

Ready to start planning your care? Call us at [800-525-2225](tel:800-525-2225) to make an appointment.

×



Memorial Sloan Kettering
Cancer Center

[About Us](#)
[Sloan Kettering Institute](#)
[The Derek Tan Lab](#)

[Research](#)

Ring Expansion Approaches to Macrocycle Synthesis

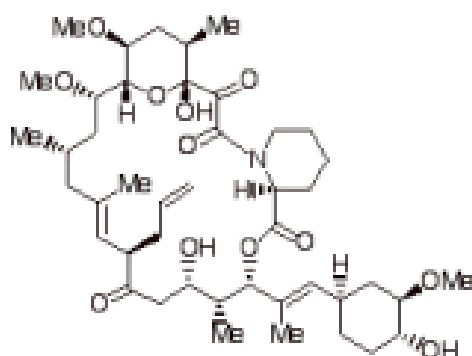
[Education & Training](#)

[News & Events](#)

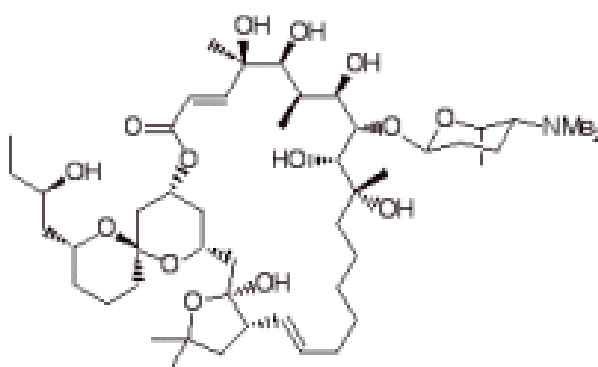
Biologically Active Macrocyclic Natural Products

Cyclization provides additional conformational restriction

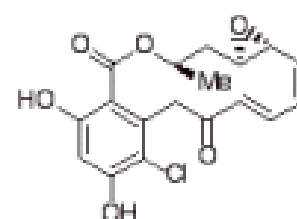
[Open Positions](#)



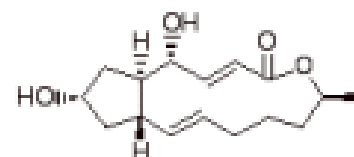
FK506



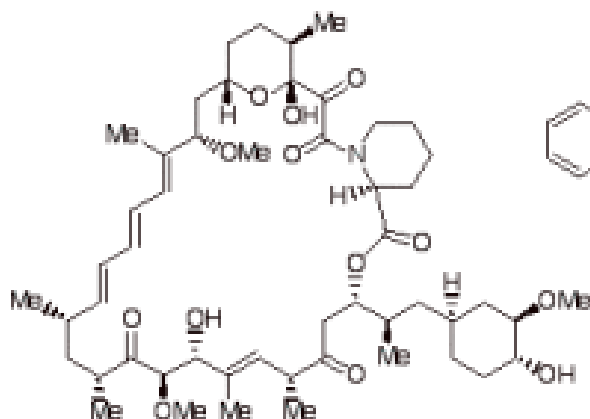
ossamycin



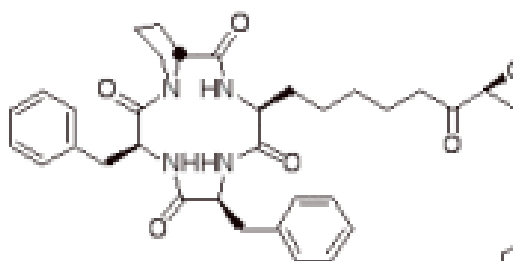
radicicol



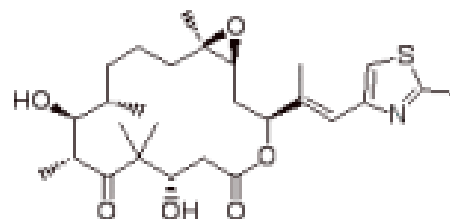
brefeldin A



rapamycin



trapoxin



epothilone B

Macrocycles are an attractive class of molecules for use in biological screening. While smaller molecules have been used to bind in enzyme active sites and other protein pockets, larger molecules, such as macrocycles, may be useful for affecting protein-protein interactions involving large surface areas.

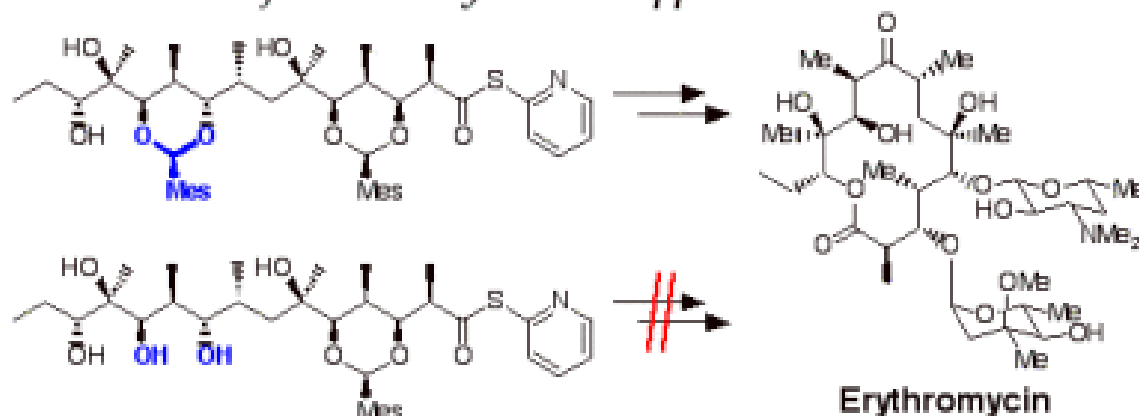
Furthermore, the potential diversity of overall 3D structures present in a library of macrocycles is enhanced by the fact that

conformation can be altered by strategic changes in substituent patterns and stereochemistry.

Target- and Diversity-Oriented Synthesis of Macrocycles

Limitations of the macrocyclization approach

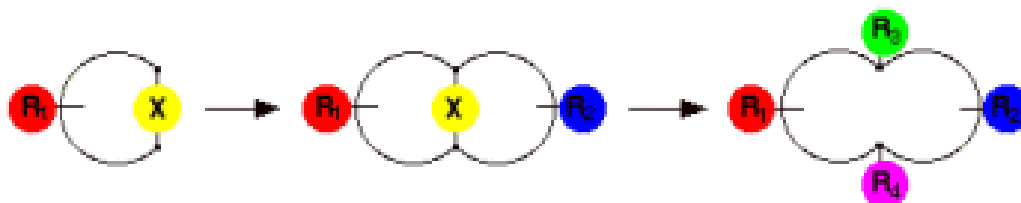
Target-oriented synthesis of macrocycles



Macrocyclization: specific reaction conditions, variable yields, sensitive to substituent patterns

• Woodward, R. B. *et al.* *J. Am. Chem. Soc.* **1981**, *103*, 3213-3215.

Diversity-oriented synthesis of macrocycles



Ring expansion: less sensitive to substituent patterns → general reaction conditions, high efficiency

Bond-exchanging ring expansion: couple building blocks concurrently → increased efficiency for D.O.S.

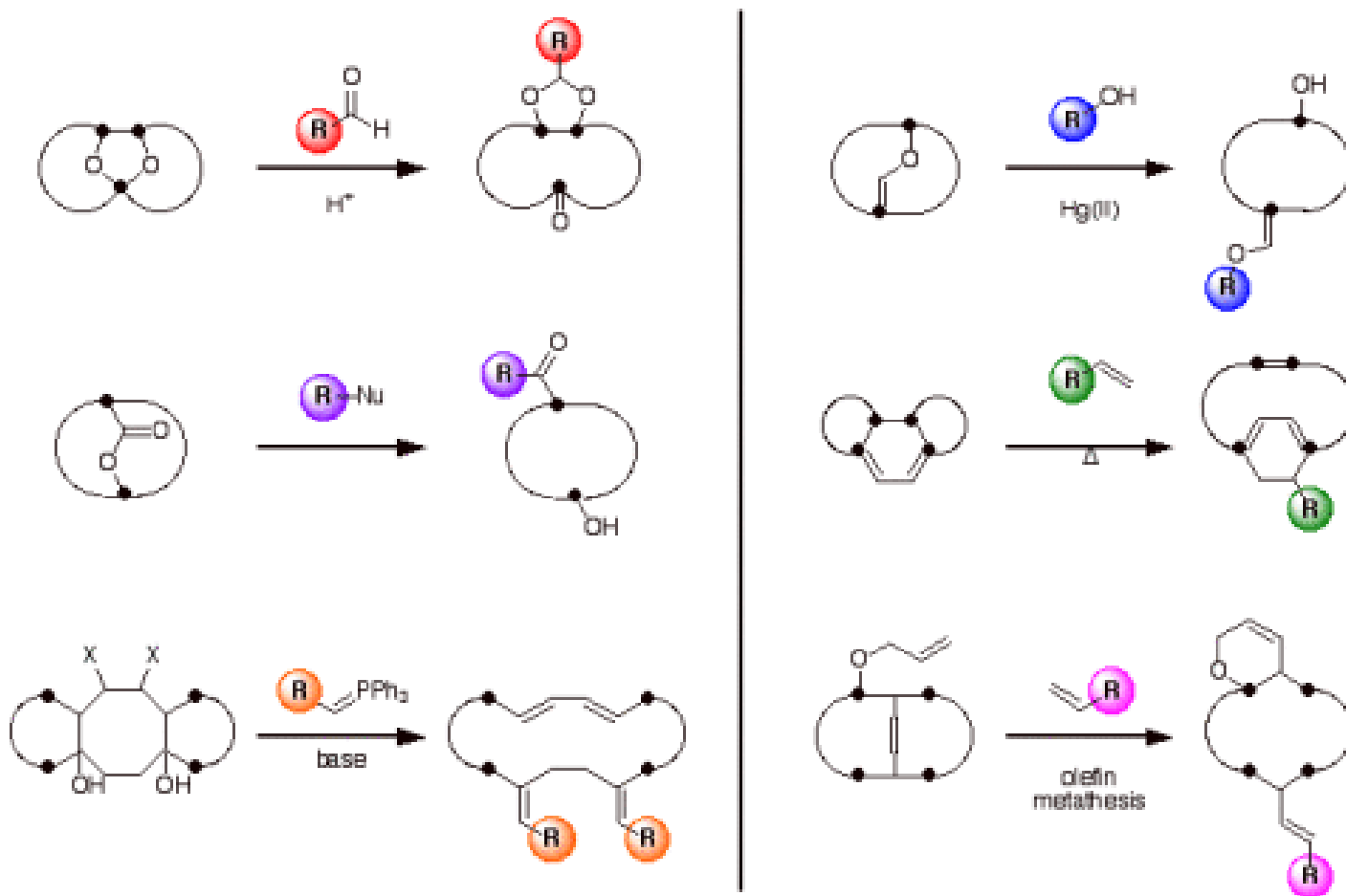
• Macrocyclization reviewed in: Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95-102.

• Ring expansion reviewed in: Stach, H.; Hesse, M. *Tetrahedron*, **1988**, *44*, 1573-1590.

Target-oriented synthesis of macrocyclic natural products is dominated by macrocyclization strategies that often require ad hoc development of reaction conditions, proceed in moderate yields, and are sensitive to ring substituent patterns. Because diversity-oriented synthesis requires efficient reactions that are general for a wide variety of substrates, ring expansion is an attractive alternative strategy for the synthesis of macrocycle and medium ring libraries.

Generalized Examples of Bond Exchanging Ring Expansions

Concurrent coupling reactions increase efficiency for diversity-oriented synthesis



The efficiency of this approach for diversity-oriented syntheses can be increased if the bond-cleaving ring expansion is performed in conjunction with bond-forming building block coupling in a “bond-exchanging” reaction. Examples of bond-exchanging reactions include nucleophilic substitution, carbonyl addition-elimination, transesterification, olefin metathesis, and tandem cycloaddition-cycloreversion. We are exploring a number of bond-exchanging ring expansion routes to macrocycles for application to diversity-oriented synthesis.

Publications

41. Principal component analysis as a tool for library design: A case study investigating natural products, brand-name drugs, natural product-like libraries, and drug-like libraries.

Wenderski, T. A.; Stratton, C. F.; Bauer, R. A.; Kopp, F.; Tan, D. S.* *Methods Mol. Biol.* 2015, 1263, 225–242.

[[Abstract](#) | [PubMed](#) | [PMC](#)]

[Overview](#)

[Leadership](#)

[Administration](#)

[History](#)

[Contact Us](#)



▾ Research

[Overview](#)

[Research programs](#)

[Research labs](#)

[Core facilities & resources](#)

▾ Education & Training

[Overview](#)

[Postdoctoral training](#)

[Gerstner Sloan Kettering Graduate School](#)

[Joint graduate programs](#)

[Programs for college & high school students](#)

▾ News & Events

[Overview](#)

[Seminars & events](#)

▾ Open Positions

[Overview](#)

[Faculty positions](#)

[Postdoctoral positions](#)

[Communication preferences](#)

[Cookie preferences](#)

[Legal disclaimer](#)

[Accessibility Statement](#)

[Privacy policy](#)

[Public notices](#)

