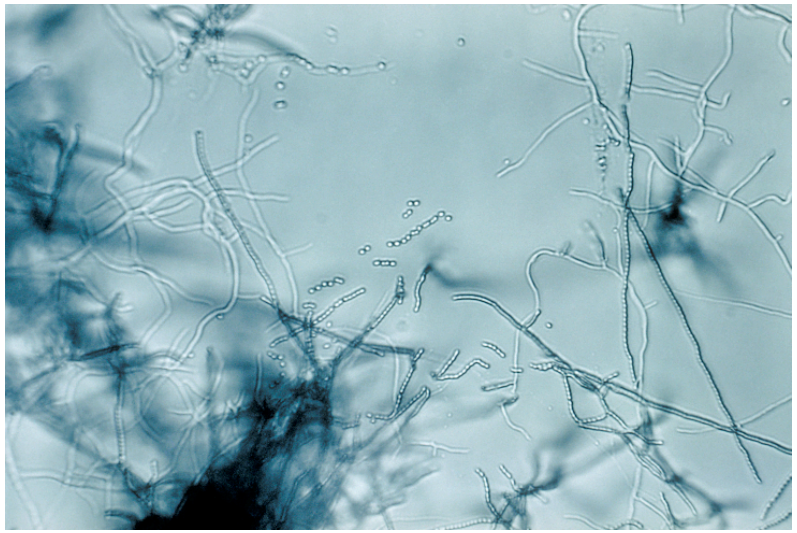
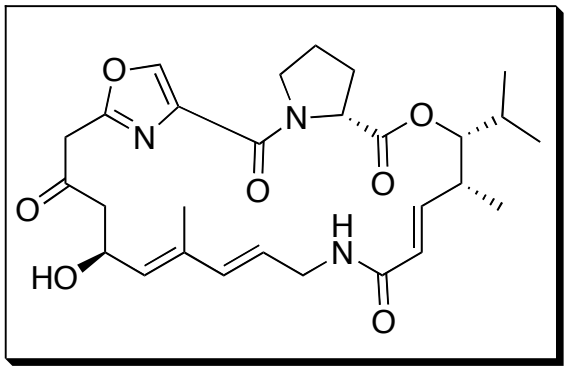
Total Synthesis of (−)-Virginiamycin M_2

Jie Wu and James S. Panek, *Angewandte Chemie International Edition,* **2010,** *49,* 6165-6168

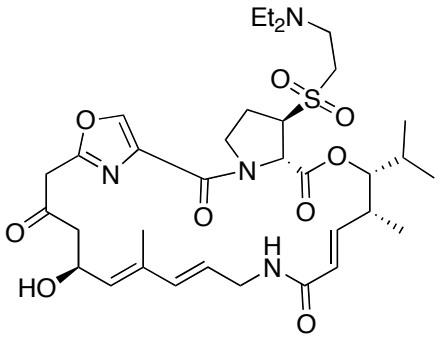


Obtained from the CDC Public Health Image Library.
Image credit: CDC/Dr. David Berd (PHIL #2983), 1972.

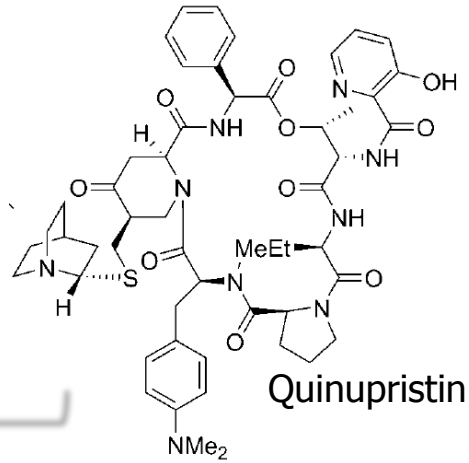


Melissa Sprachman
Current Literature
September 4, 2010

Antibiotics from *Streptomyces*



Dalfopristin (Type A)



Quinupristin (Type B)

Synercid

Combination therapy against *staphylococci* and vancomycin-resistant *Enterococcus faecium,* administered intravenously, approved in 1999.

-Type A and Type B streptogramins act in synergy; the *in vitro* activity of the mixture is at least 10 times greater than the sum of the individual activities.

-Both Type A and Type B streptogramins inhibit protein synthesis via action on the peptidyltransferase domain of 50S ribosomal subunits.

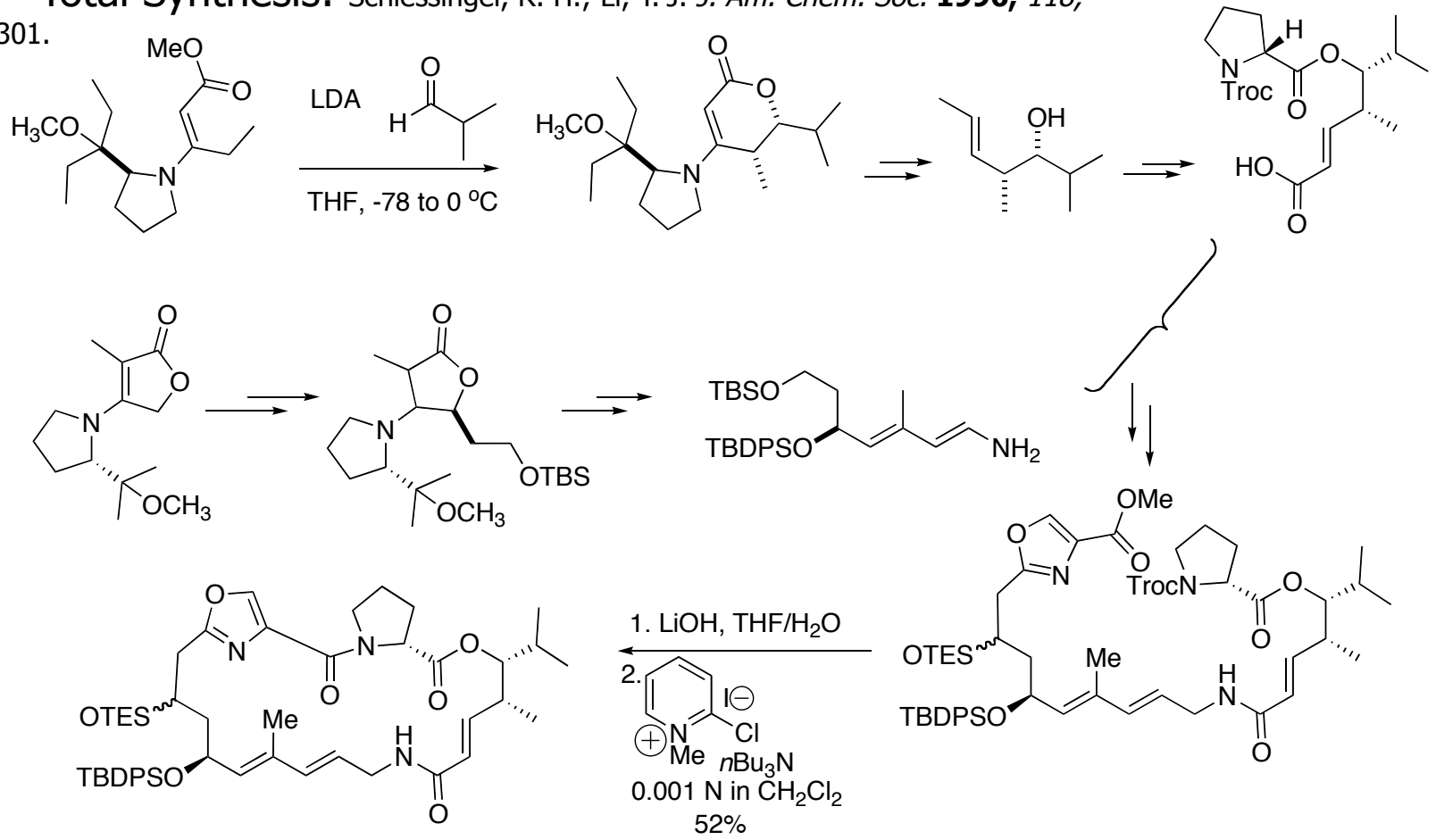
-The compounds bind specifically to non-overlapping regions of the ribosome in a 1:1 stoichiometry.

-Binding of Type A antibiotics increases the binding affinity for Type B antibiotics, but the opposite scenario does not occur.

Barrière, J. C.; Bouanchaud, D.; Desnoottes, J. F.; Paris, J. M. *Expert Opin. Invest. Drugs* **1994,** *3,* 115-131.

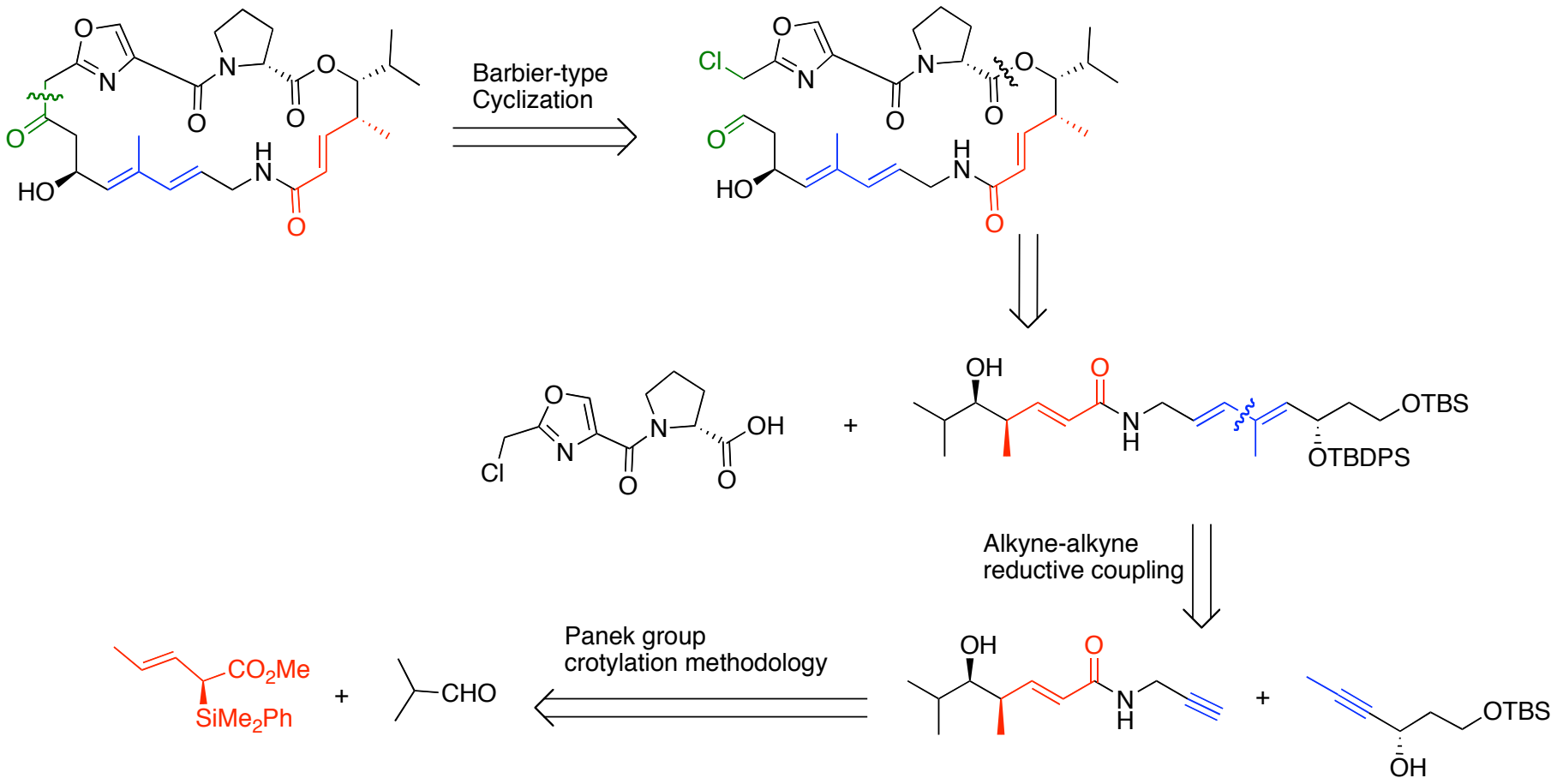
Viriginiamycin Synthesis and Semisynthesis

1st Total Synthesis: Schlessinger, R. H.; Li, Y.-J. *J. Am. Chem. Soc.* **1996,** *118,* 3301.



Stereochemistry of vinylogous aldol product and diene controlled by chiral auxiliary; macrocycle closed via amide bond formation; 21 steps, 2.2% yield, 16 steps longest linear (numbers do not include auxiliary attachment).

Panek Group Retrosynthesis



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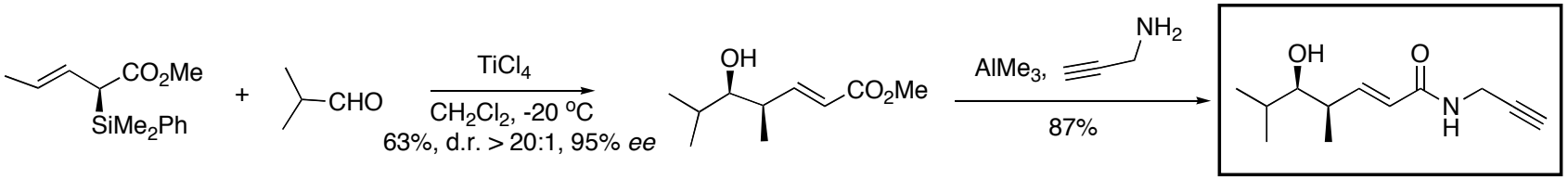
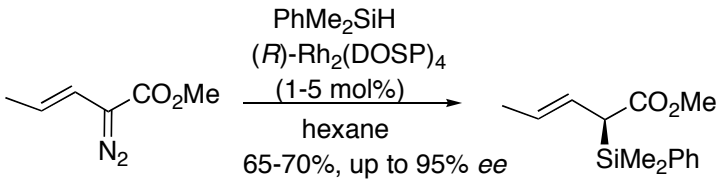
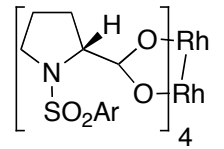
Terminal Alkyne Synthesis: Asymmetric Crotylation



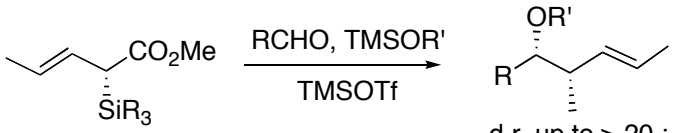
Silane synthesis via Si-H insertion (Davies et al. *TL* **1997,** *38,* 1741-1744.)





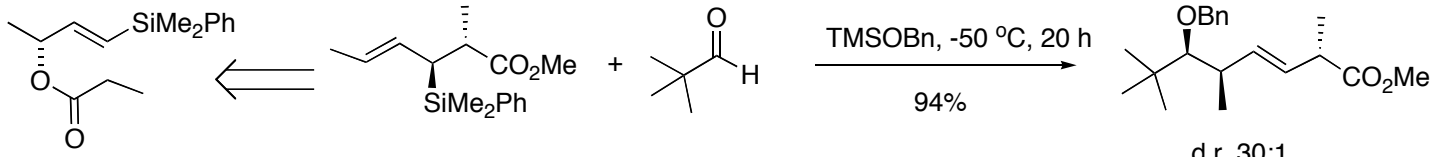
(*R*)-Rh$_2$(DOSP)$_4$
Ar = *p*-$C_{12}H_{25}C_6H_4$

Application of optically active crotyl silanes toward vinylogous aldol products (*Org. Lett.* **2010,** *12,* 2112-2115.



d.r. up to > 20 : 1
ee up to 97%

Previously cited methodology: Asymmetric additions of optically active (*E*)-crotyl silanes
(Panek et al. *J. Org. Chem.* **1992**, *57,* 5790-5792.



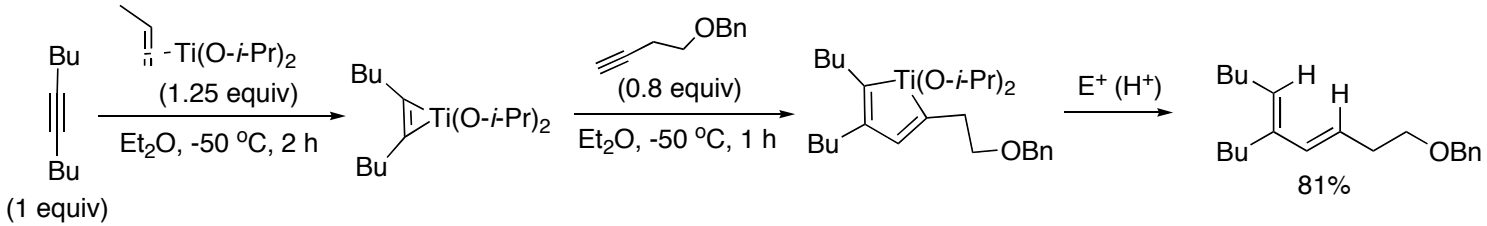
(Claisen Rearrangement via (*E*)-enolate)

d.r. 30:1

Vinyl silane synthesis and application: Sparks, M. A.; Panek, J. S. *J. Org. Chem.* **1991,** *56,* 3431-3438.

Alkyne-Alkyne Reductive Coupling

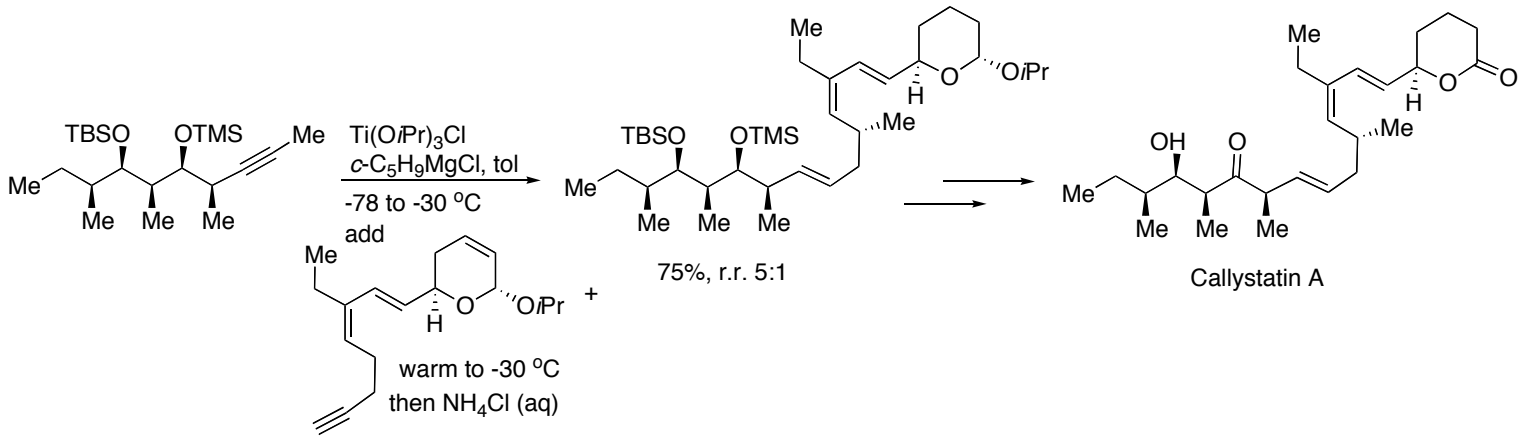
Stereoselective Synthesis of Functionalized Conjugated Dienes



Reaction tolerates amides, esters, alkynyl silanes, and silyl ethers in good yields and fair regioselectivities (3:2 to 9:1 to single regioisomer). Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999,** *121,* 7342-7344.

Note: Characterization of Group 4 Metal-alkyne complexes: Buchwald et al. *J. Am. Chem. Soc.* **1987,** *109,* 2544-2546.

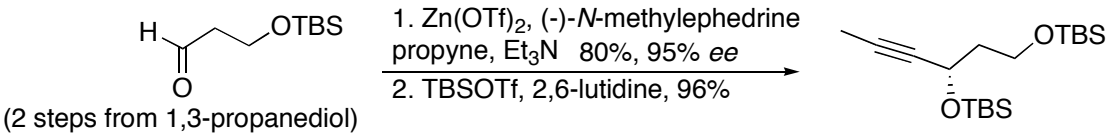
Application to Polyketide Natural Product Synthesis



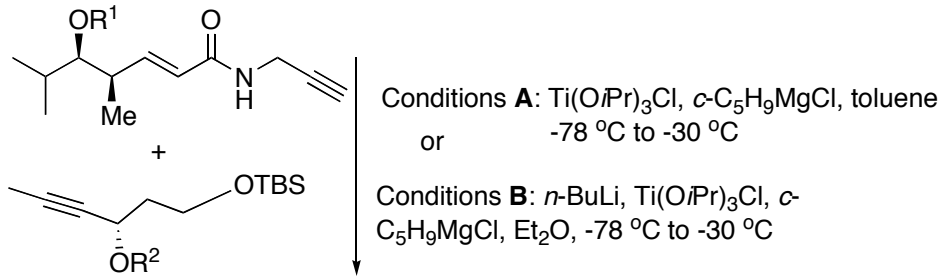
Reichard, H. A.; Rieger, J. c.; Micalizio, G. C. *Angew. Chem. Int. Ed.* **2008,** *47,* 7837-7840. General methodology development: Shimp, H. L.; Micalizio, G. C. *Org. Lett.* **2005,** 7 5111-5114.

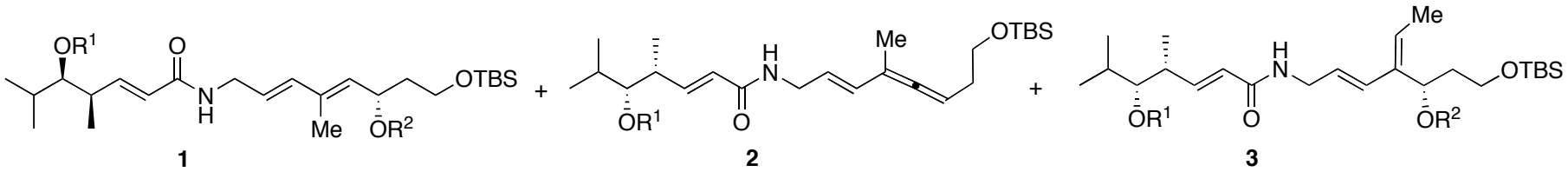
Application of Reductive Coupling

Synthesis of coupling partner:



Carreira's alkyne addition protocol (general: *J. Am. Chem. Soc.* **2000,** *122,* 1806-1807.

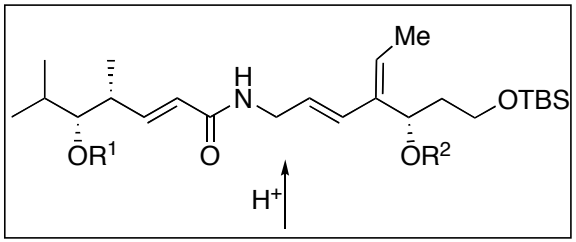


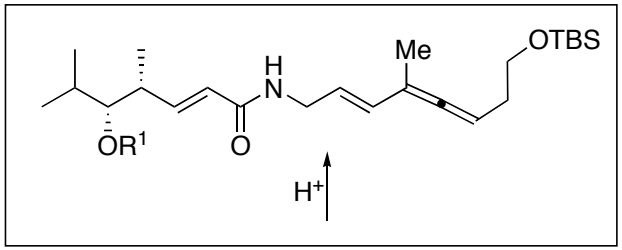


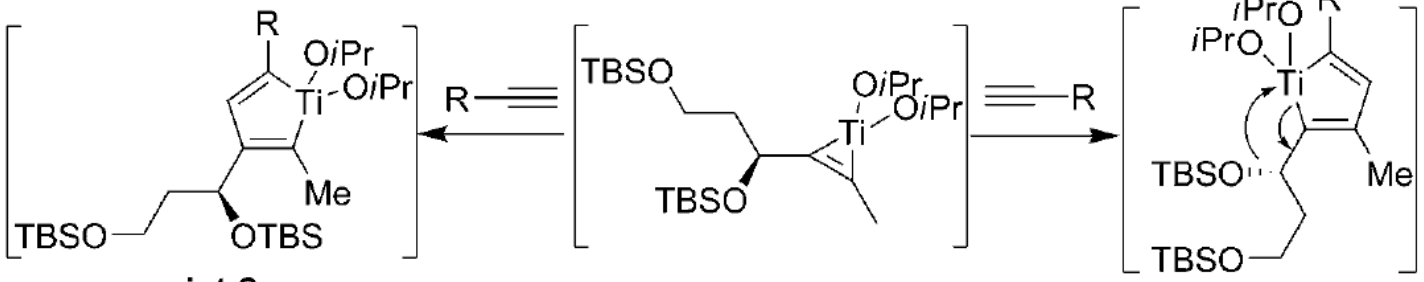
R^1	R^2	Conditions	Yield 1	Yield 2	Yield 3
Bn	TBS	A	0%	19%	45%
Ac	TBS	A	0%	39%	49%
H	H	B	58%	16%	0%
Ac	H	B	71%	0%	0%

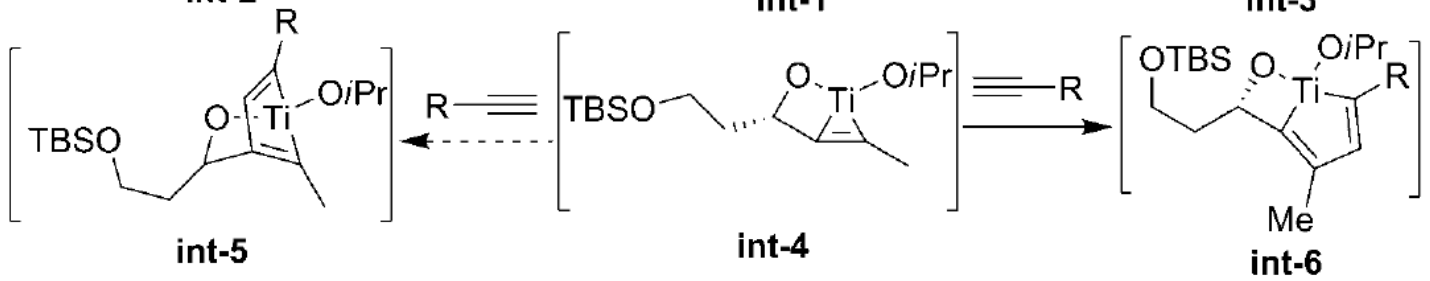
Most favorable substrate for synthesis

Proposed Alkyne-Titanium Intermediates

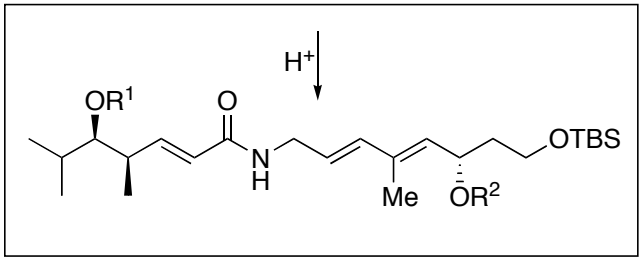








Unfavorable due to strain associated with a bridgehead alkene



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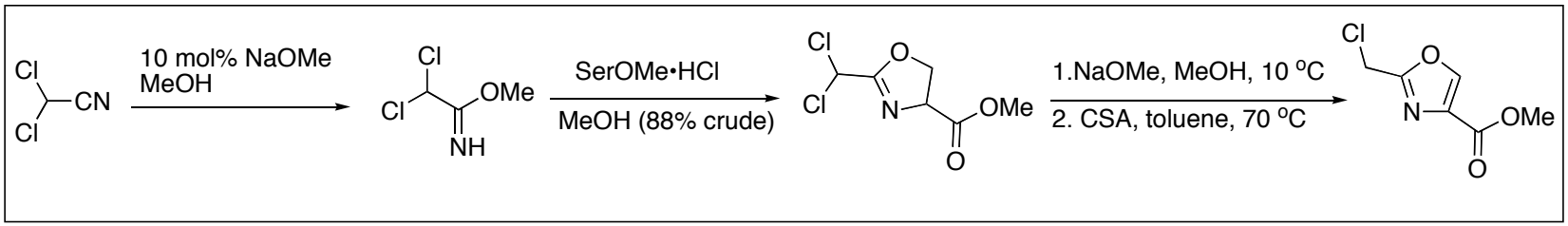
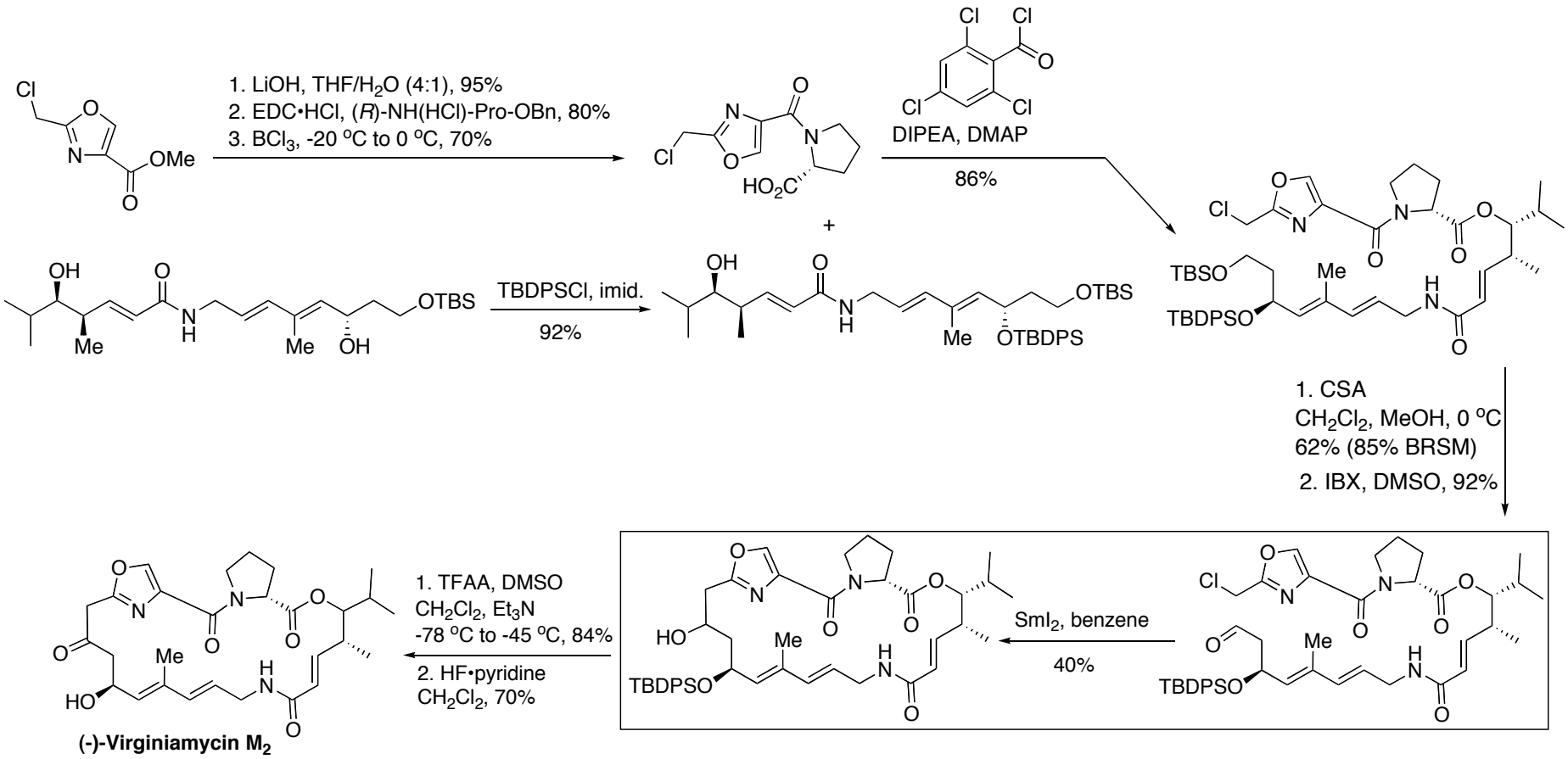
Completion of the Synthesis

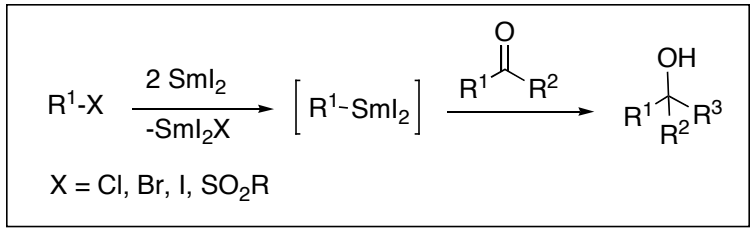


Hermitage et al. *Org. Process Res. Dev.* **2001,** *5,* 37-44.

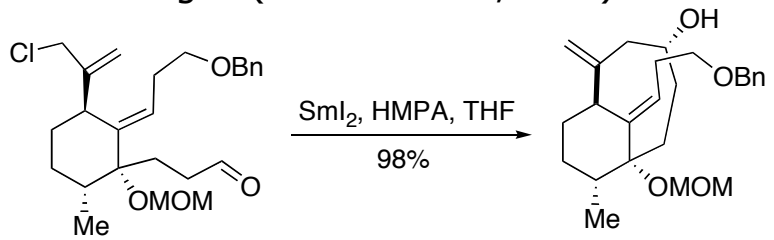


Barbier Cyclizations in Natural Product Synthesis

Review: Nicolaou et al. *Angew. Chem. Int. Ed.* **2009,** *48,* 7140-7165.



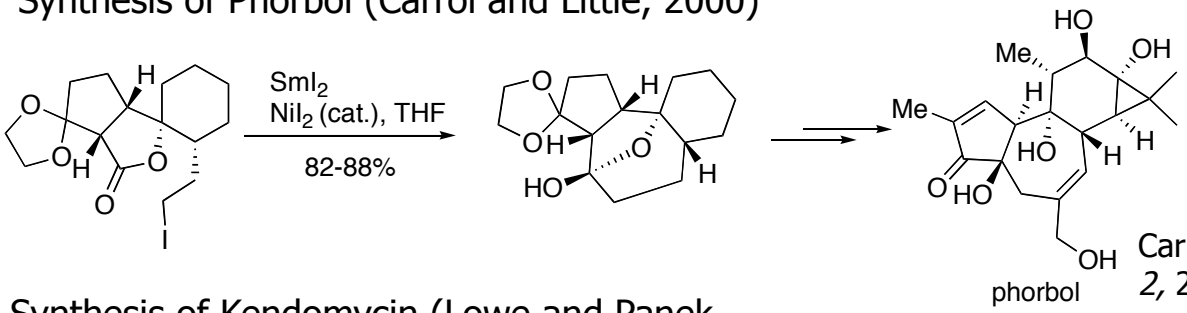
Model system of vinigrol (Matsuda et al., 1997).



vinigrol model

Matsuda et al. *Tetrahedron* **1999,** *55,* 14369-14380.

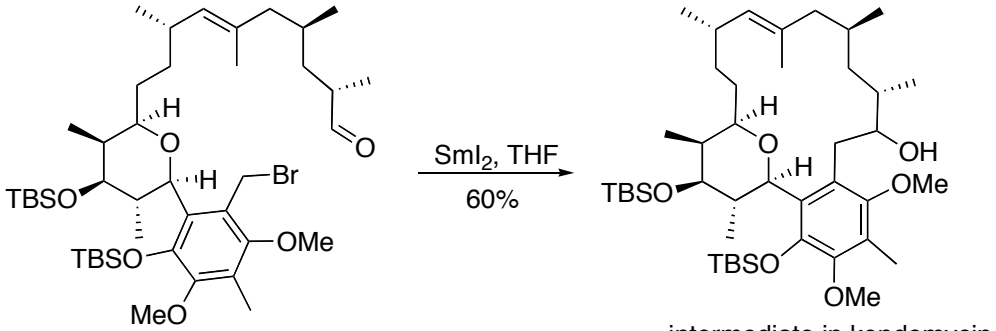
Synthesis of Phorbol (Carrol and Little, 2000)



phorbol

Carroll, G. L.; Little, R. D. *Org. Lett.* **2000,** *2,* 2873-2876.

Synthesis of Kendomycin (Lowe and Panek, 2008)



intermediate in kendomycin synthesis

-1st example of Samarium-mediated Barbier cyclization for macrocycle closure in natural product synthesis (16-membered)

Lowe, J. T.; Panek, J. S. *Org. Lett.* **2008,** *10,* 3813-3816.

Summary and Outlook

- The antibiotic (−)-Virginiamycin M_2 was synthesized in 19 steps and 6.0% overall yield from the optically active (*E*) chiral silane. The longest linear sequence was 10 steps.
- Key transformations include application of crotyl silane addition toward a vinylogous aldol product, a regio- and stereo-selective titanium mediated alkyne-alkyne coupling reaction, and a samarium diodide mediated Barbier-type cyclization.
- The 23-membered macrocycle is the largest ring reported to be synthesized by a Barbier type reaction to date.