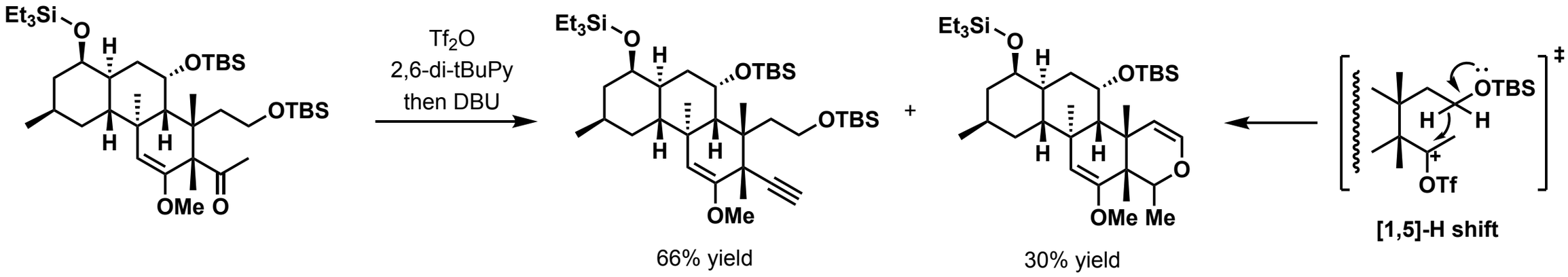
norzoanthmine

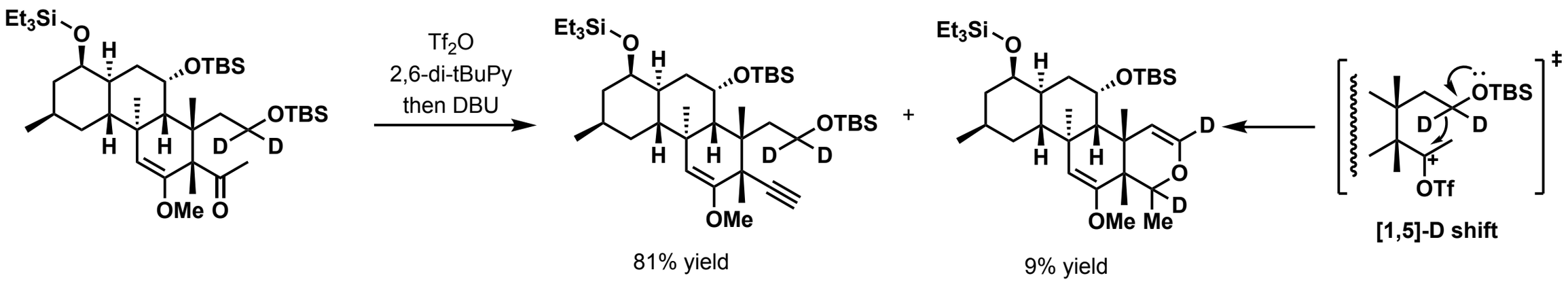
- Isolated by Uemura *et al.* in 1995 from *Zoanthus* sp.
- Strong inhibition on the the growth of P-388 murine leukemia cell lines and human platelet aggregation
- A promising candidate for an antiosteoporotic drug
- Stereoselectively synthesized by Masaaki Miyashita et al. in 41 steps with an overall yield of 3.5% (an average of 92% yield each step).



Miyashita, M. *Science* **2004**, *305*, 495-499.

Norzoanthamine: Deuterium KIE inhibits the [1,5]-hydrogen shift



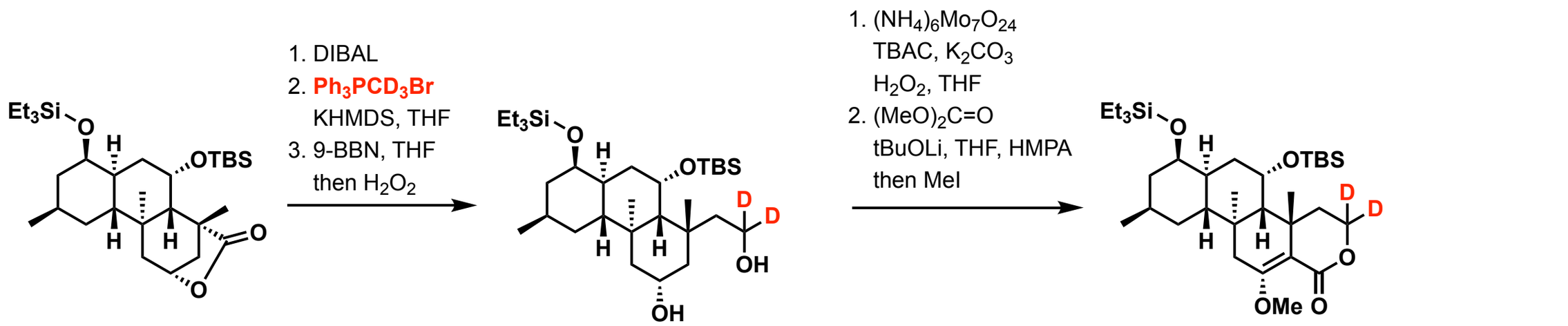


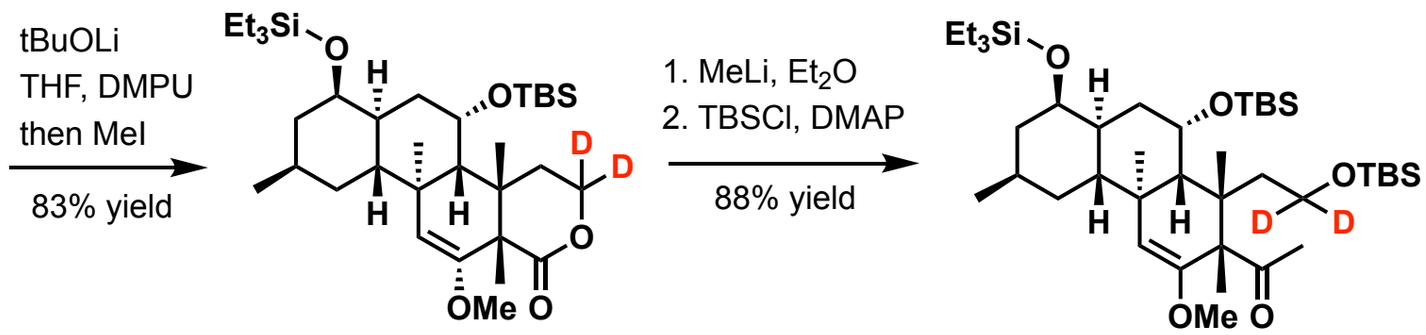
$k_H/k_D = 4.1$

Miyashita, M. *Science* **2004**, *305*, 495-499.

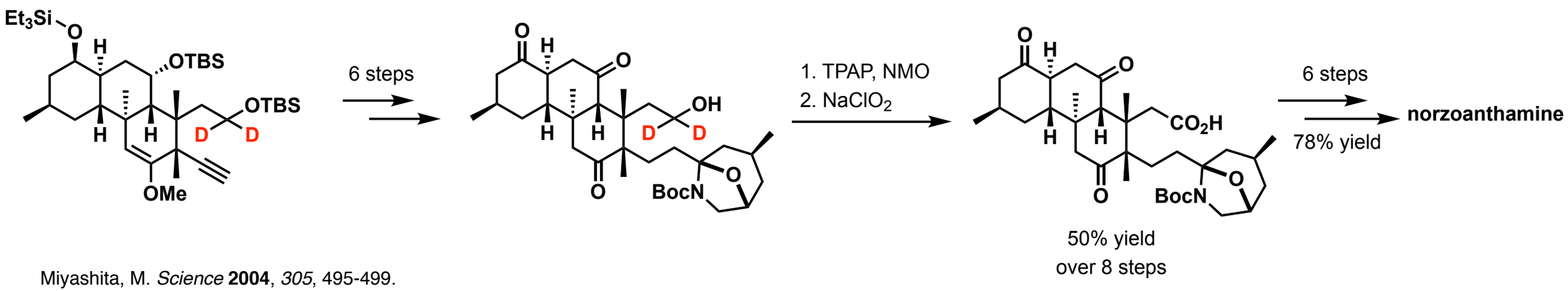
Norzoanthamine: Deuterium KIE inhibits the [1,5]-hydrogen shift

Introducing deuterium



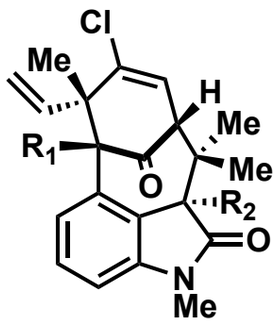


Removing deuterium



Miyashita, M. *Science* **2004**, *305*, 495-499.

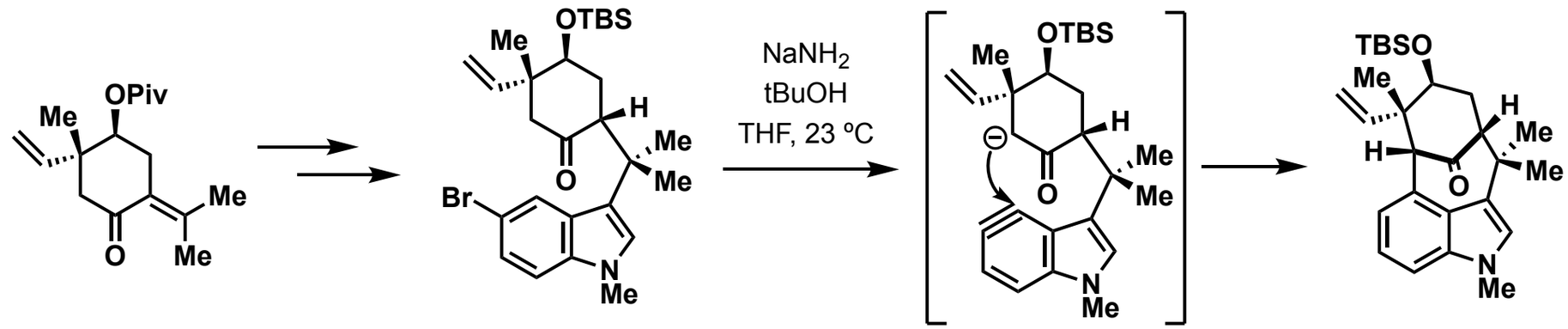
Welwitindolinones

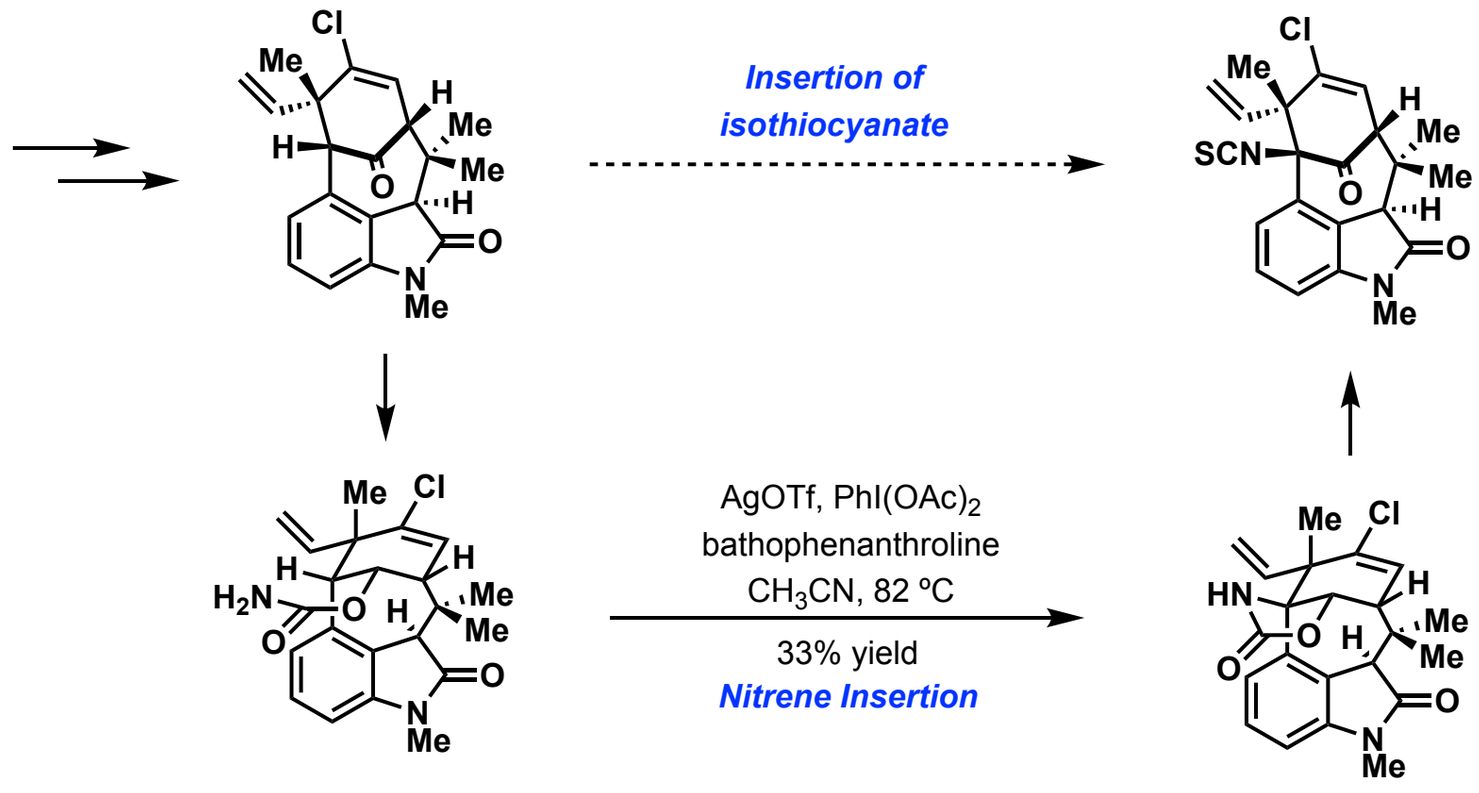


N-methylwelwitndolinone C

R_1 = -NCS, -NC
R_2 = H, OH

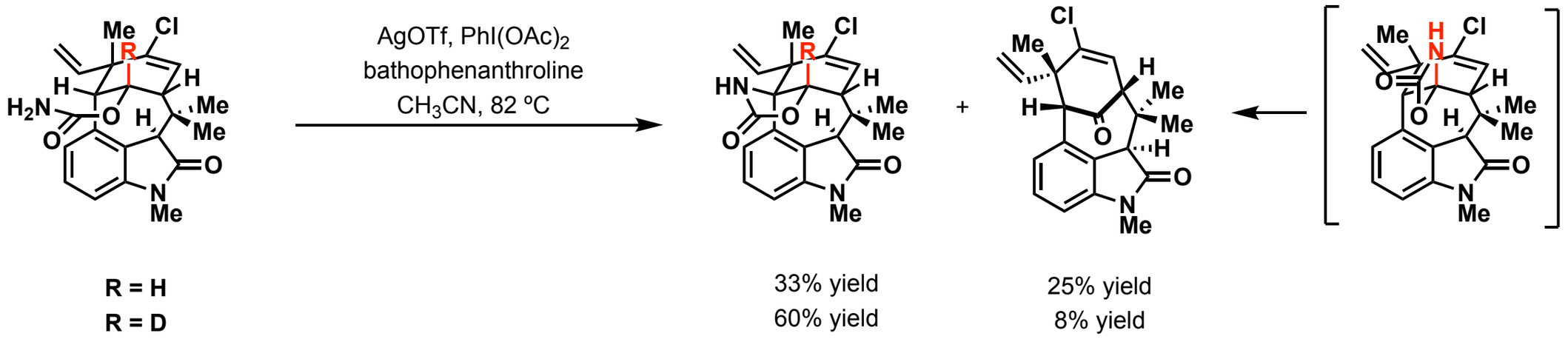
- Isolated in 1994 and 1999
- [4.3.1]Bicyclic framework
- Promising activity against drug-resistant cancer cells

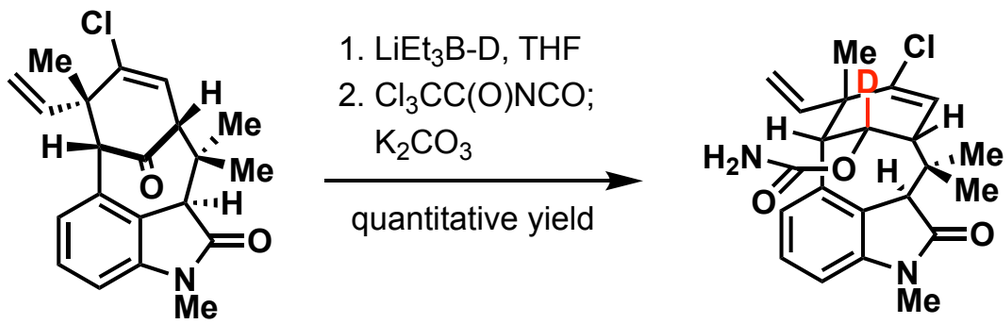




Garg. N. *J. Am. Chem. Soc.* **2011**, *133*, 15797-15799.
Garg, N. *J. Am. Chem. Soc.* **2012**, *134*, 1396-1399.

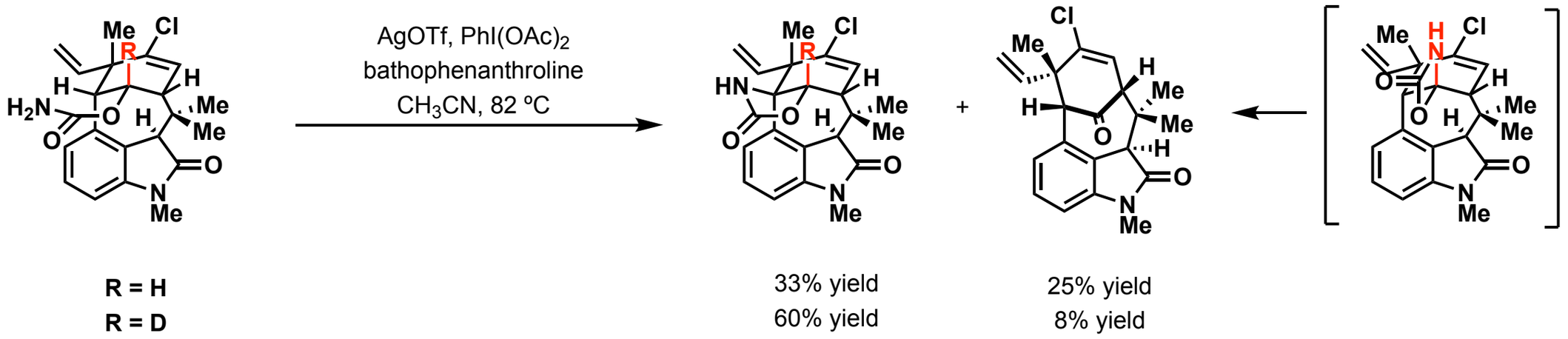
Welwitindolinones: Deuterium KIE improves nitrene insertion

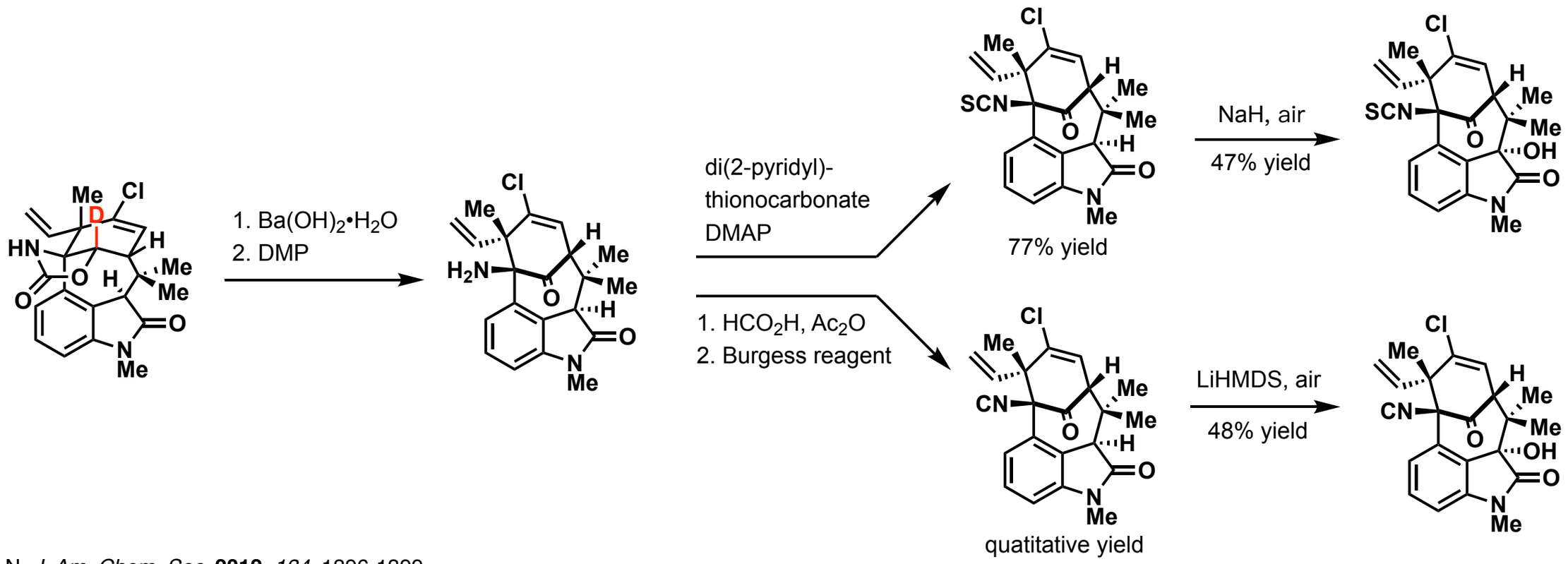




Garg, N. *J. Am. Chem. Soc.* **2012**, *134*, 1396-1399.

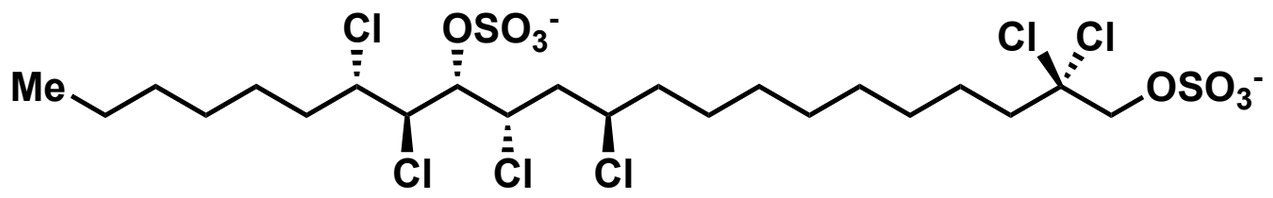
Welwitindolinones: Deuterium KIE improves nitrene insertion





Garg, N. *J. Am. Chem. Soc.* **2012**, *134*, 1396-1399.

Danicalipin A

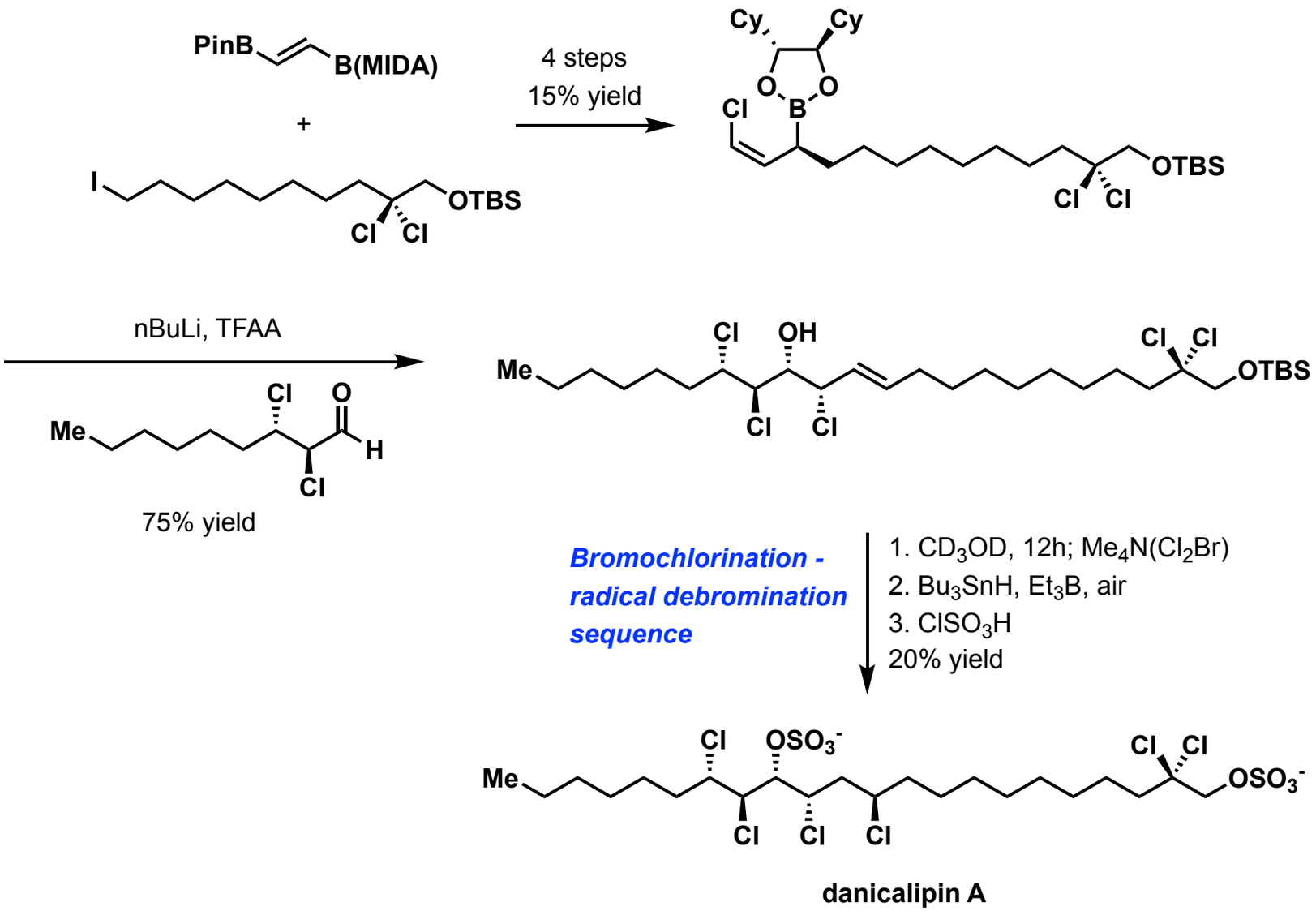


danicalipin A

- Comprise >90% of all polar lipids in the flagellar membrane of freshwater *Ochromonas danica* algae
- Two anionic sulfate moieties: one at the terminus; one near the otherwise hydrophobic center
- Synthesized by Noah Burns et al. in 2% yield in 8 steps, which is the shortest.

Burns, N. *J. Am. Chem. Soc.* **2016**, *138*, 5150-5158.

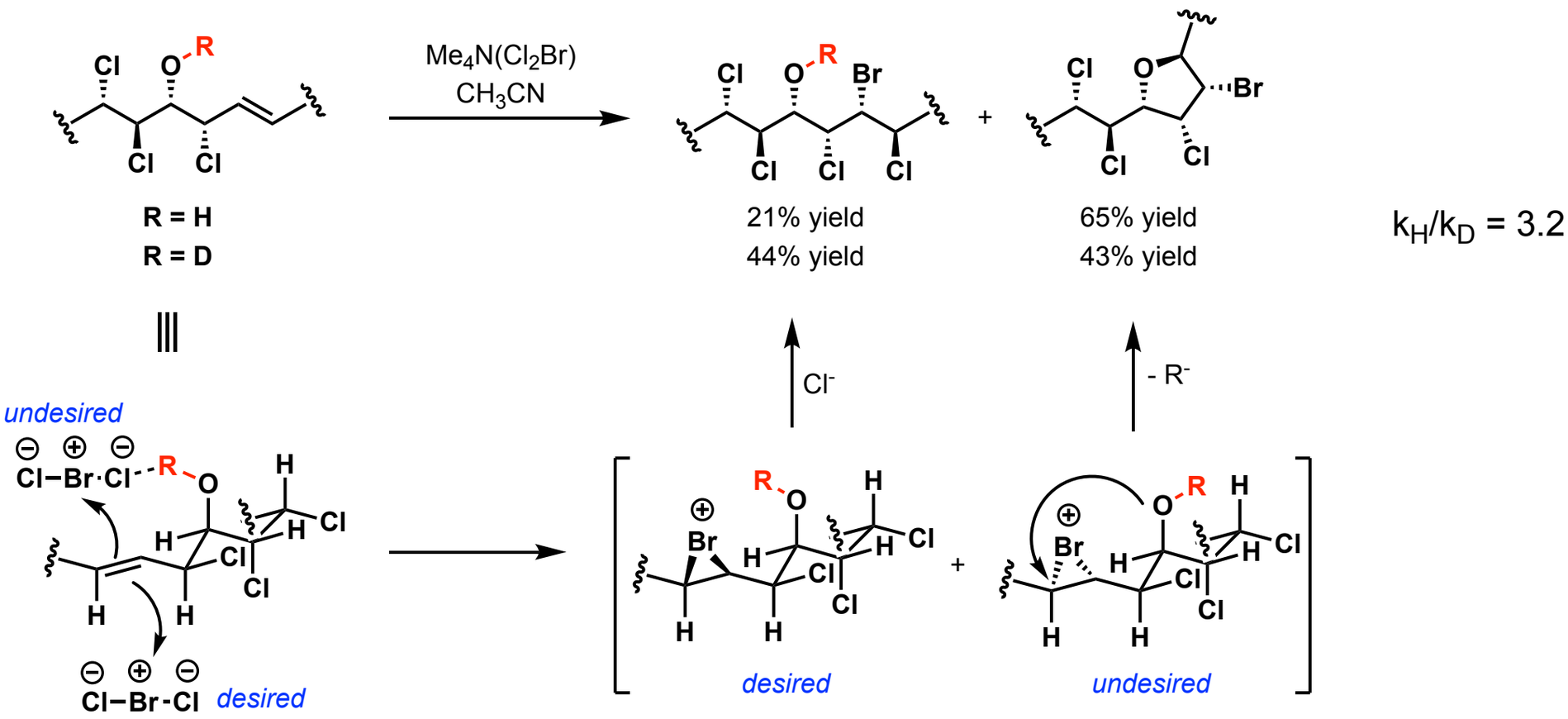
Danicalipin A



danicalipin A

Burns, N. *J. Am. Chem. Soc.* **2016**, *138*, 5150-5158.

Danicalipin A



- Deuteration renders the hydrogen bonding of secondary alcohol less effective.
- Bromium formation is reversible and deprotonation of the alcohol during bromoetherification is selective determining.

Burns, N. *J. Am. Chem. Soc.* **2016**, *138*, 5150-5158.

Application of Deuterated Compounds

Total synthesis: modify reaction selectivity

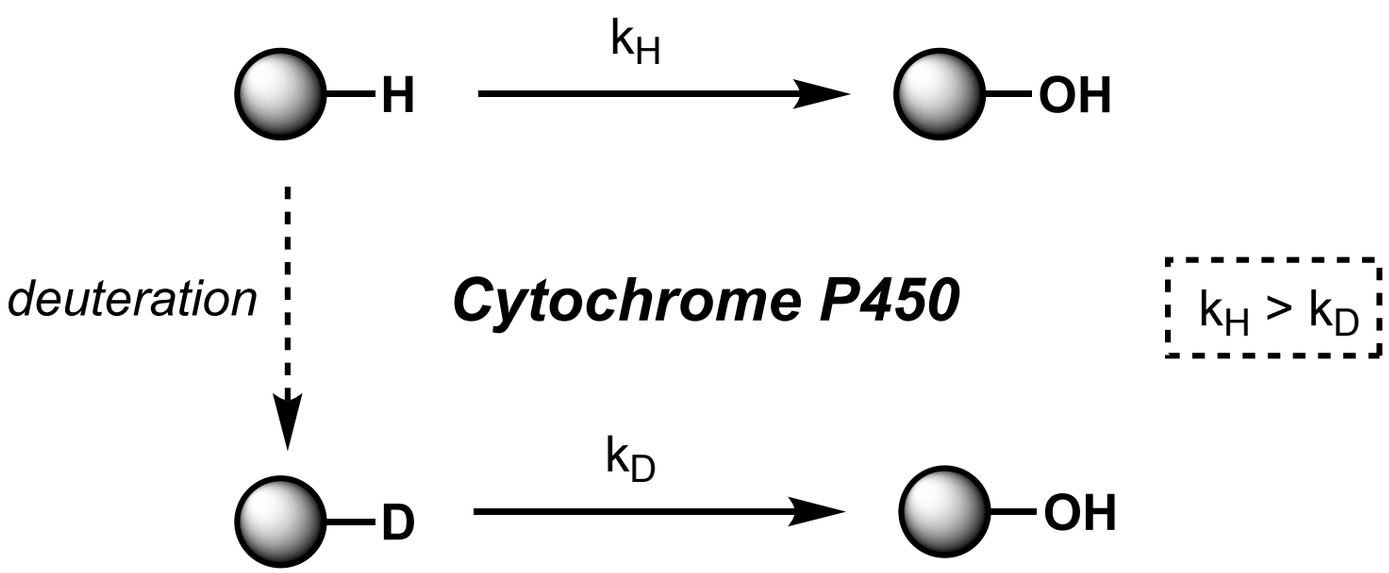
Drug development: enhance metabolic stability

Mass spectrometry internal standards

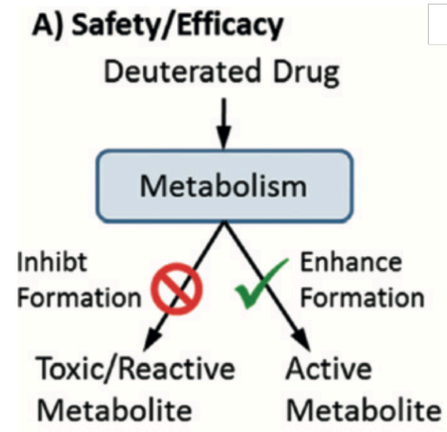
Clarification of organic reaction mechanisms

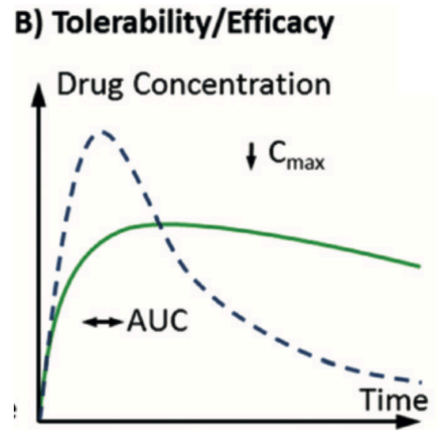
Elucidation of biosynthetic routes

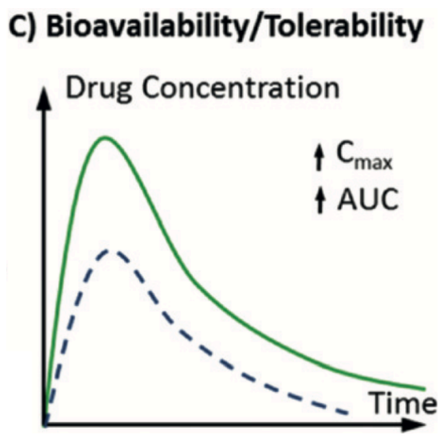
Applying Deuterium to Improve Existing Drugs



- The major metabolizing enzymes in humans belong to cytochrome P450 enzyme family.
- Significant KIEs have been observed for several P450-catalyzed reactions.
- Potential deuterated drug benefits:
  - A reduced dosage or dosing regimen
  - A smaller potential for drug-drug interactions
  - A lower incidence of side effects

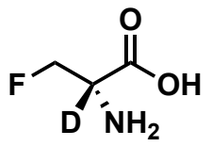
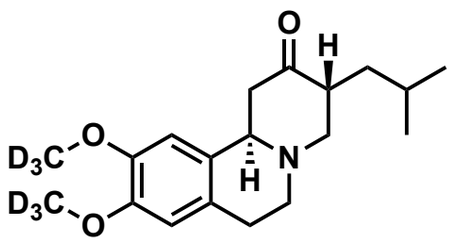
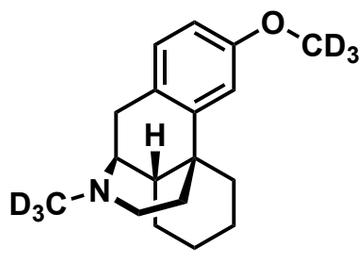
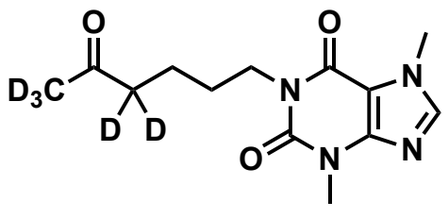






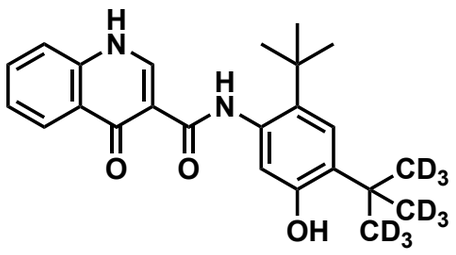
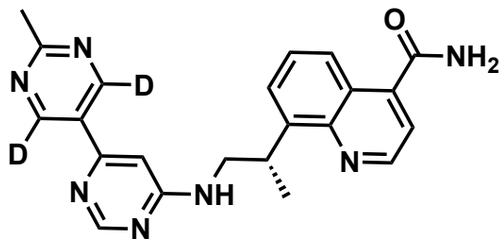
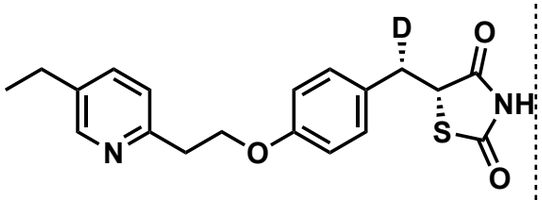
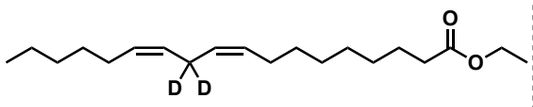
Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid M. *Angew. Chem. Int. Ed.* ***2018***, *57*, 1758-1784.

Deuterium clinical drug candidates

Chemical Structure	Compound	Status	Beneficial Deuterium Effect
	Fludalnine (MK-0641)	First deuterated drug candidate to enter clinic (1970s) Discontinued	Reduce toxic metabolite, 3-fluorolactate
	Austedo® Deutertrabenazine (SD-809)	First deuterated drug approved (2017) Approved	Reduce rate of active metabolite demethylation driven by CYP2D6
	d_6-dextromethorphan (AVP-786)	Phase 3	Reduce formation of toxic metabolite by CYP2D6
	d_5-pentoxifylline (CT-499)	Phase 2	Reduce metabolism speed; primary metabolite raising up to 3 times than that of pentoxifylline

Sabounjian, L. A. *Clin. Pharmacol. Drug Dev.* **2016**, *5*, 314-425.
Atzrodt, J.; Derdau, V.; Kerr, W. J.; Reid M. *Angew. Chem. Int. Ed.* ***2018***, *57*, 1758-1784.
https://www.concertpharma.com/research/documents/CTP-499ASN2014PosterFINAL14NOV2014.pdf
https://en.wikipedia.org/wiki/Deuterated_drug#VX-561_(Vertex/Concert)

Deuterium clinical drug candidates

Chemical Structure	Compound	Status	Beneficial Deuterium Effect
	d_9-ivacaftor (VX-561)	Phase 2	Reduce rate of tert-butyl group oxidation and in vivo clearance by CYP3A4
	VX-984	Phase 1	Reduce aldehyde oxidase(AO)-driven metabolism
	d_1-(*R*)-pioglitazone (DRX-065)	Phase 1	Stabilize preferred R-enantiomer to obtain mitochondrial function modulation without affected by S-isomer
	d_2-linoleic acid ethyl ester (RT001)	Phase 1/2	Limit lipid peroxidation

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https://www.cancer.gov/publications/dictionaries/cancer-drug/def/dna-dependent-protein-kinase-inhibitor-vx-984
https://en.wikipedia.org/wiki/Deuterated_drug#VX-561_(Vertex/Concert)