Apoptosis and Apoptolidin

Hao Xie

Organic Supergroup Meeting

July 5, 2006

The definition of apoptosis

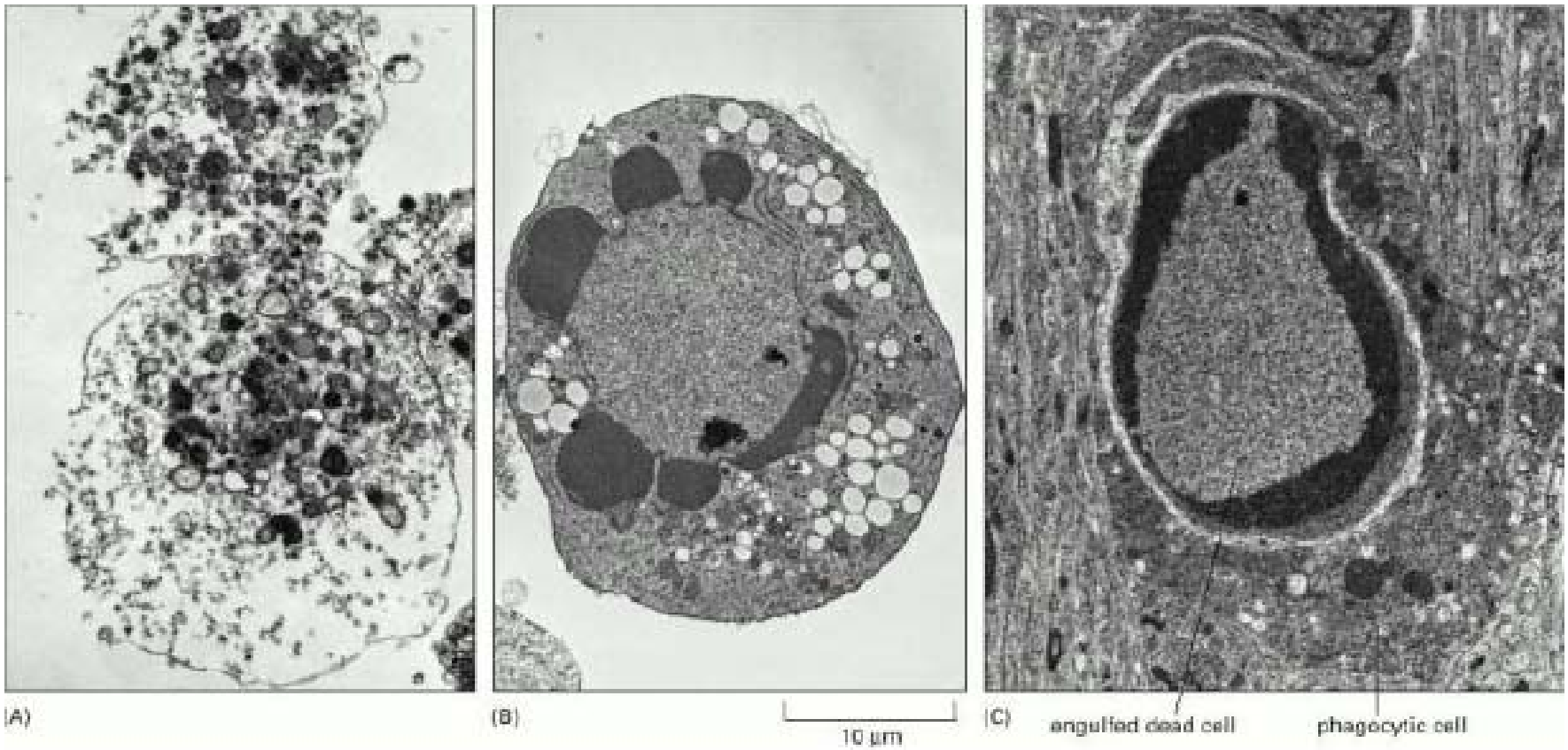
Apoptosis --- programmed cell death.

Necrosis --- death of cells that is less orderly than apoptosis.

Molecular Biology of the Cell 4th ed. Alberts, B., Johnson, A.; Lewis, J.; Raff, M.; Roberts, K.; Walter, P. **2002**.

Hengartner, M. O. *Nature* **2000**, *407*, 770-776.

Apoptosis *vs.* Necrosis



Necrosis: Cell lysis occurs, more destructive process.

Apoptosis: Cells undergo death neatly without damaging their neighbors.

Molecular Biology of the Cell 4th ed. Alberts, B.; Johnson, A.; Lewis, J.; Raff, M.; Roberts, K.; Walter, P. **2002**.

Functions of apoptosis

1. Cell damage

   The capability of apoptosis is damaged or the initiation of apoptosis is blocked → Cancer.

2. Homeostasis

   The number of cells should be constant within a certain range → in tumor or Alzheimer's disease, homeostasis is often disrupted.

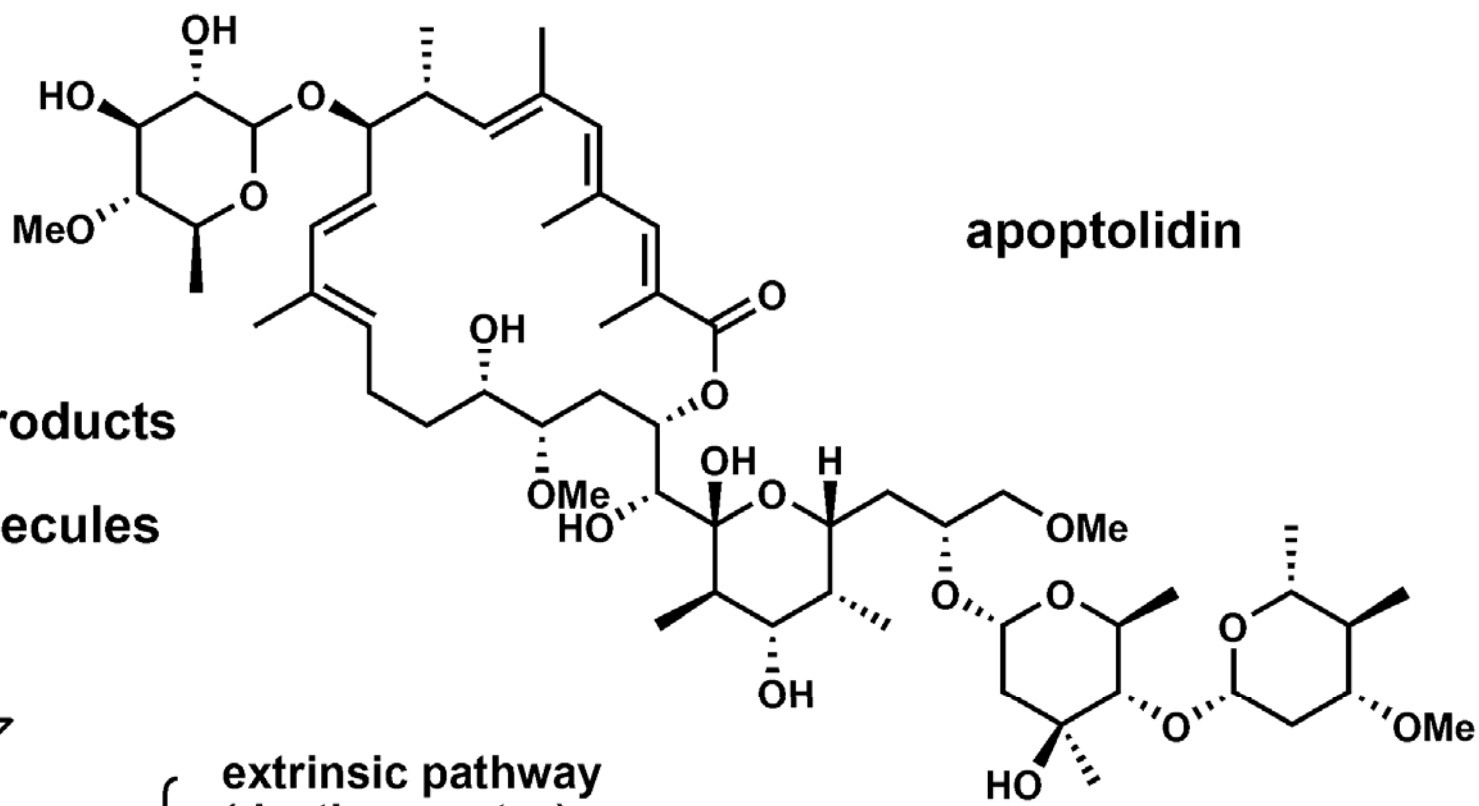
3. Development

   Selective apoptosis is crucial for tissue development in multicellular organisms.

4. Immune cell regulation

   Apoptosis of potentially damaging immature B or T cells → Preventing autoimmune reactions.

Outline: Natural products & Apoptosis



Natural Products

Small Molecules

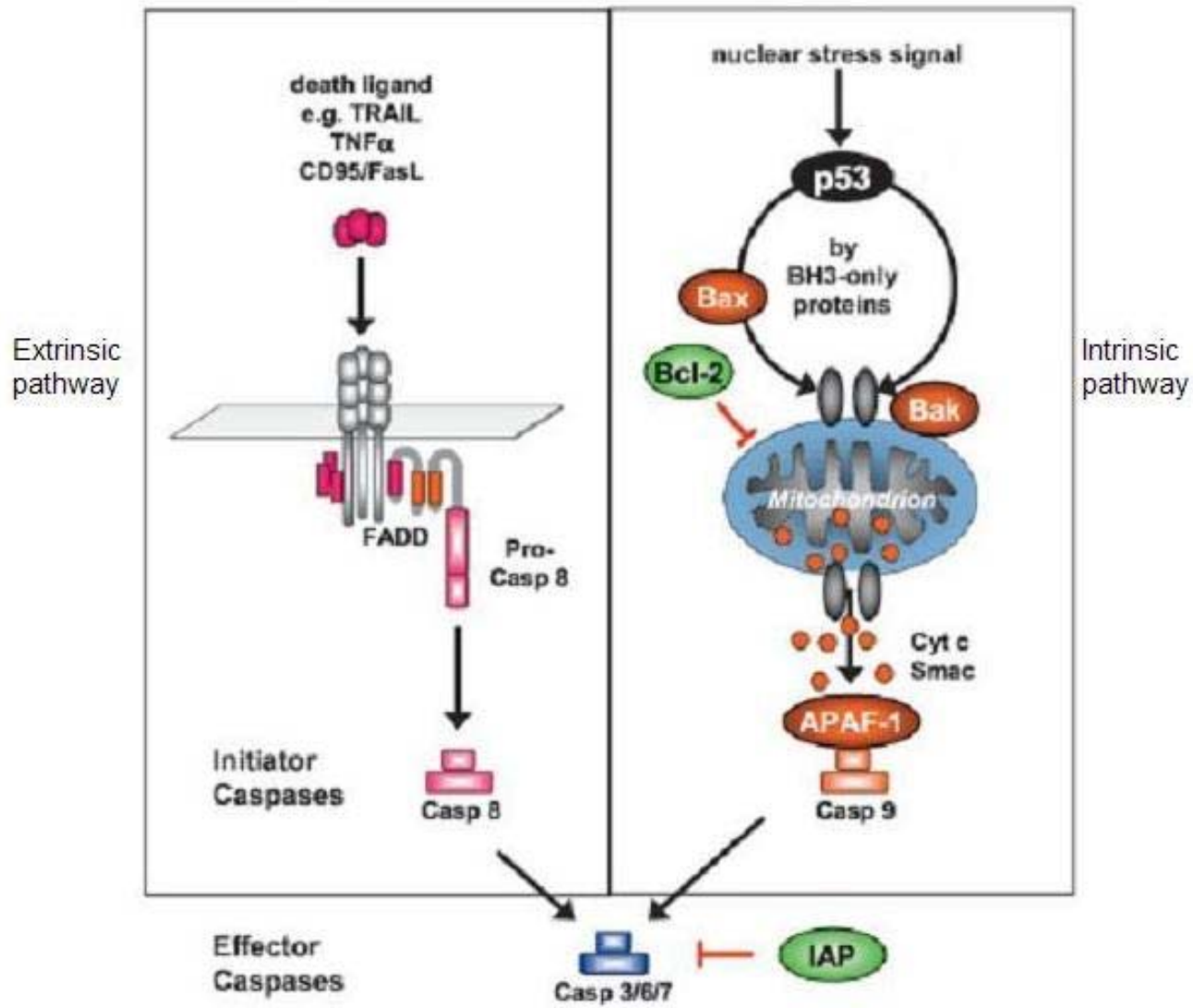
Apoptosis

extrinsic pathway
(death-receptor)

intrinsic pathway
(mitochondrial)

Daniel, P. T.; Koert, U.; Schuppan, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 872-893.

Apoptotic pathways in mammalian cells



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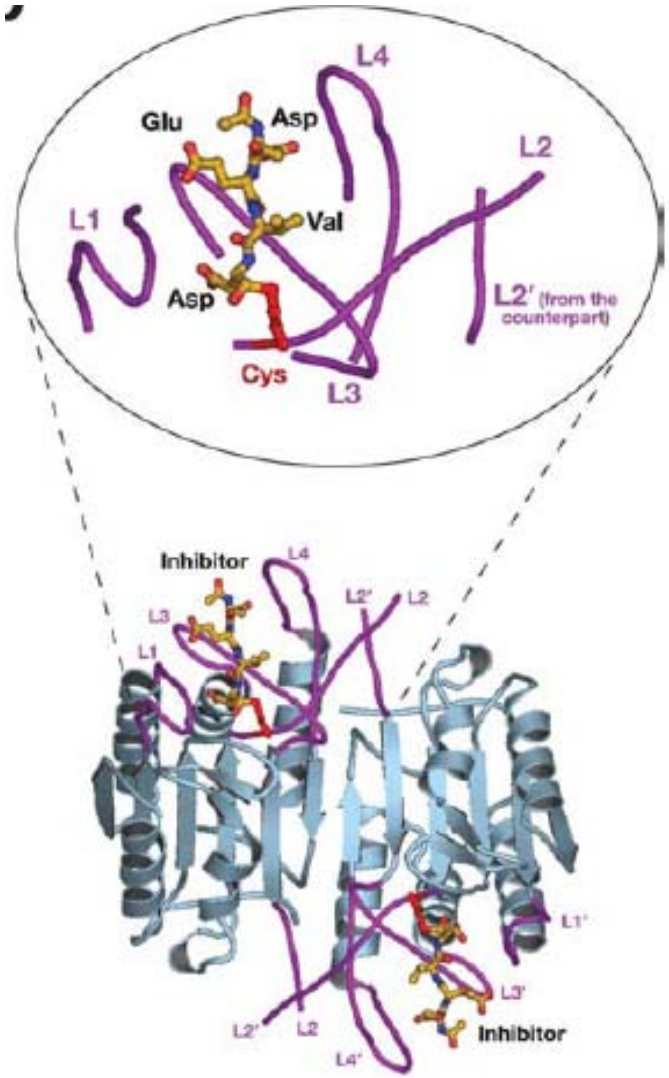
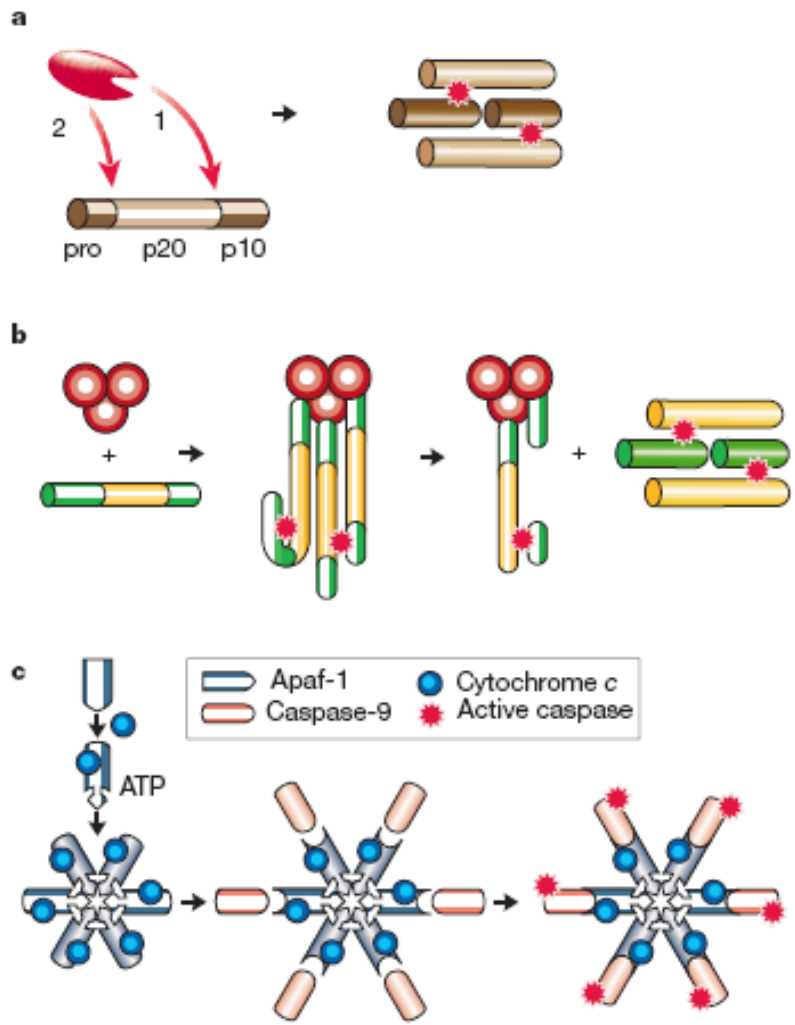
Caspases: “central executioners” of apoptosis



1. Caspases are a family of cysteine proteases and cleave their substrates at specific aspartic acids.
2. Caspases are synthesized as proenzymes, which should be activated to execute their functions.
3. The functions of caspases involve the cleavage of cytosolic proteins, the cleavage of nuclear lamin, and freeing the DNAse in the cell nucleus.
4. Caspase activity can be eliminated through mutation or use small pharmacological inhibitors.

Yan, N.; Shi, Y.; *Annu. Rev. Cell. Dev. Biol.* **2005**, *21*, 35-56.

Mechanisms of caspase activation



a. Cleavage by an upstream caspase.

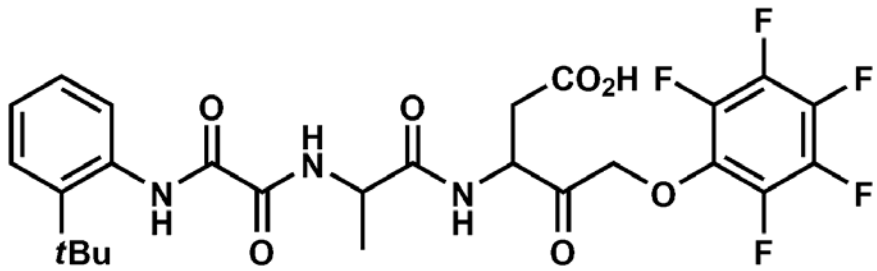
b. Induced proximity.

c. Association with a regulatory subunit to form a wheel-like **heptamer**.

Hengartner, M. O. *Nature* **2000**, *407*, 770-776.

Kim, H.; Du, F.; Fang, M.; Wang, X. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 17545-17550.

Caspases as drug targets



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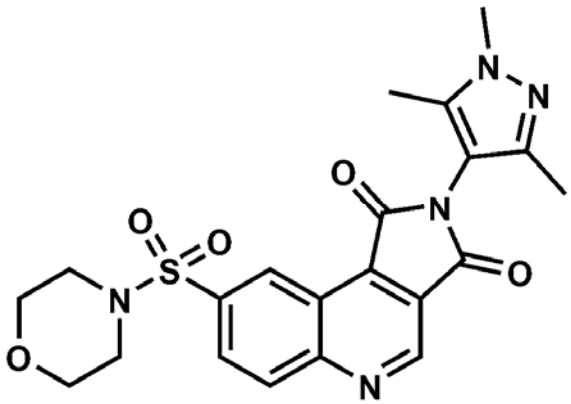
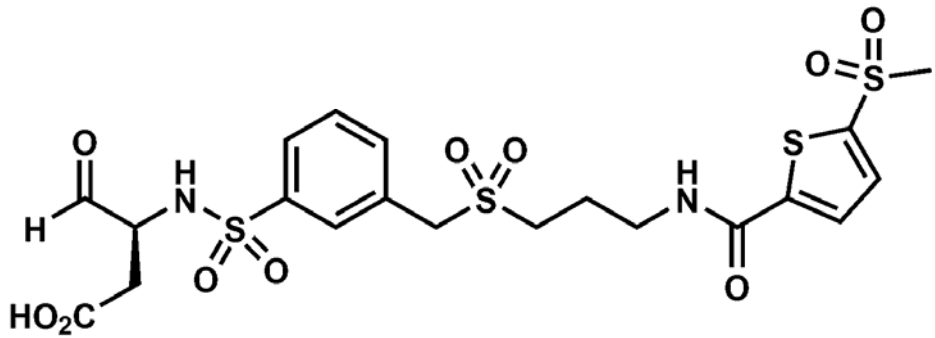


Ivatchenko's caspase-3 inhibitor



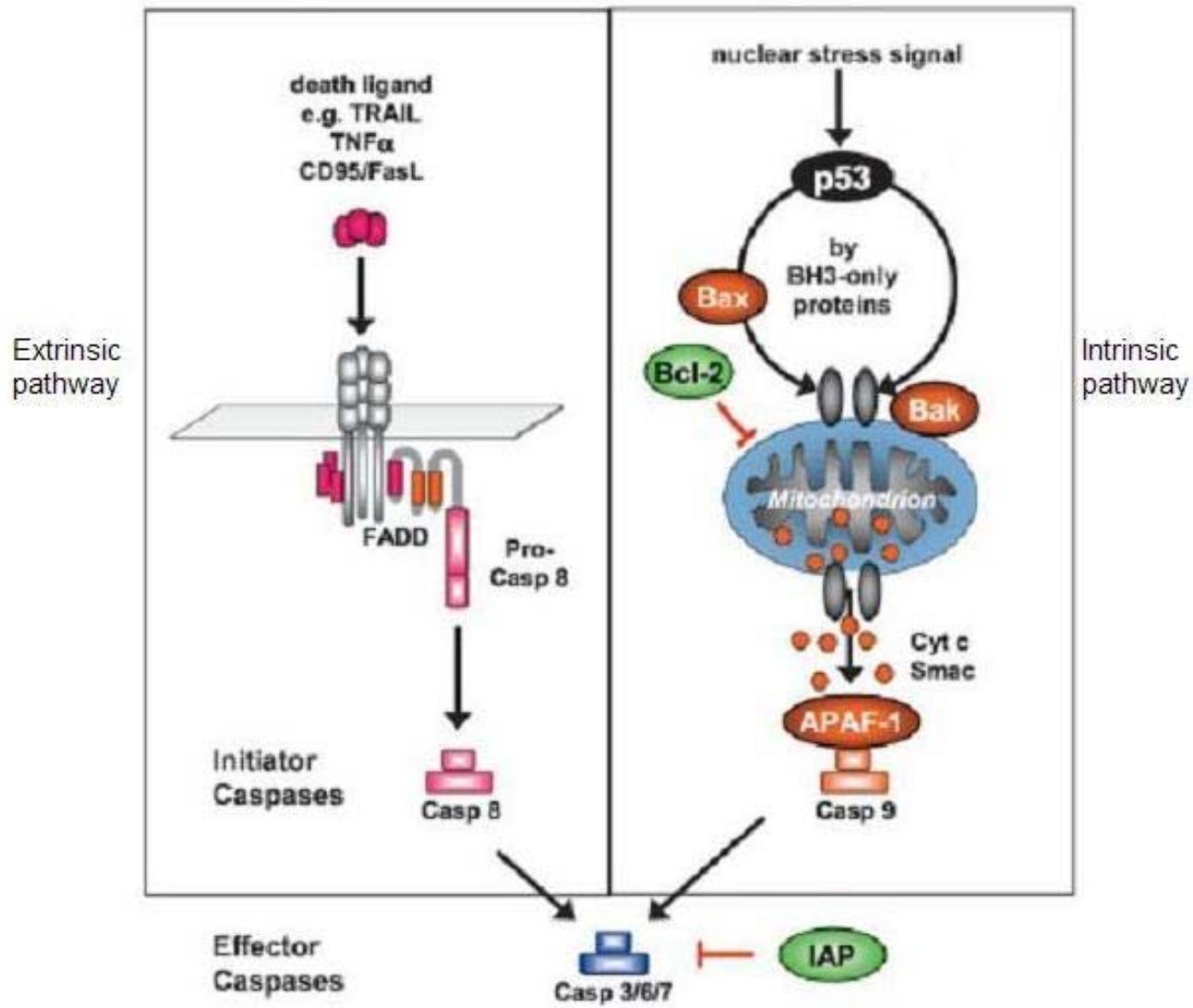
Sunesis' caspase-3 inhibitor

The inhibitors usually contain a strong electrophilic group and bind with cysteine irreversibly.

Daniel, P. T.; Koert, U.; Schuppan, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 872-893.

Talannian, R. V.; Brady, K. D.; Cryns, V. L. *J. Med. Chem.* **2000**, *43*, 3351-3371.

Apoptotic pathways in mammalian cells



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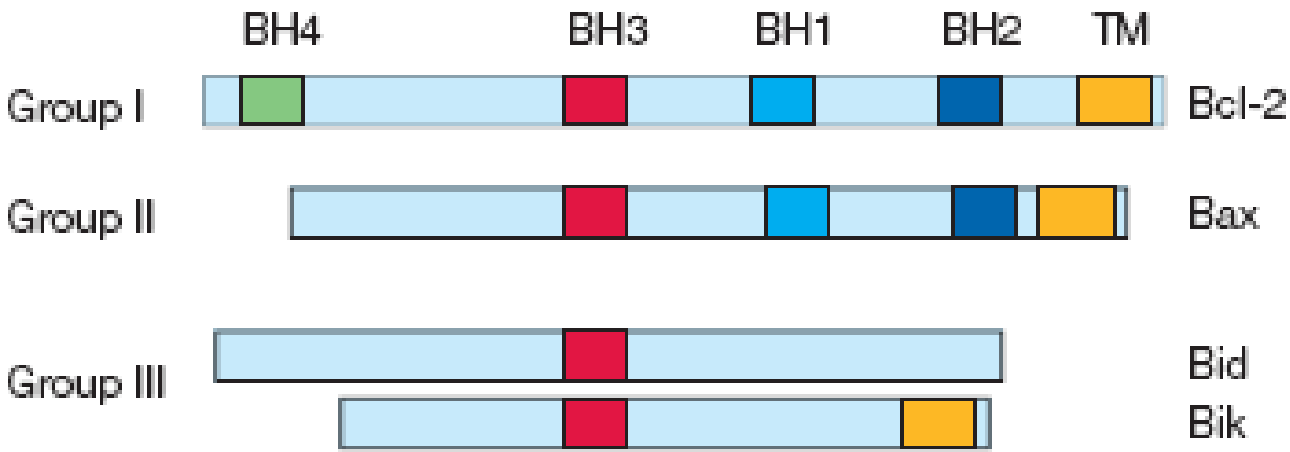
Regulators: Bcl-2 family



Group I: Bcl-2 and Bcl-XL possess anti-apoptotic activity.

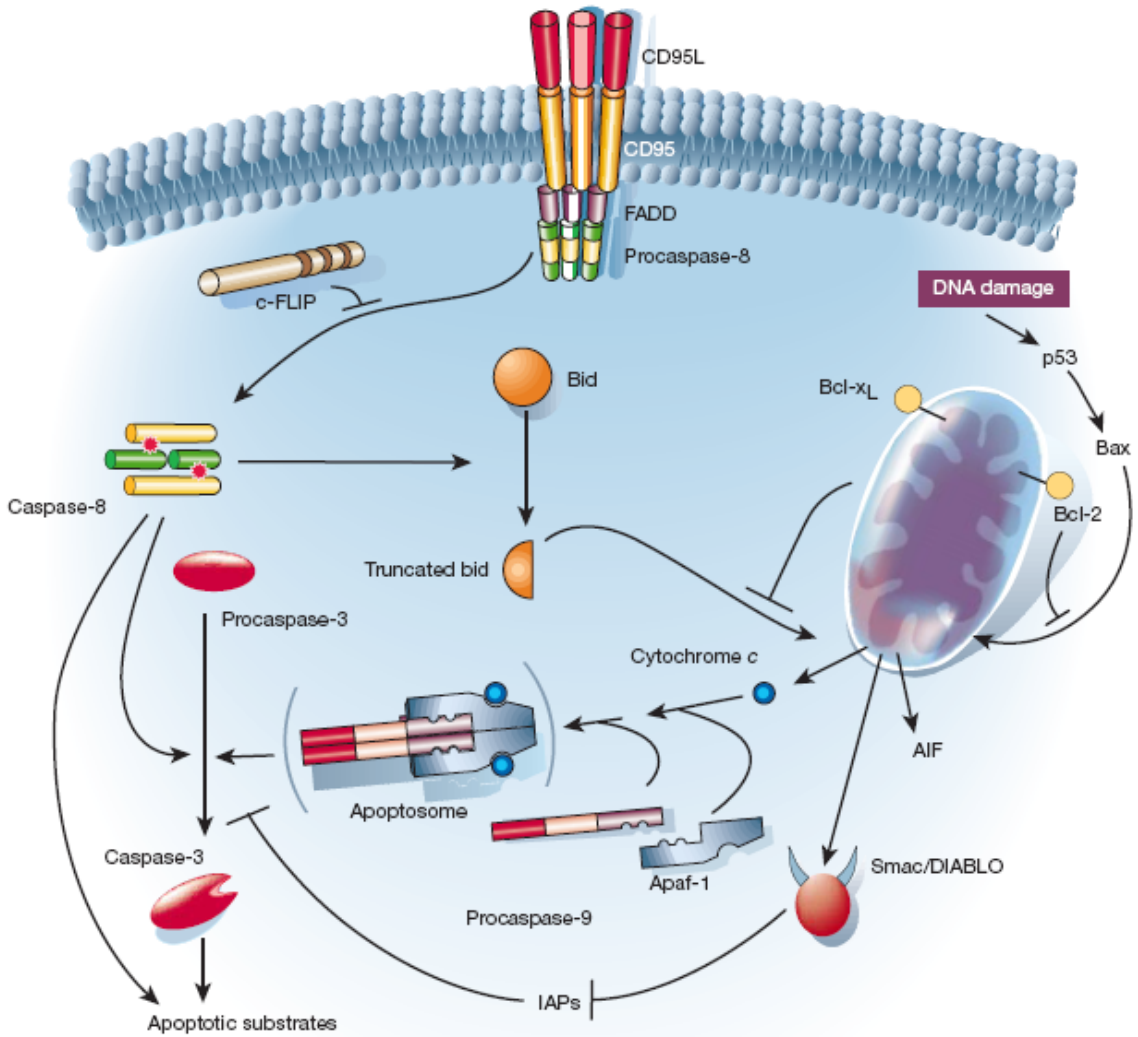
Group II and III: Bax, Bak and Bid, Bik possess pro-apoptotic activity.

Bcl-2 family members meet at the surface of mitochondria and control homeostasis of the mitochondria.

Protein interaction between Bcl-2 family members is mediated through α-helical BH3 domain.

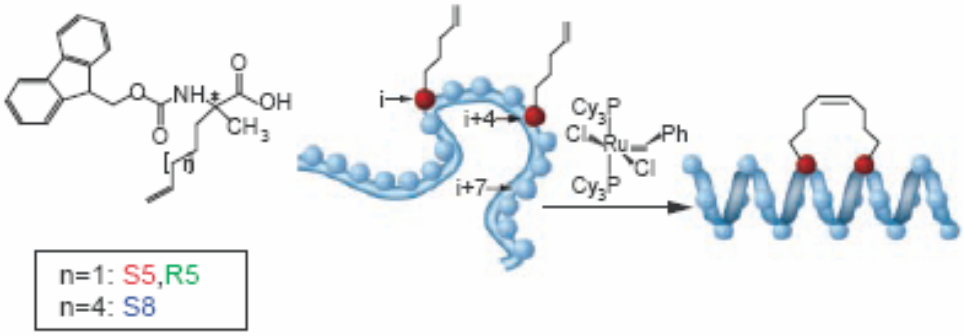
Hengartner, M. O. *Nature* **2000**, *407*, 770-776.

Bid: a link between intrinsic & extrinsic pathways



Hengartner, M. O. *Nature* **2000**, *407*, 770-776.

A hydrocarbon-stapled BH3 Helix



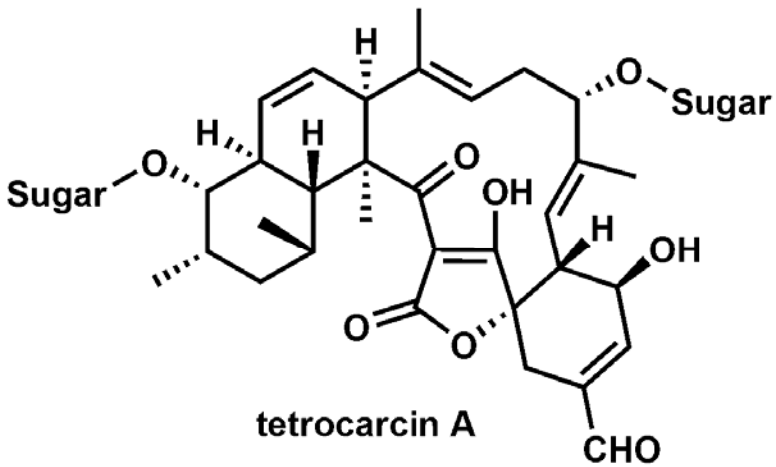
Compound	Sequence
BID BH3	EDIIRNIARHLAQVGDSN$_L$DRSIW
SAHB$_A$	EDIIRNIARHLA*VGD*N$_L$DRSIW
SAHB$_{A\,(G\rightarrow E)}$	EDIIRNIARHLA*VED*N$_L$DRSIW
SAHB$_B$	EDIIRNI*RHL*QVGDSN$_L$DRSIW
SAHB$_C$	EDIIRNIA*HLA*VGDSN$_L$DRSIW
SAHB$_D$	EDIIRNIAR*LAQVGD*N$_L$DRSIW

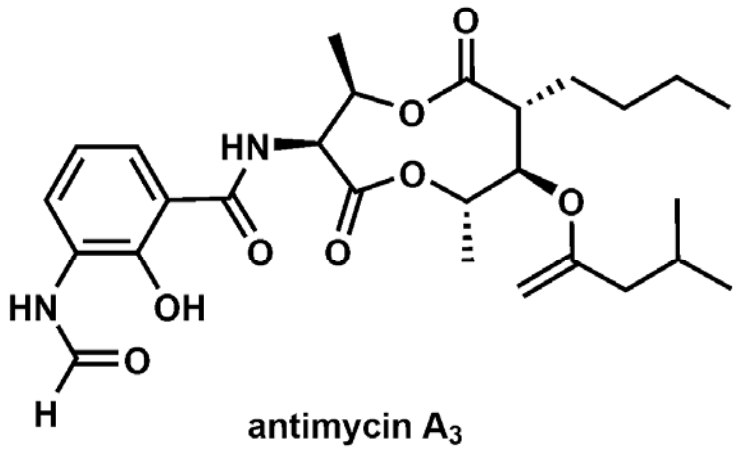
*=S5, *=R5, *=S8, N$_L$=norleu

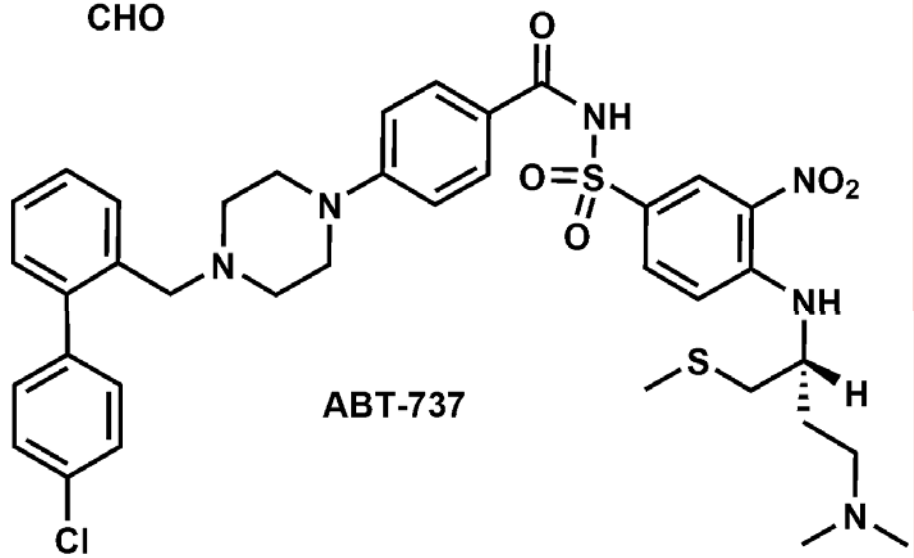
1. SAHBs (stabilized α-helix of Bcl-2 domains) are helical, protease-resistant, and cell-permeable molecules.
2. SAHBs bind with increased affinity to multidomain Bcl-2 member pockets.
3. SAHBs promote apoptosis.

Walensky, L. D.; Kung, A. L.; Escher, I.; Malia, T. J.; Barbuto, S.; Wright, R. D.; Wagner, G.; Verdine, G. L.; Korsmeyer, S. J. *Science* **2004**, *305*, 1466-1470.

Bcl-2 Inhibitors



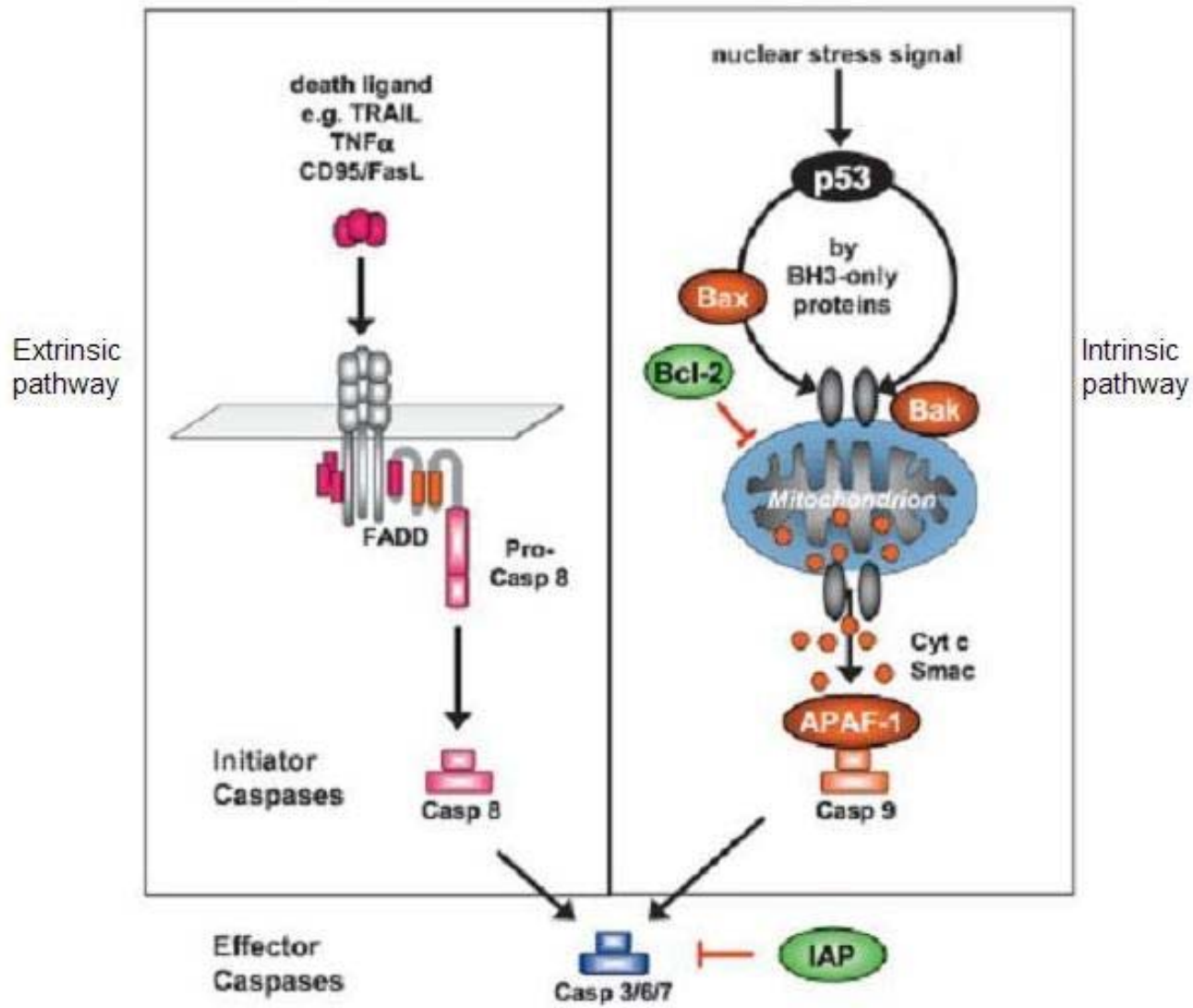




Daniel, P. T.; Koert, U.; Schuppan, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 872-893.

Oltersdorf, T.; Elmore, S. W.; Shoemaker, A. R.; Armstrong, R. C.; Augeri, d. J.; Belli, B. A.; Bruncko, M.; Deckwerth, T. L.; Dinges, J.; Hajduk, P. J; Joseph, M. K.; et. al. *Science* **2005**, *435*, 677-681.

Apoptotic pathways in mammalian cells



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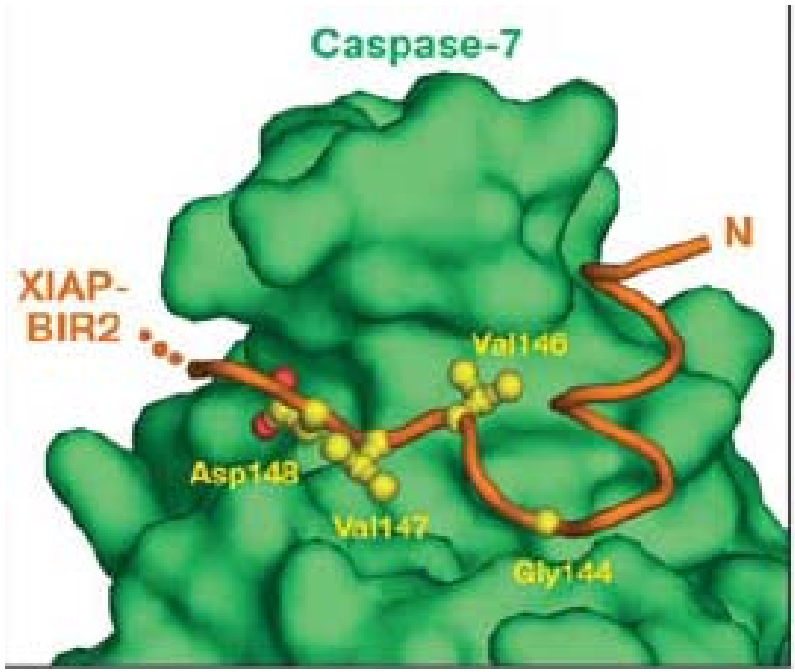
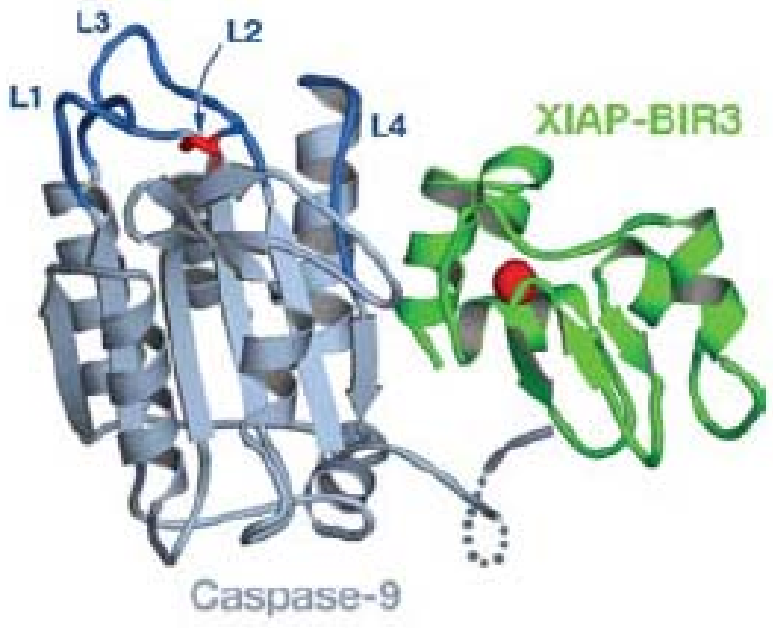
Regulators: IAP family

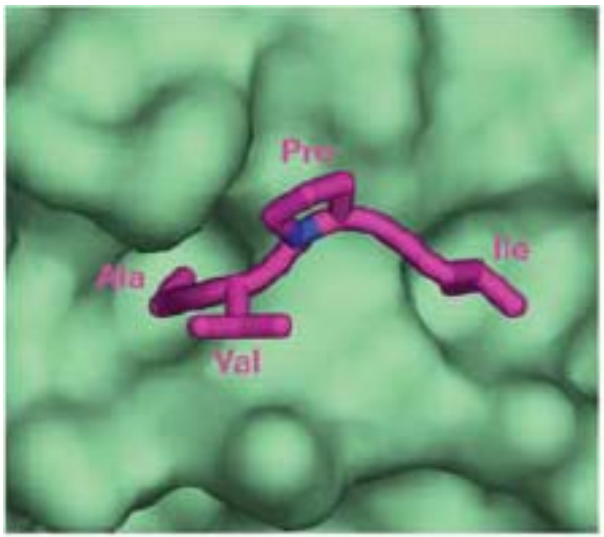




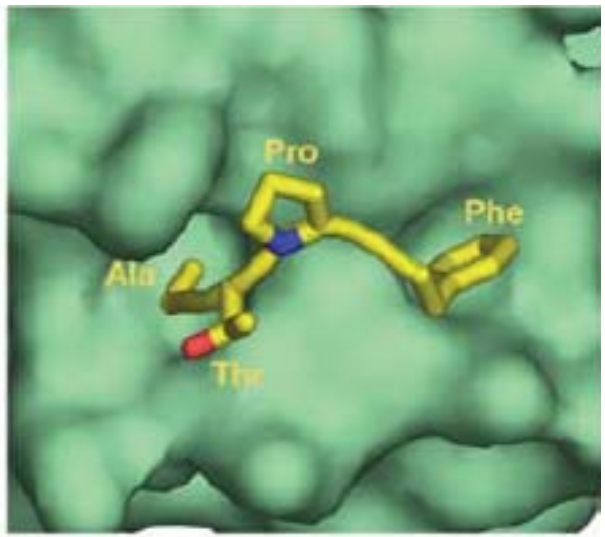
1. IAP members inhibit apoptosis by either binding to procaspases to prevent their activation or binding to caspases to inhibit their activity.
2. IAP members have at least one conserved zinc-binding BIR domain.

Yan, N.; Shi, Y. *Annu. Rev. Cell. Dev. Biol.* **2005**, *21*, 35-56.

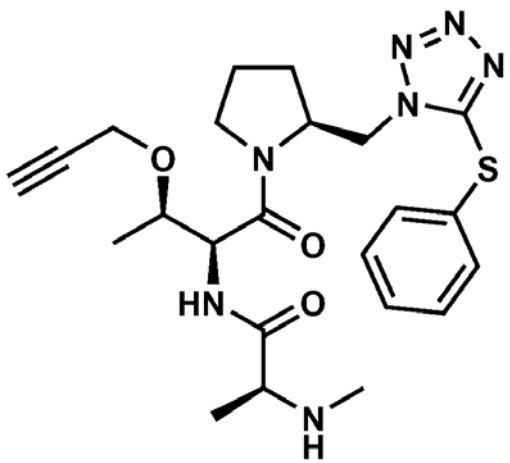
Smac-mediated removal of caspase-9 inhibition by XIAP



AVPI (Smac)
bound to BIR3 of XIAP



ATPF (Caspase-9)
bound to BIR3 of XIAP

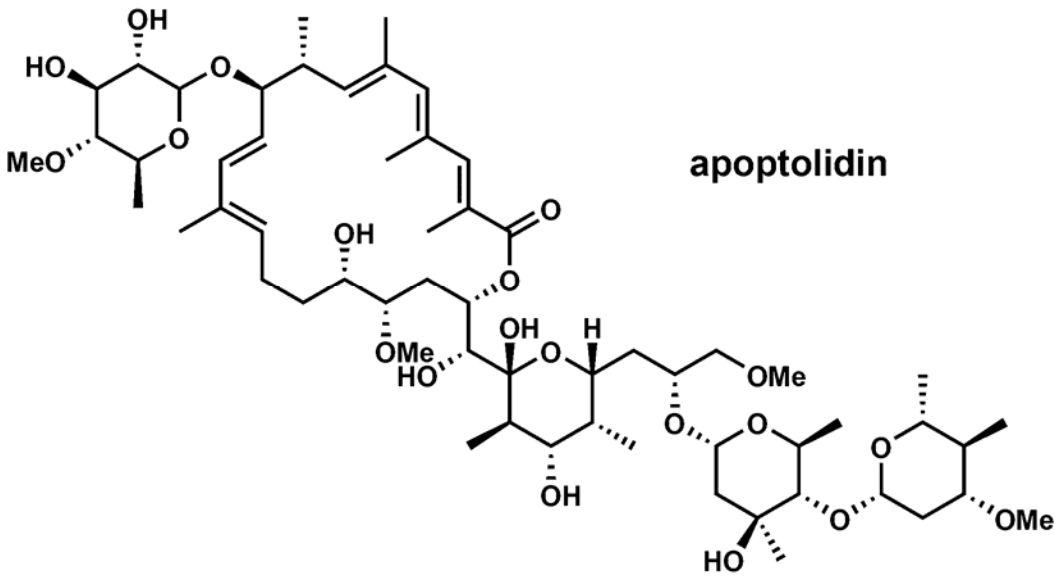


A Smac mimic

Yan, N.; Shi, Y.; *Annu. Rev. Cell. Dev. Biol.* **2005**, *21*, 35-56.

Li, L.; Thomas, R. M.; Suzuki, H.; De Brabander, J. K.; Wang, X., Harran, P. G. *Science* **2004**, *305*, 1471-1474.

Apoptolidin

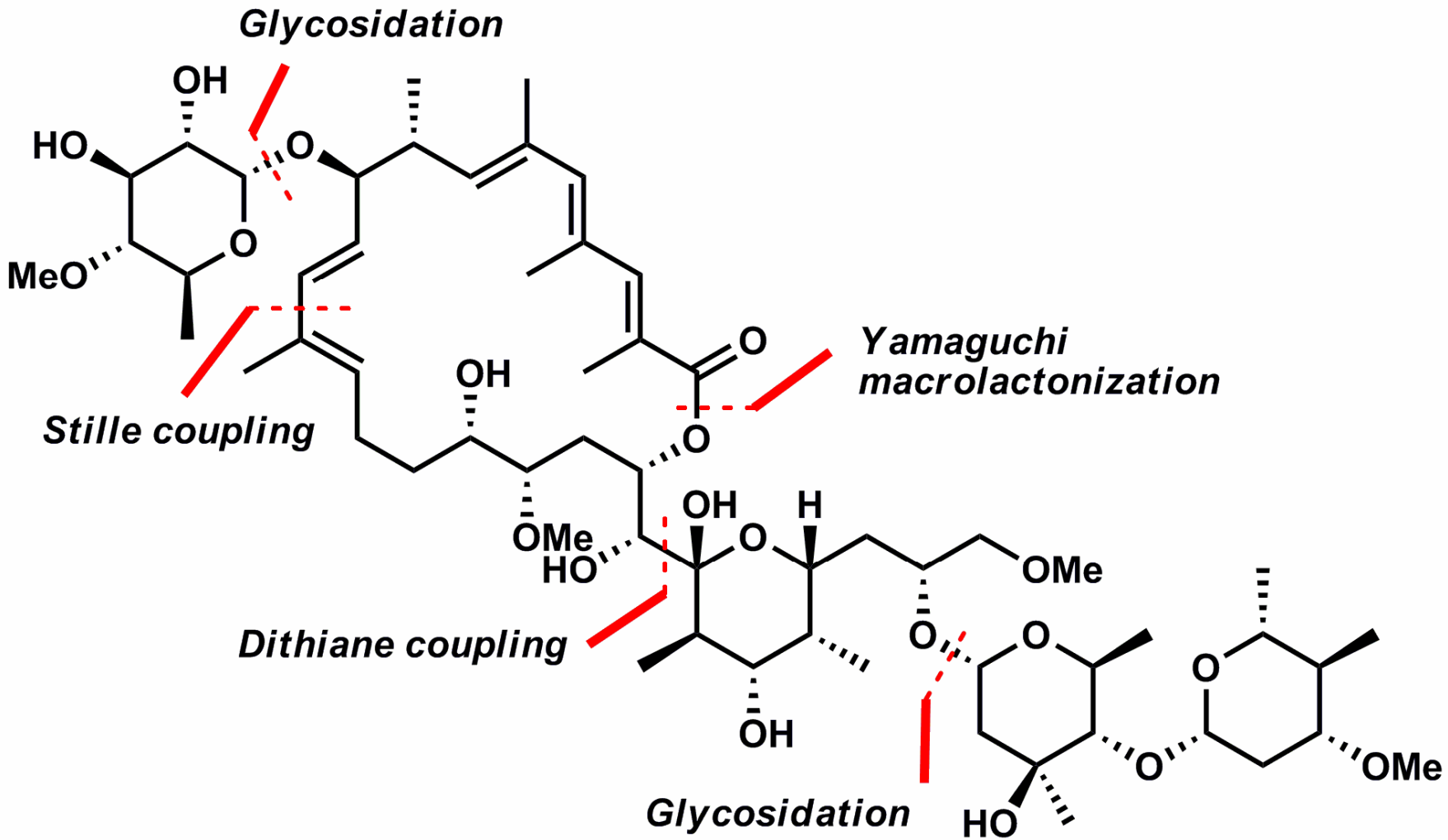


1. Apoptolidin was isolated from *Nocardiopsis* sp. in 1997.
2. Apoptolidin induces apoptosis of rat glia cells transformed with the adenovirus E1A oncogene (IC_{50} = 11 ng/mL).
3. Apoptolidin inhibits oxidative phosphorylation by targeting the mitochondrial F_0F_1 ATP synthase.

Hayakawa, Y.; Kim, J. W.; Adachi, H.; Shin-ya, K.; Seto, F. H. *J. Am. Chem. Soc.* **1998**, *120*, 3524-3525.

Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 14766-14771.

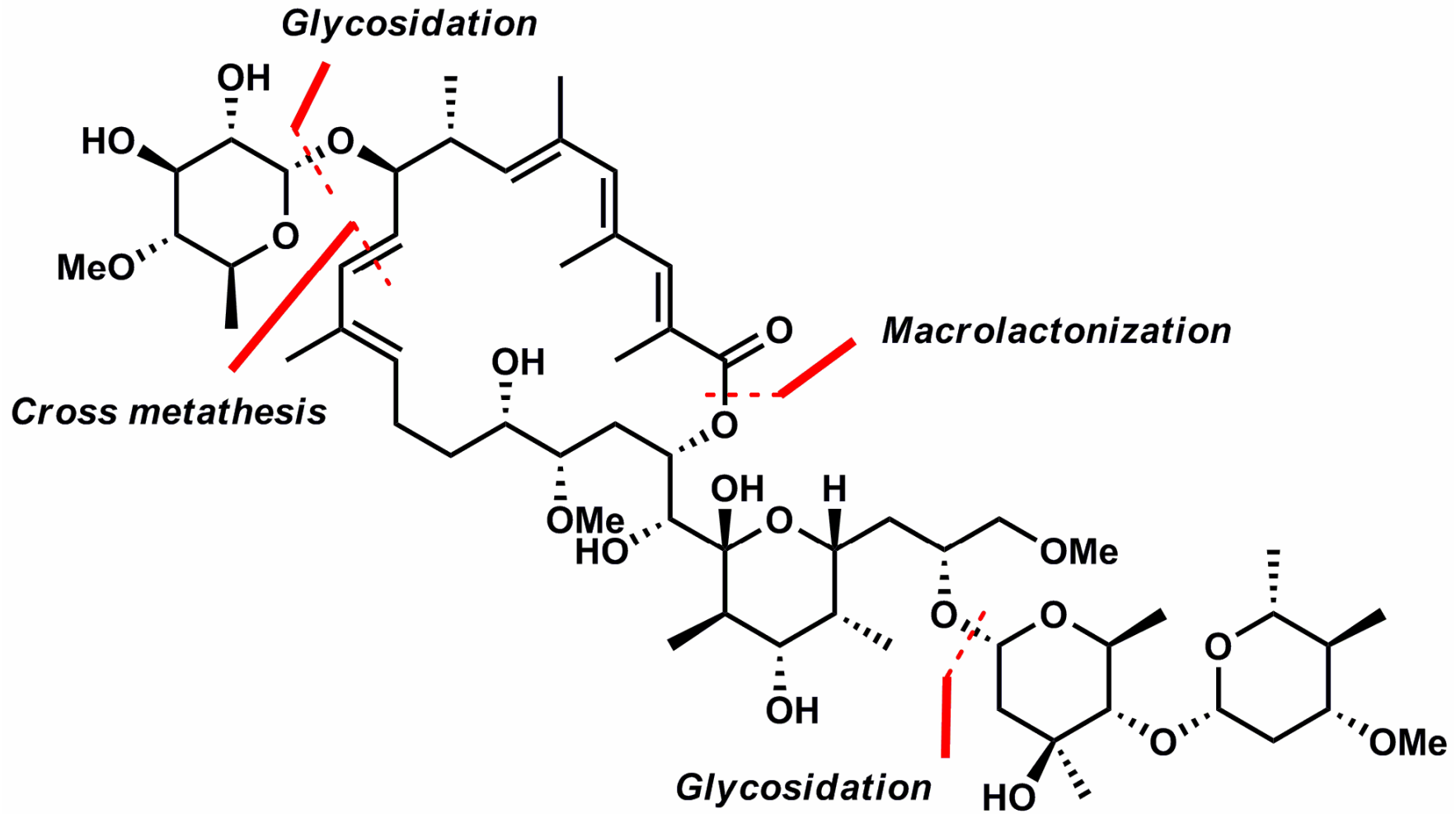
Nicolaou's retrosynthetic analysis



Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Wei, H, Weyershausen, B. *Angew. Chem. Int. Ed.* **2001**, *40*, 3849-3857.

Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y., Weyershausen, B.; Mitchell, H. J.; Wei, H.; Guntupalli, P.; Hepworth, D. Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433-15454.

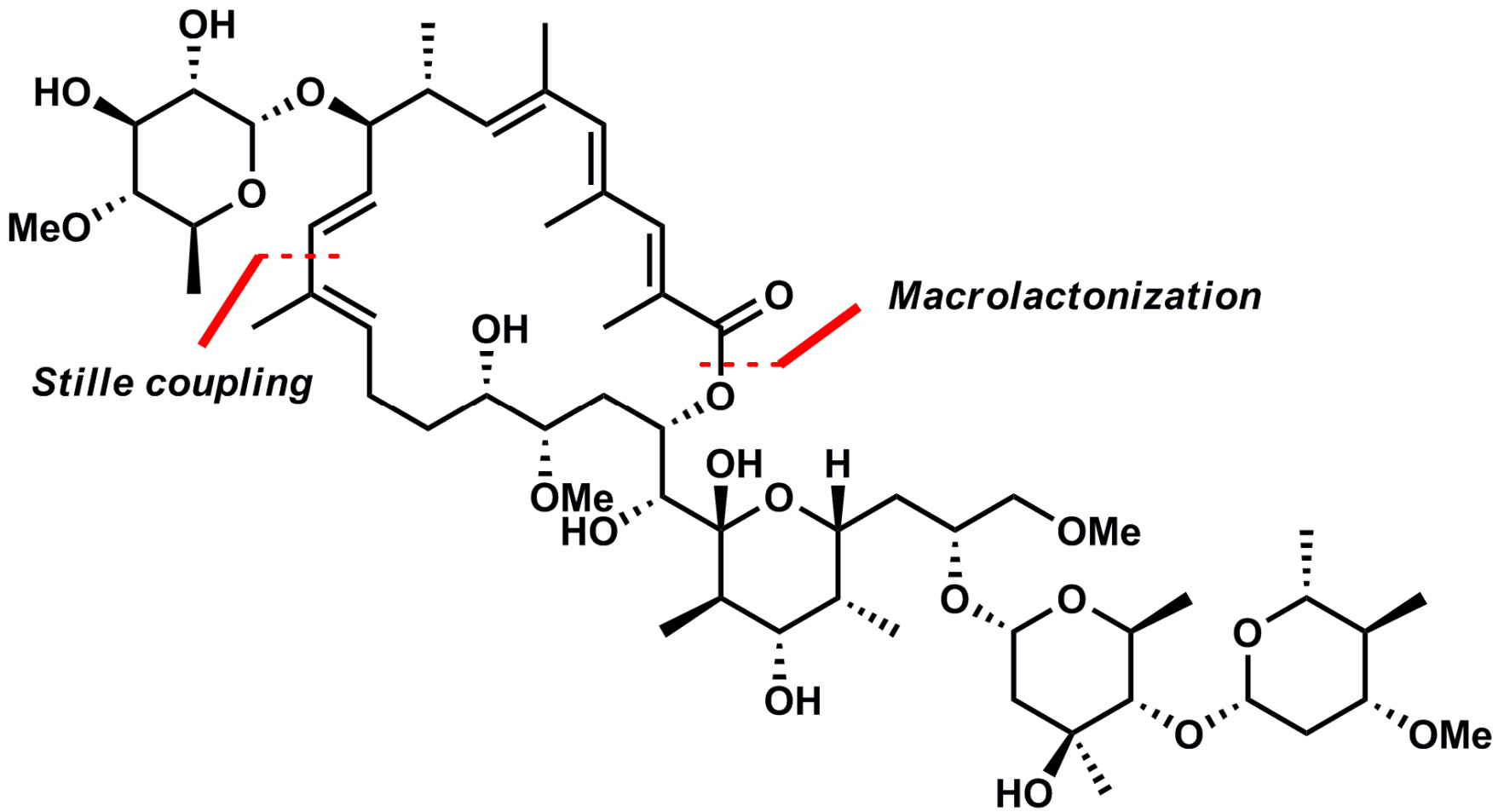
Crimmins' retrosynthetic analysis



Crimmins, M. T.; Christie, H. S.; Chaudhary, K.; Long, A. *J. Am. Chem. Soc.* **2005**, *127*, 13810-13812.

Crimmins, M. T.; Long, A. *Org. Lett.* **2005**, *7*, 4157-4160.

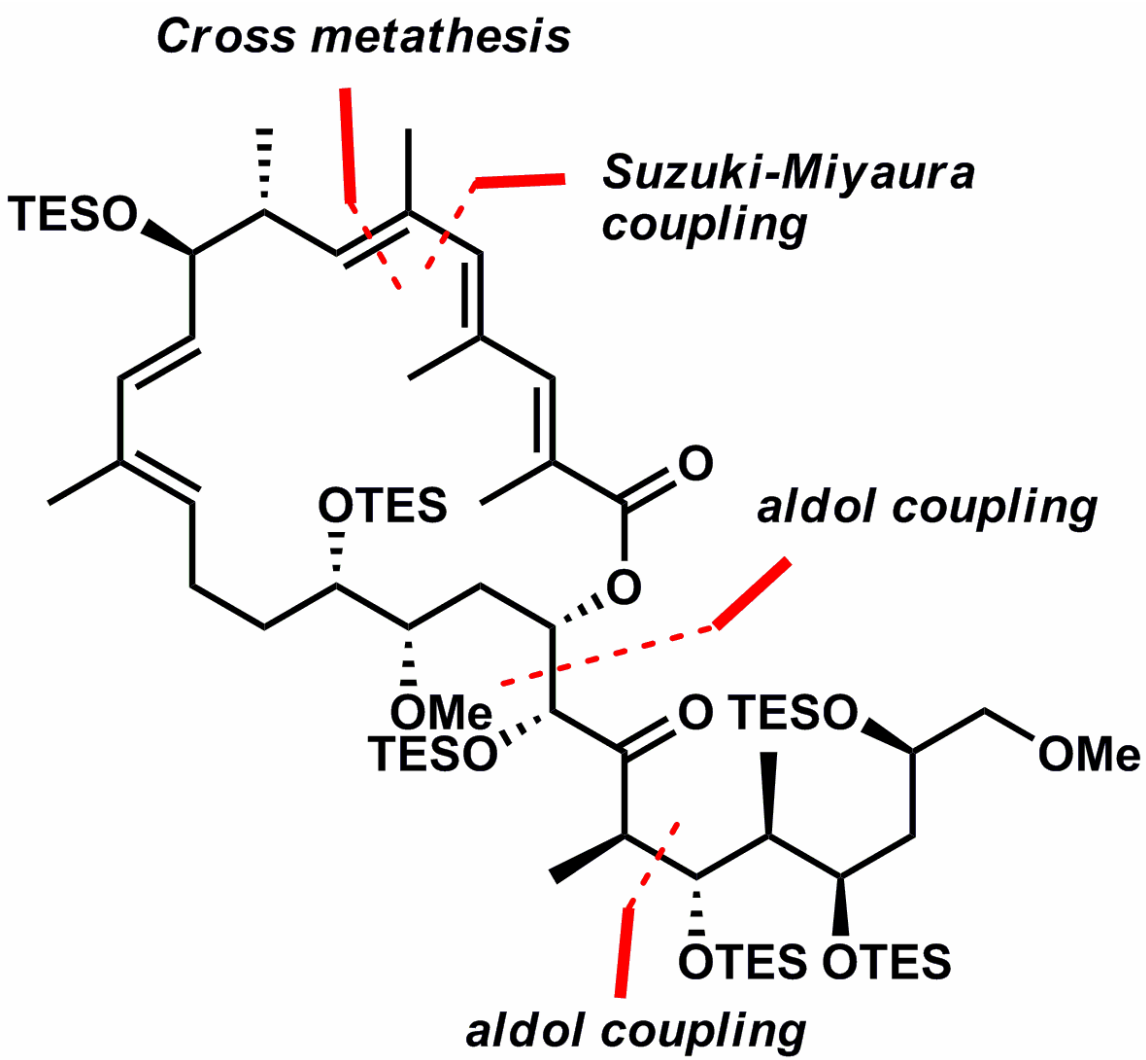
Koert's retrosynthetic analysis



Schuppan, J.; Wehlan, H.; Keiper, S.; Koert, U. *Angew. Chem. Int. Ed.* **2001**, *40*, 2063-2066.

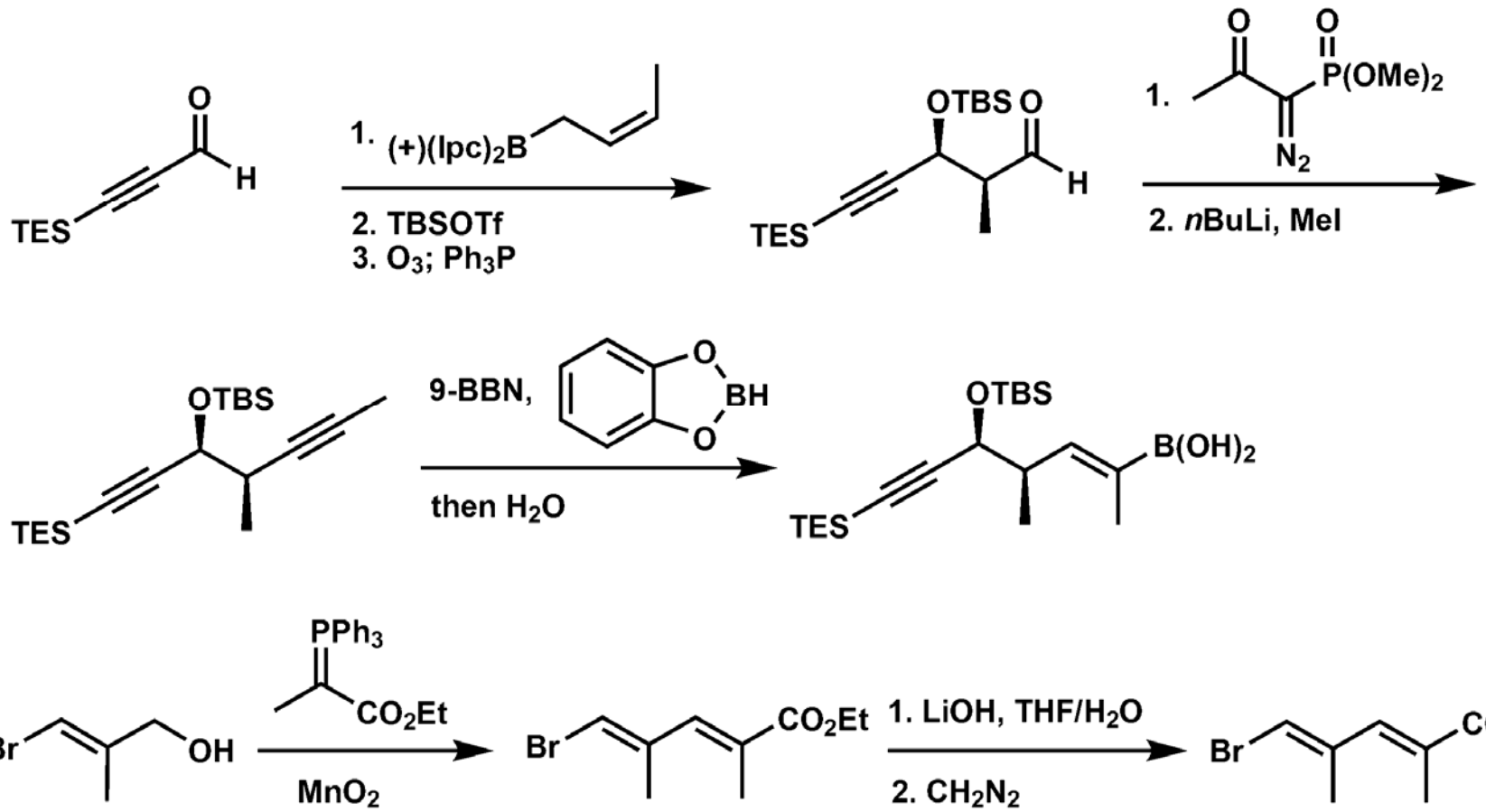
Wehlan, H.; Dauber, M.; Fernaud, M.; Schuppan, J.; Mahrwald, R.; Ziemer, B.; Garcia, M. J.; Koert, U. *Angew. Chem. Int. Ed.* **2004**, *43*, 4597-4601.

Sulokowski's retrosynthetic analysis



Wu, B.; Liu, Q.; Sulikowski, G. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 6673-6675.

Nicolaou's synthesis of apoptolidin



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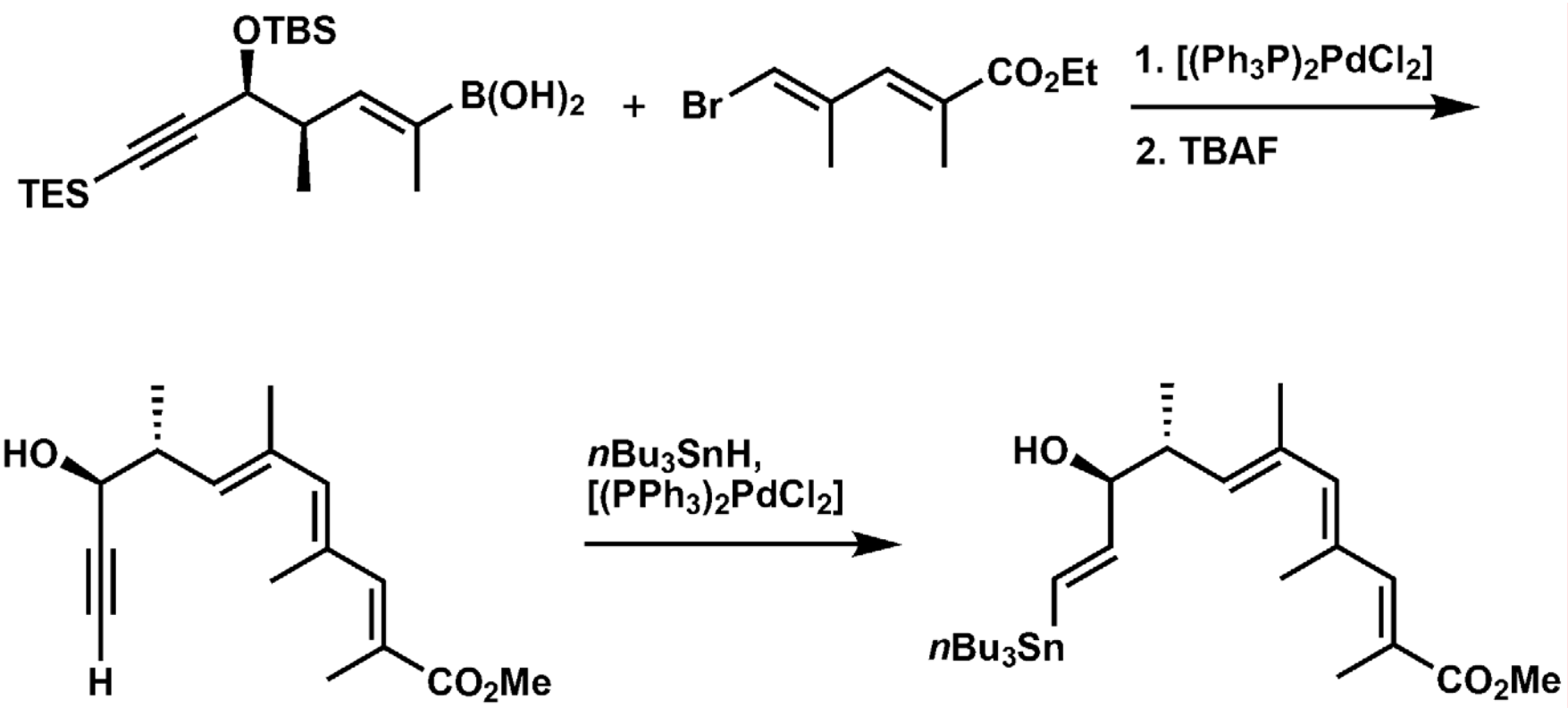

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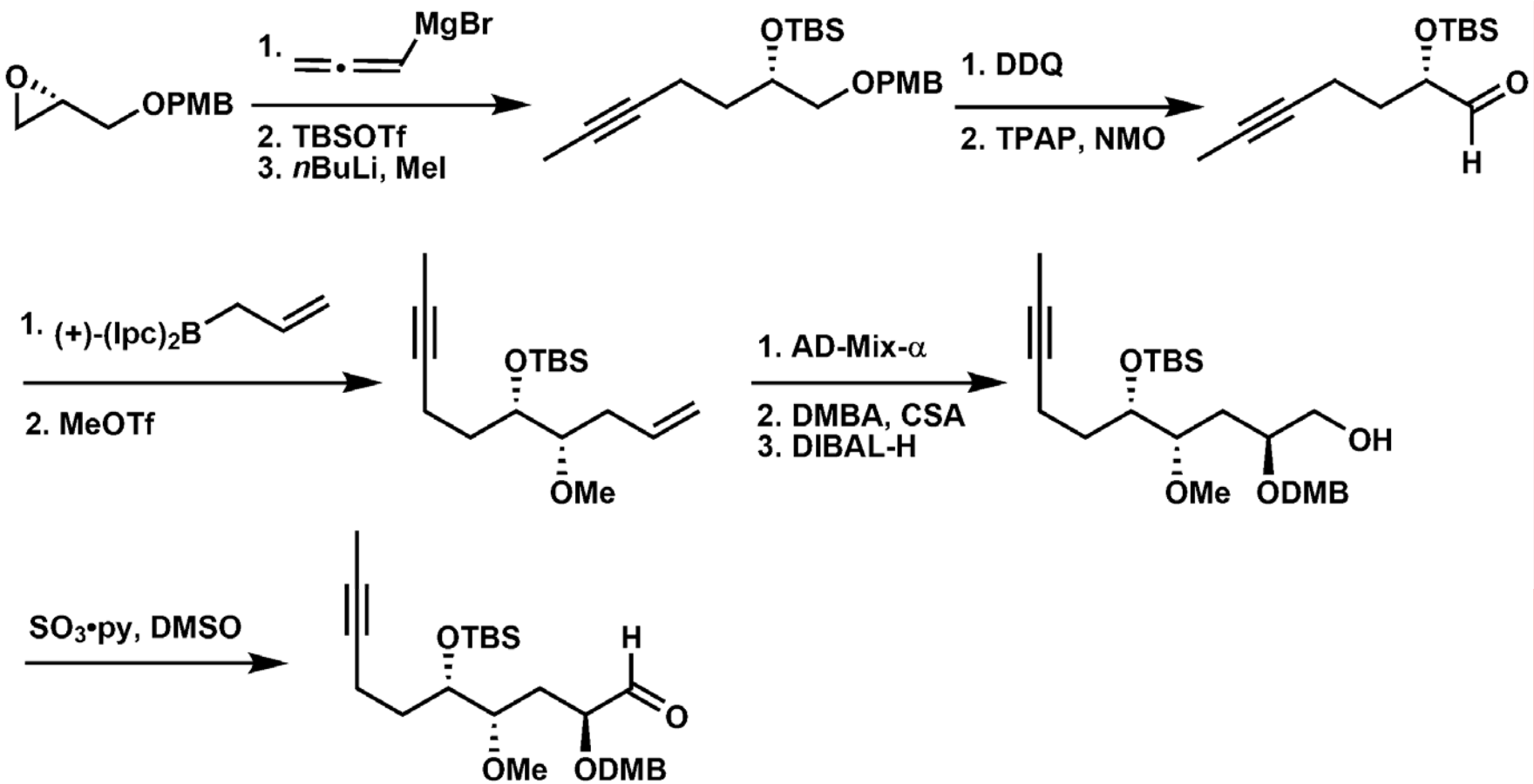

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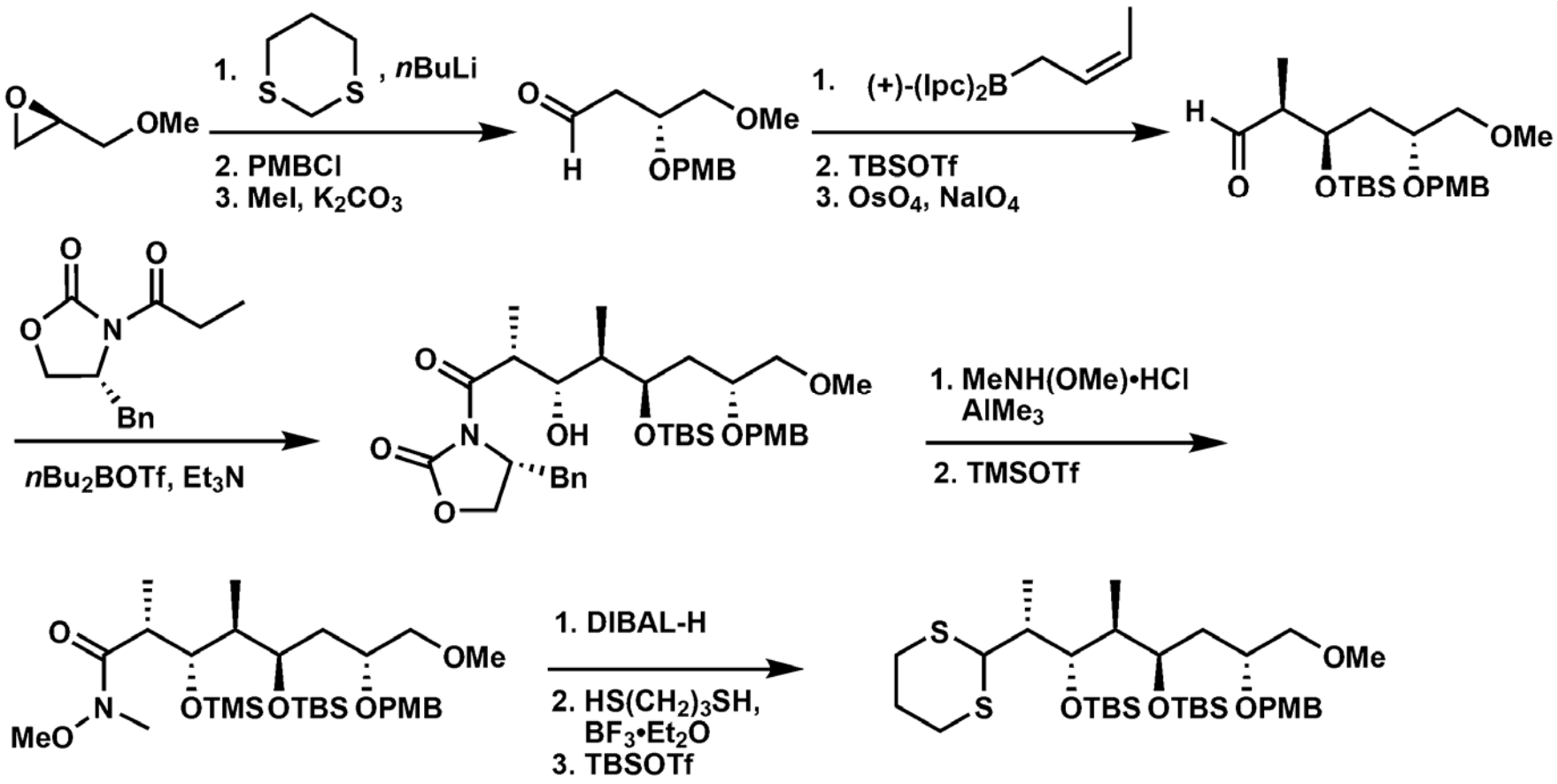

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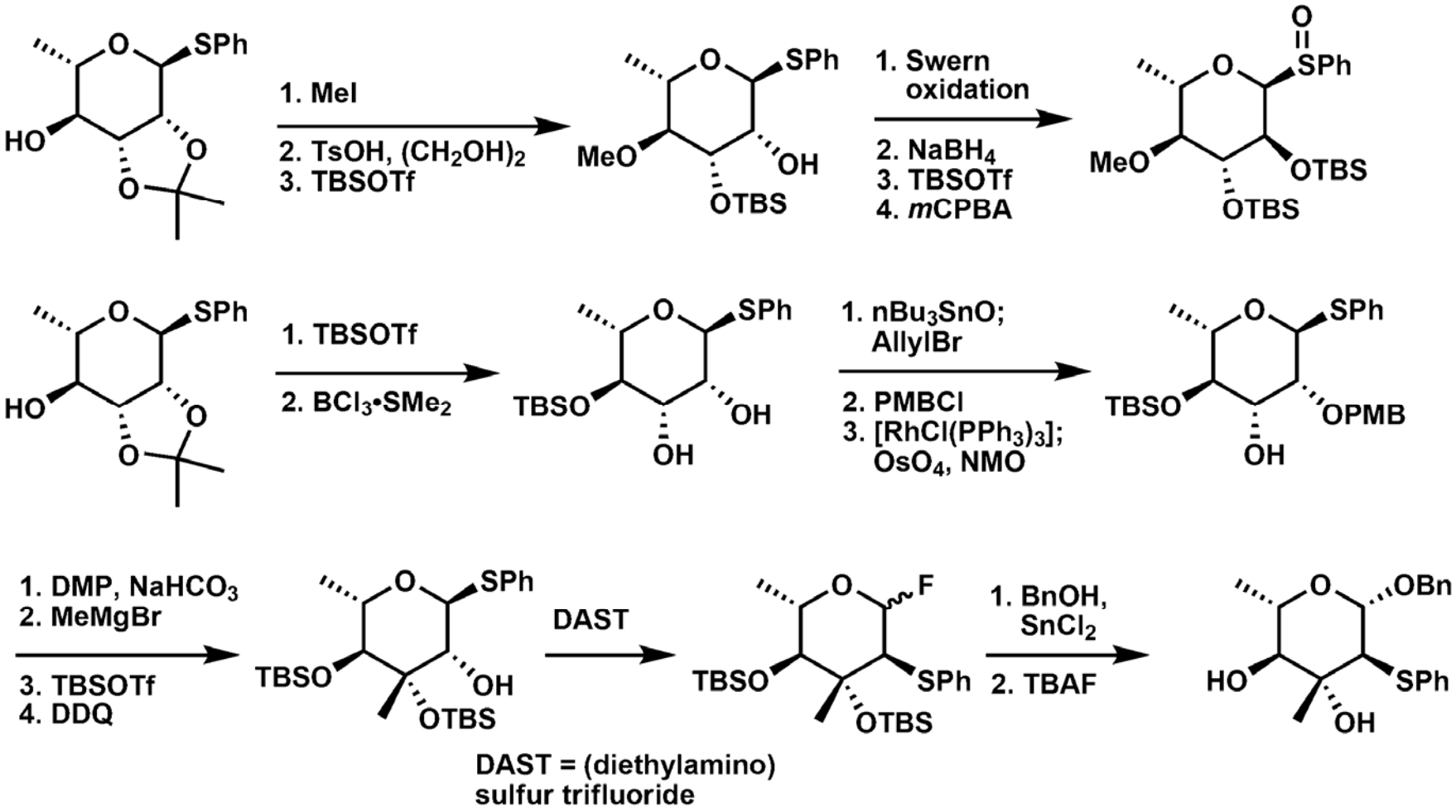

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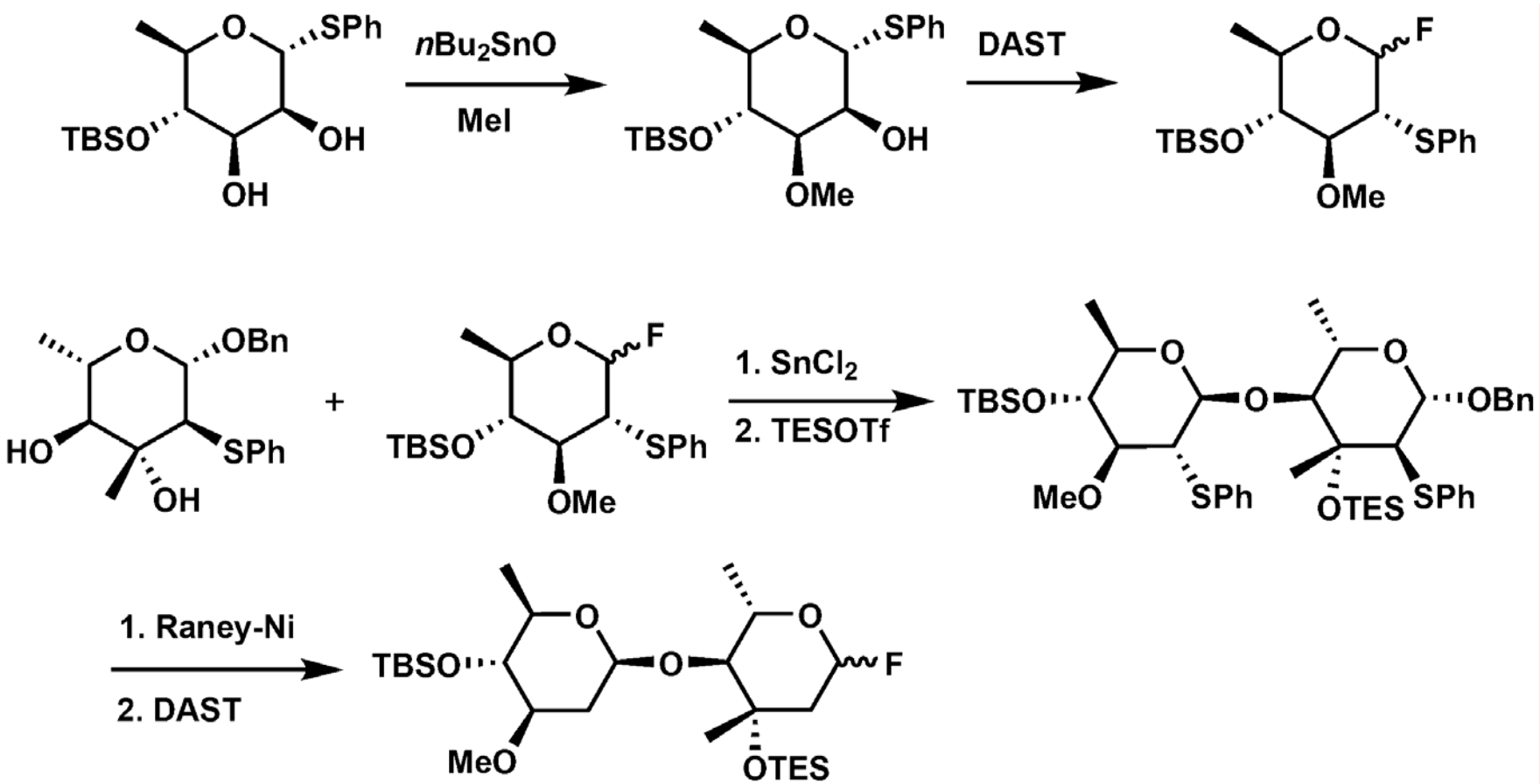
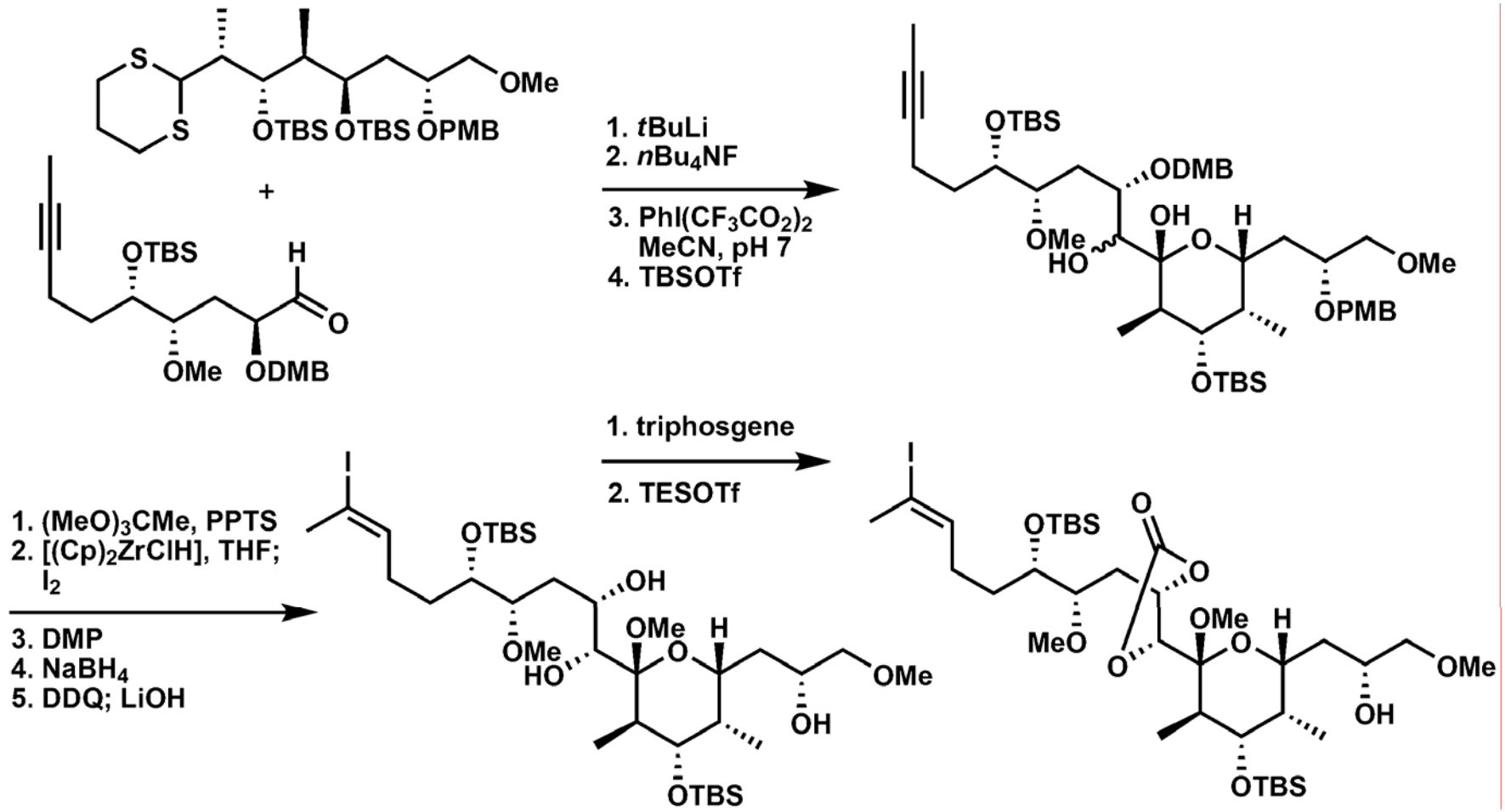


Nicolaou's synthesis of apoptolidin



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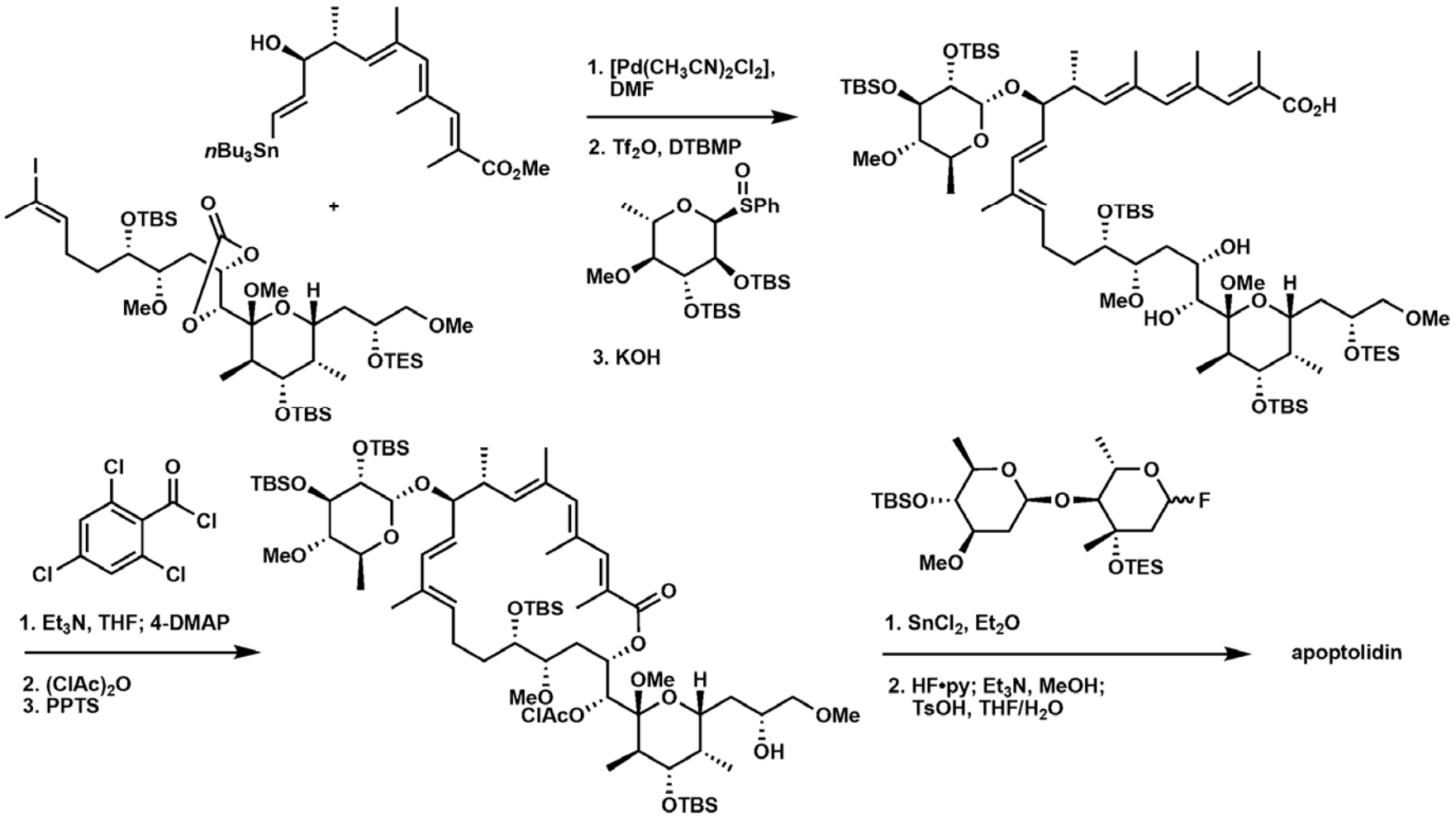
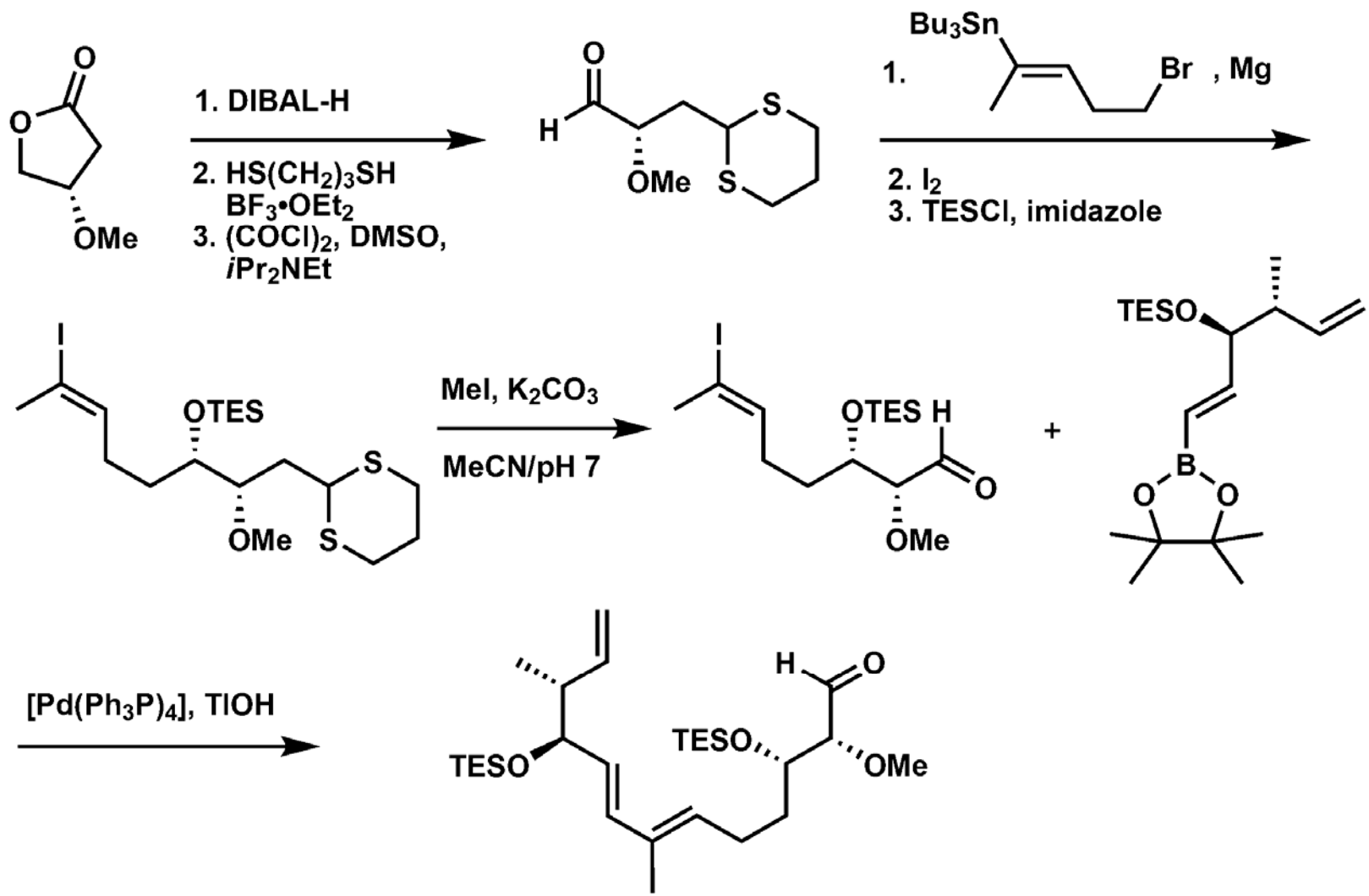
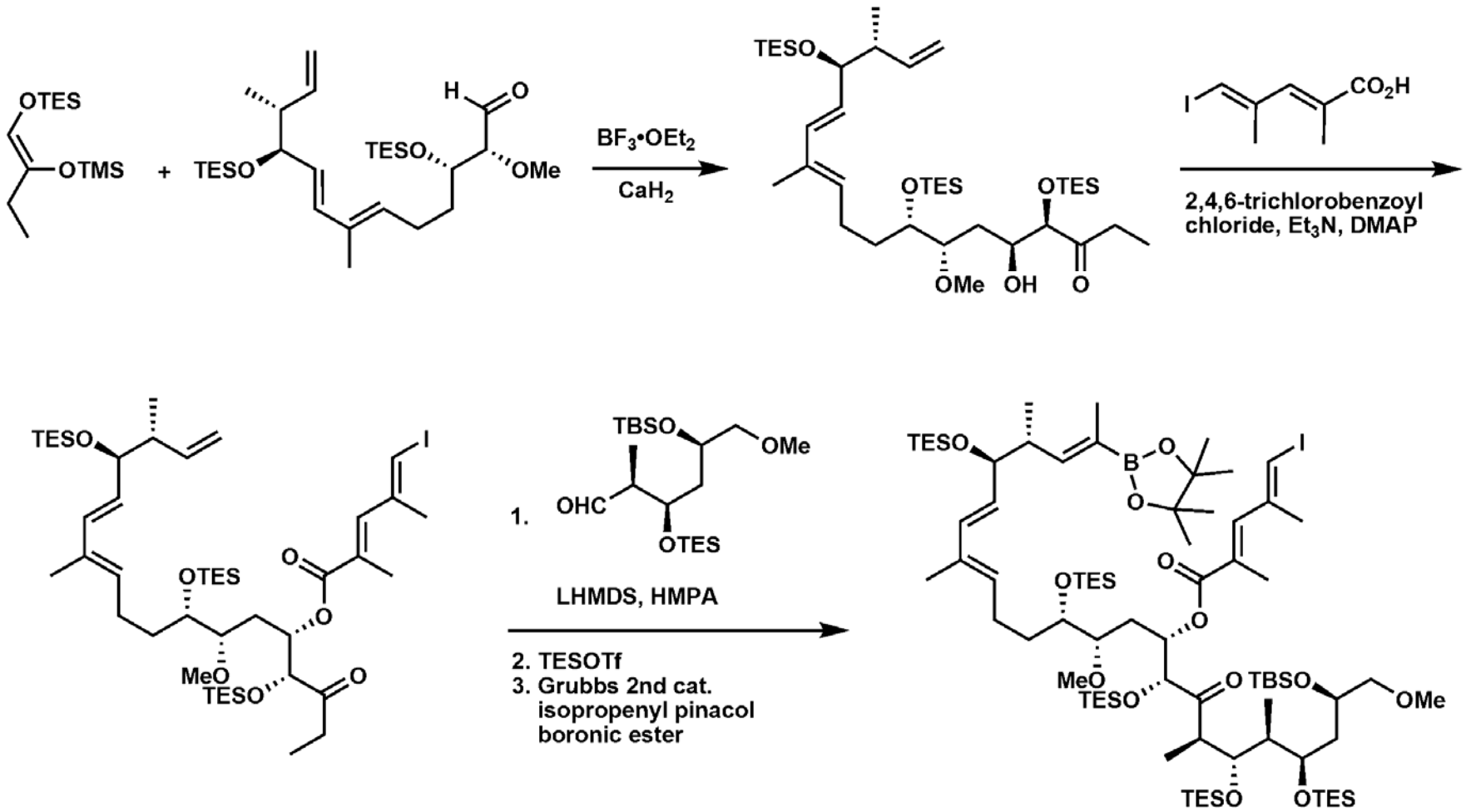


Sulikowski's synthesis of apoptolidinone



Sulikowski's synthesis of apoptolidinone



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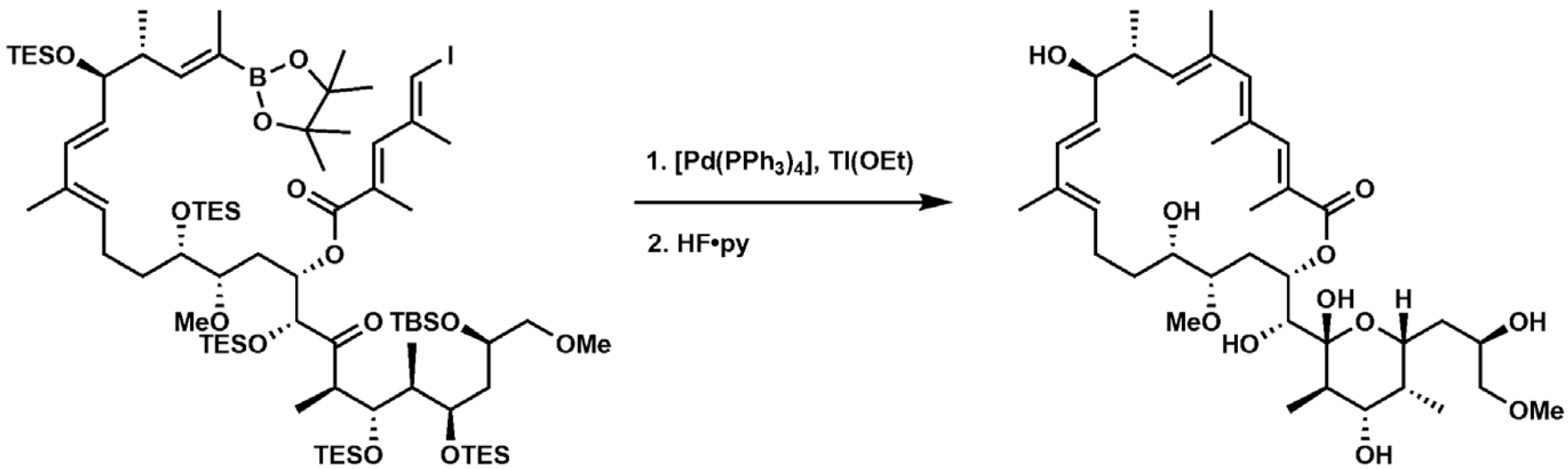
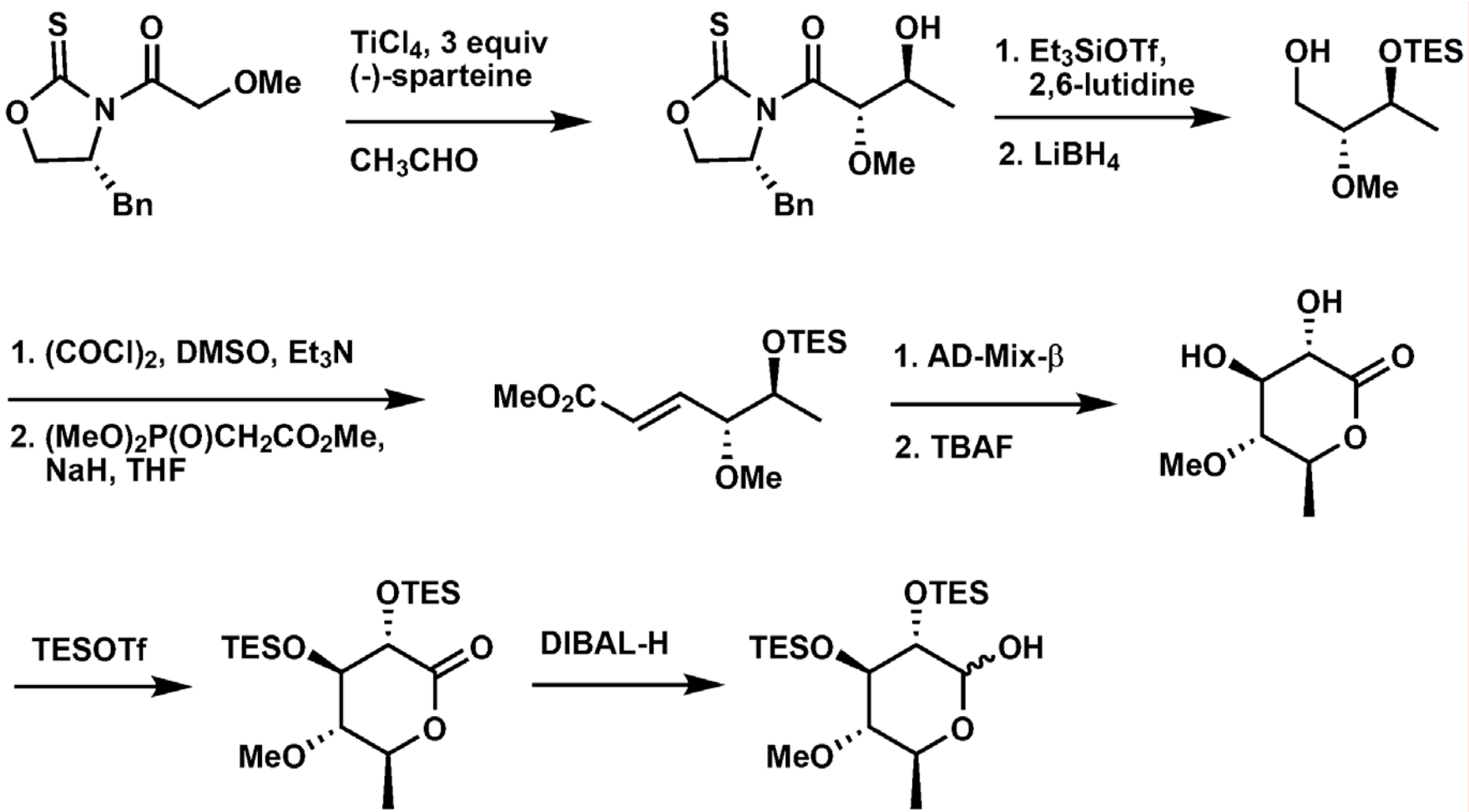
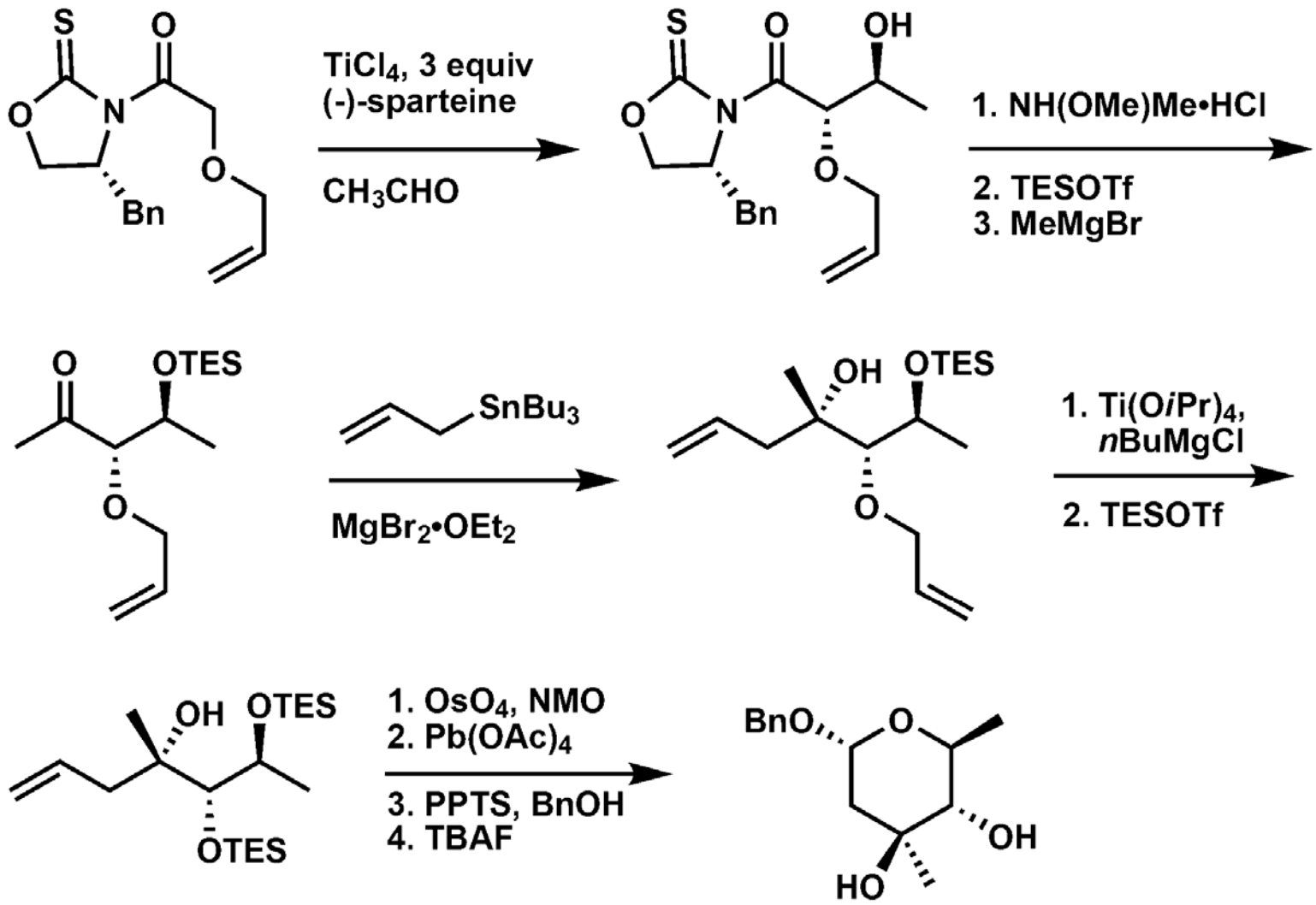


Crimmins' synthesis of apoptolidin sugars



Crimmins' synthesis of apoptolidin sugars



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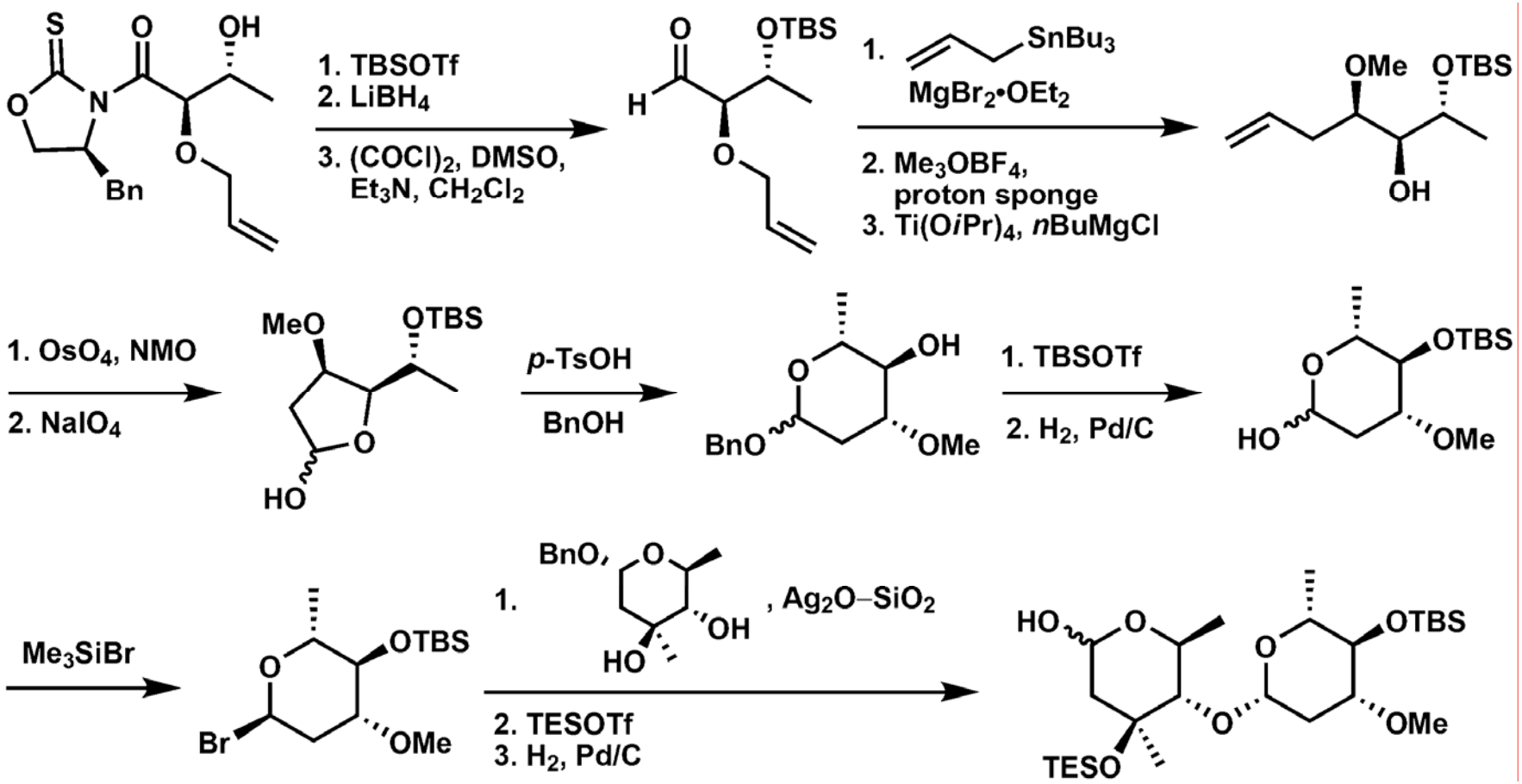
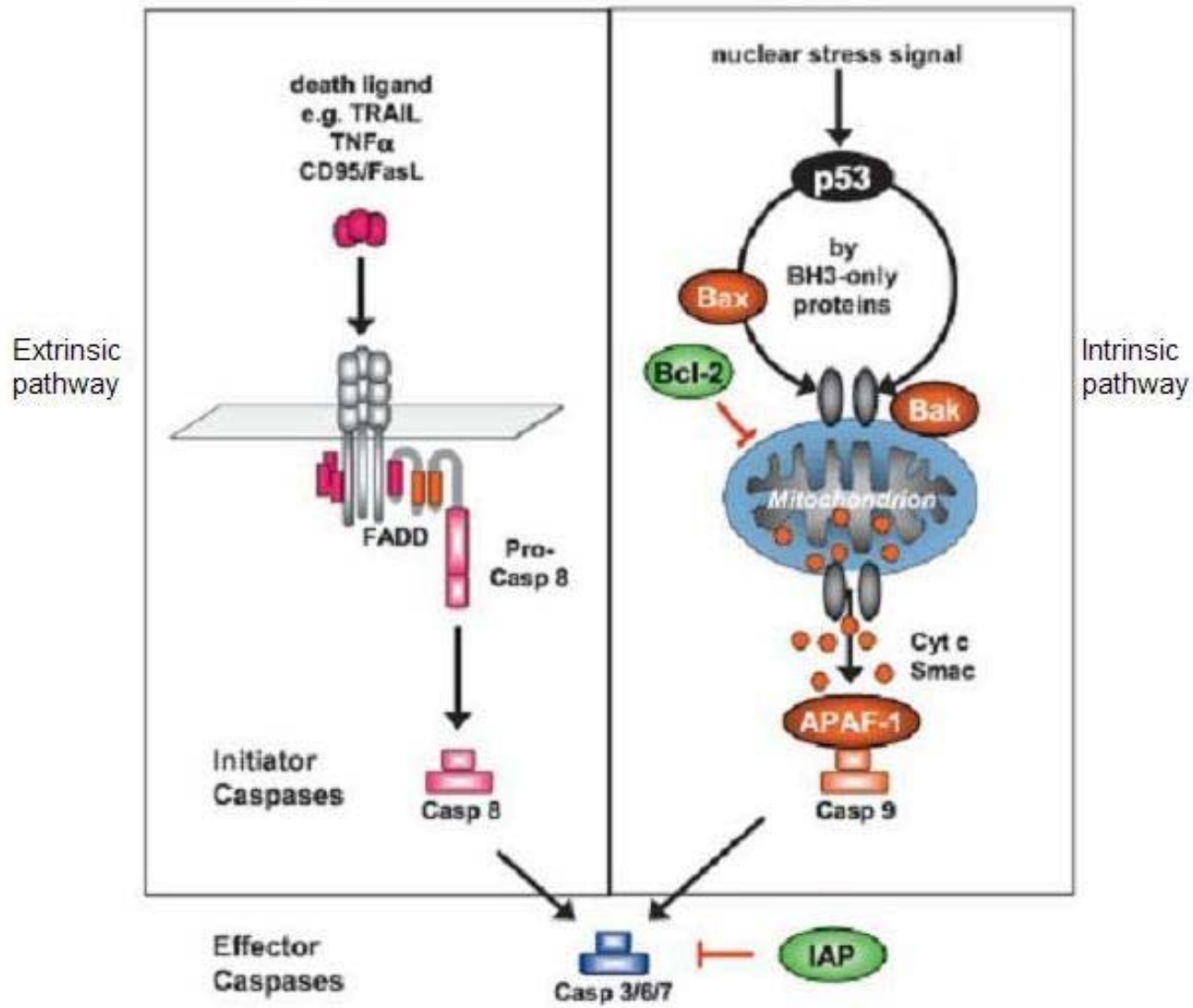


Apoptotic pathways in mammalian cells



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