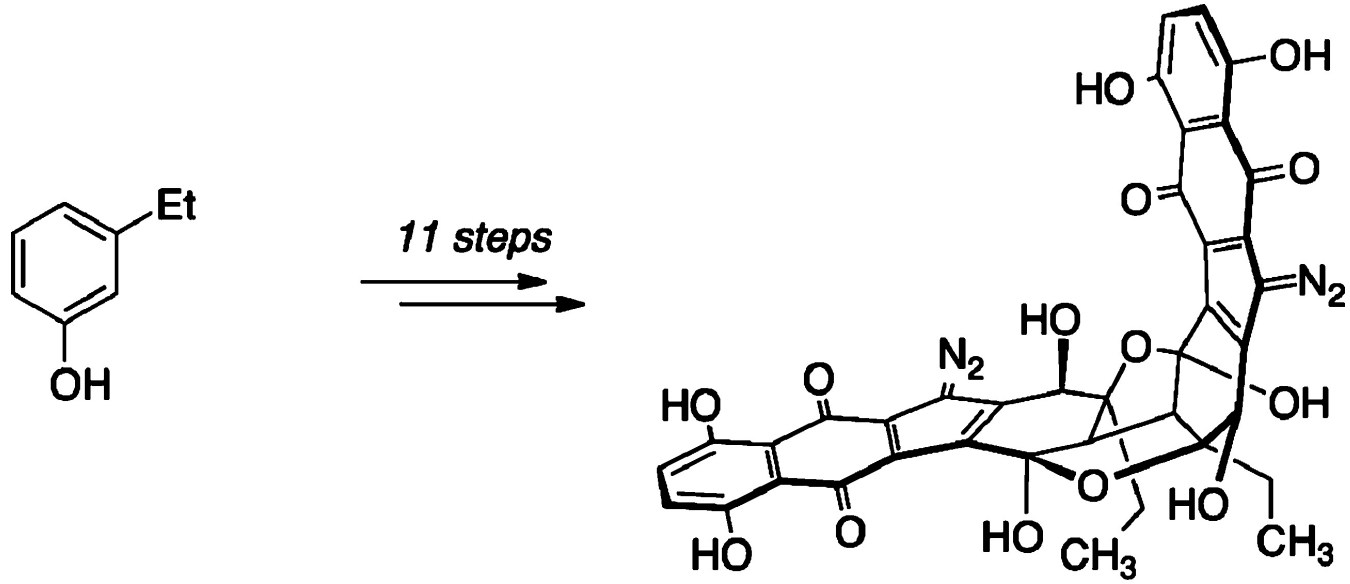
11-Step Enantioselective Synthesis of (−)-Lomaiviticin Aglycon

Seth B. Herzon, Liang Lu, Christina M. Woo, and Shivajirao L. Gholap *J. Am. Chem. Soc.* ASAP DOI 10.1021/ja200034b



lomaiviticin aglycon (**3**)

Melissa Sprachman
Current Literature
February 26, 2011

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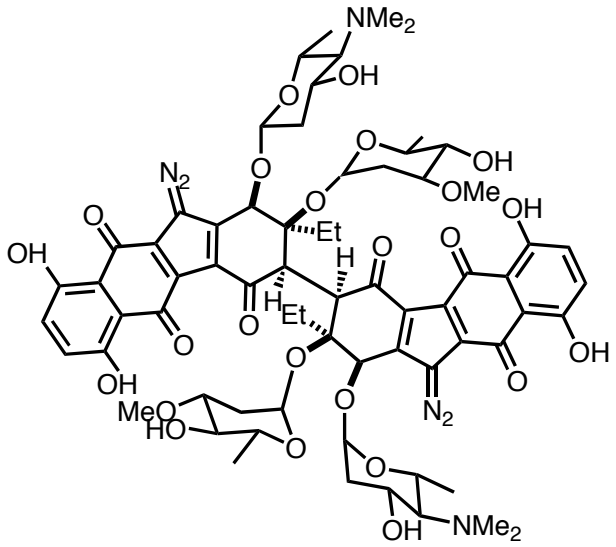
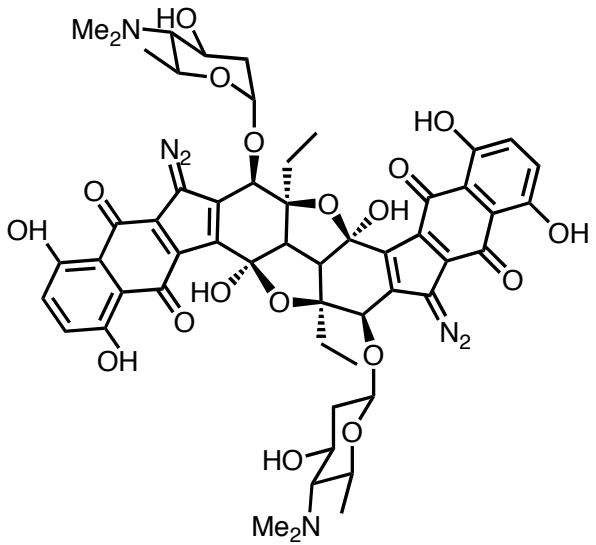
DOI: 10.1021/ja200034b

Isolation and Preliminary Biological Activity



lomaiviticin A



lomaiviticin B

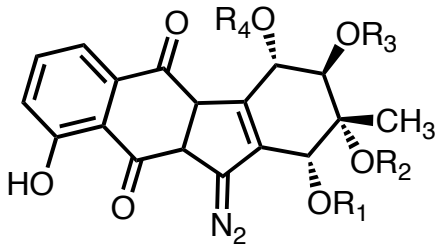
- The lomaiviticins (red solids) were isolated from the fermentation broth of an actinomycetes strain *LL*-371366, which was initially isolated from the core a host ascidian.

The fermentation broth exhibited potent DNA-damaging activity (detected by biochemical induction assay) and was cytotoxic against a number of cancer cell lines.

Lomaiviticin A exhibited activity against a variety of cancer cell lines (IC_{50} values of 0.01 – 98 ng/mL).

He et al. *J. Am. Chem. Soc.* **2001,** *123,* 5362-5363.

Related Natural Products: The Kinamycins



	R_1	R_2	R_3	R_4
kinamycin A	H	Ac	Ac	Ac
kinamycin B	H	Ac	H	H
kinamycin C	Ac	H	Ac	Ac
kinamycin D	Ac	H	Ac	H
kinamycin E	Ac	H	H	H
kinamycin F	H	H	H	H
kinamycin G	Ac	CO*i*Pr	Ac	Ac
kinamycin H	CO*i*Pr	H	Ac	Ac
kinamycin I	CO*i*Pr	H	CO*i*Pr	Ac
kinamycin J	Ac	Ac	Ac	Ac

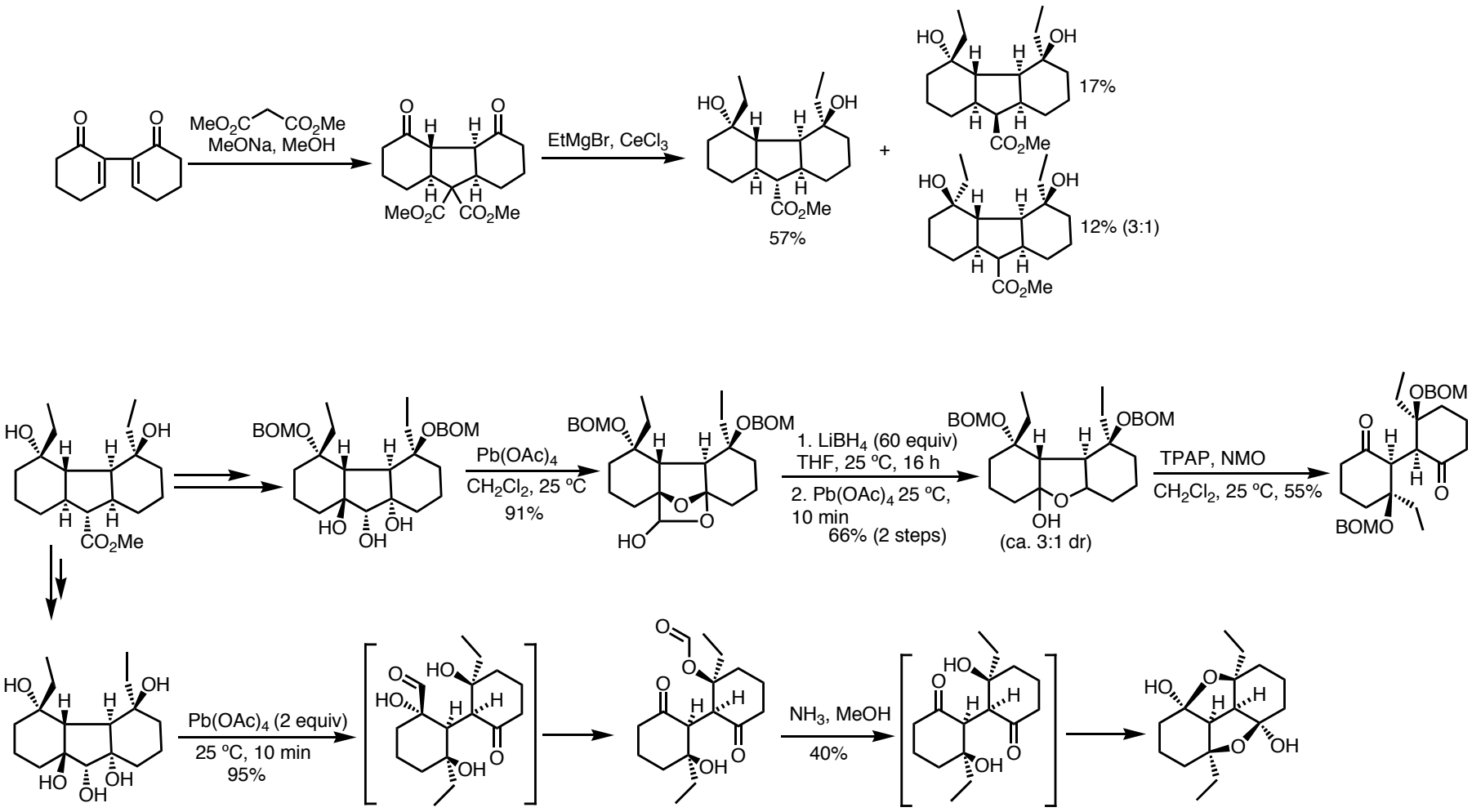
K¨pke, T.; Zaleski, J. M. *Anticancer Agents Med. Chem.* **2008,** *8,* 292-304.

Completed Syntheses**:** **Kinamycin C**: Lei, X.; Porco, J. A. *J. Am. Chem. Soc.* **2006,** *128,* 14790-14791.

Kinamycins C, F, and J: Nicolaou et al. *J. Am. Chem. Soc.* **2007,** *129,* 10356-10367. (John's Current Literature August 2007).

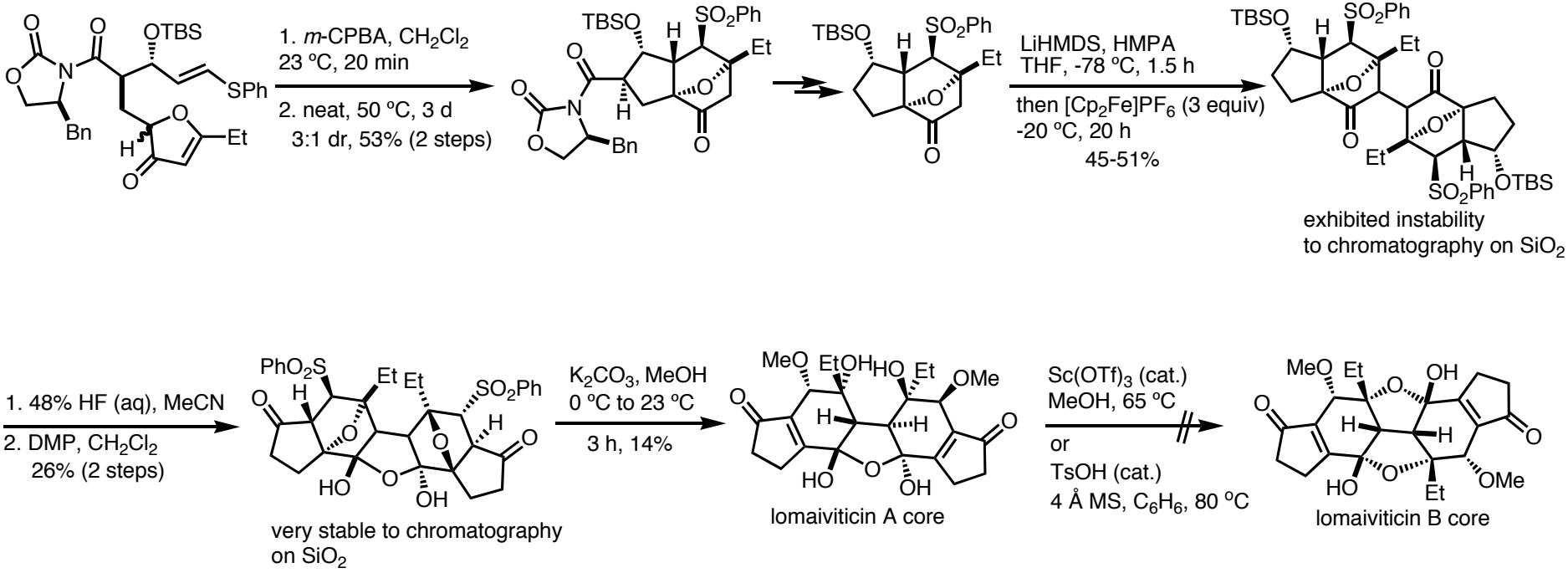
Kinamycin F: Herzon et al. *J. Am. Chem. Soc.* **2010,** *132,* 2540-2541.

Model Systems and Construction of the Central Bond



Nicolaou et al. *Angew. Chem. Int. Ed.* **2006,** *45,* 2076-2081.

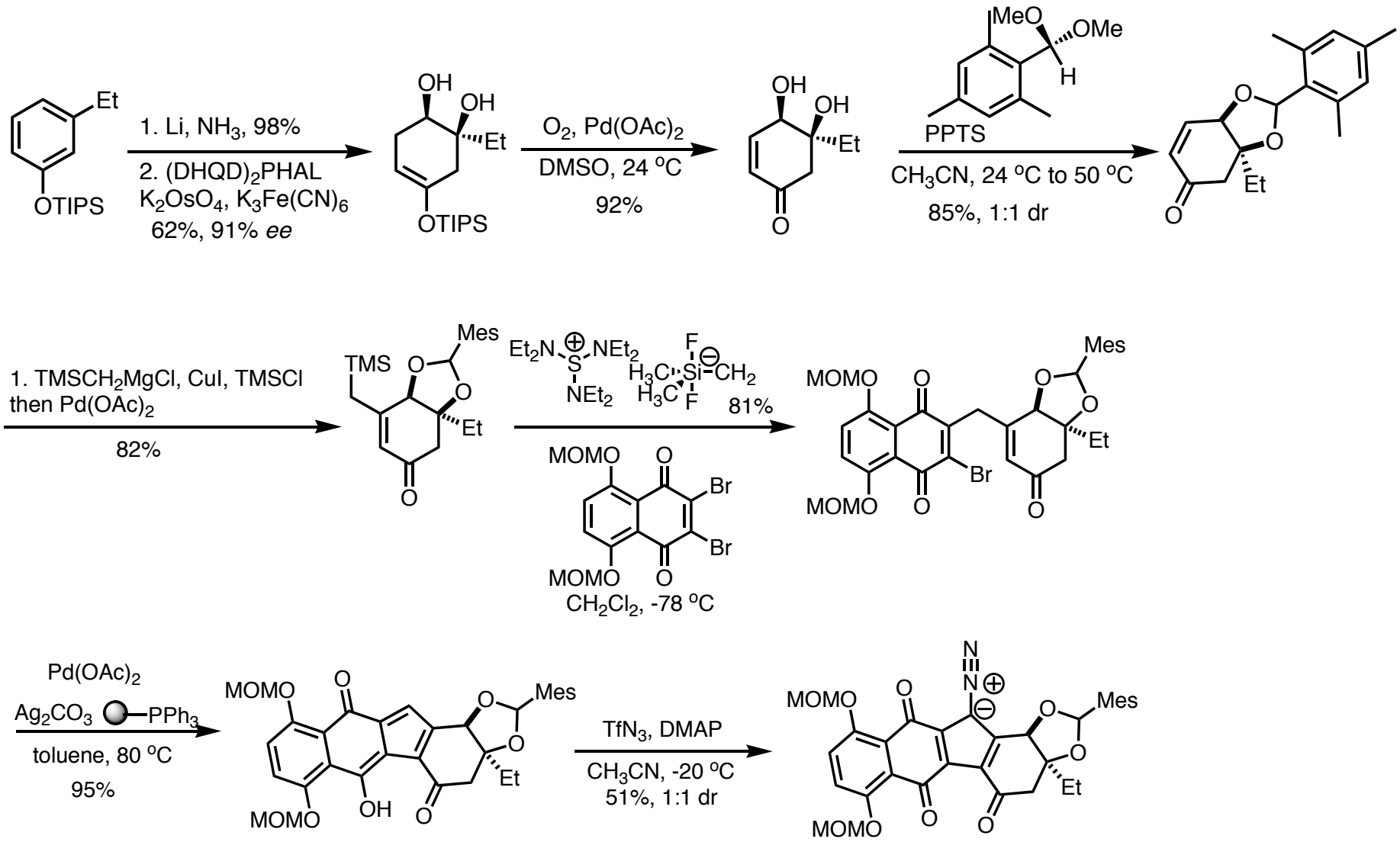
Model Systems and Construction of the Central Bond



Key Findings:
-Fully stereoselective oxidative enolate coupling
-Stability of the lomaiviticin A core as the hydrate

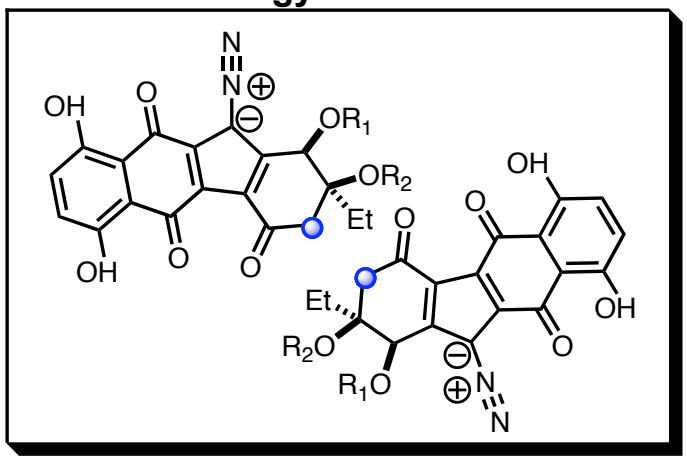
Krygowski, E. S.; Murphy-Benenato, K.; Shair, M.D.
Angew. Chem. Int. Ed. **2008,** *47,* 1680-1684.

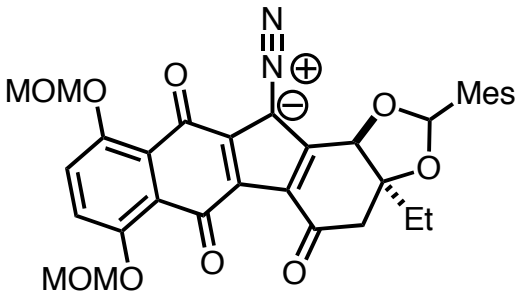
Herzon Group Forward Synthesis



End Game: Oxidative Dimerization

General Strategy

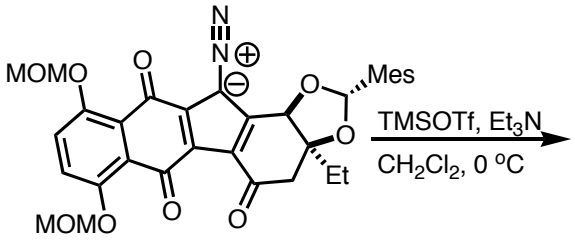




Both diastereomers and derivatives

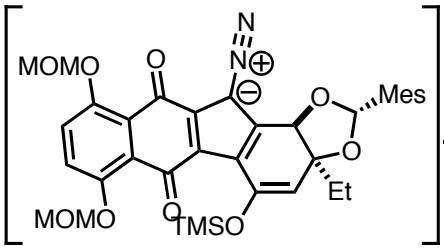
> 1500 experiments

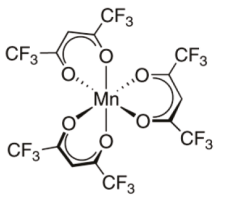
Desired Product not formed



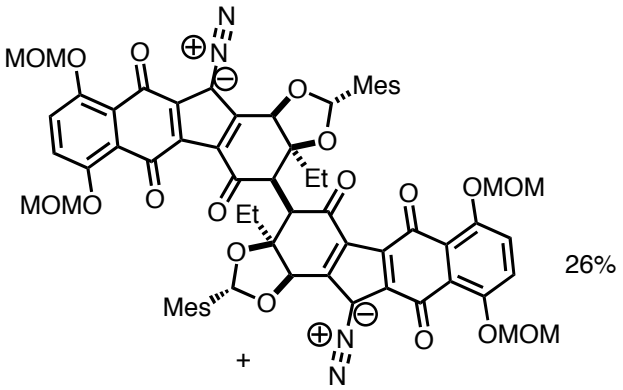
TMSOTf, Et_3N

CH_2Cl_2, 0 °C





PhH, 21 °C



26%

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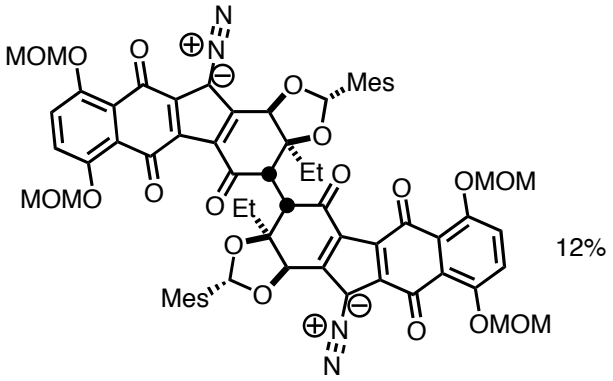

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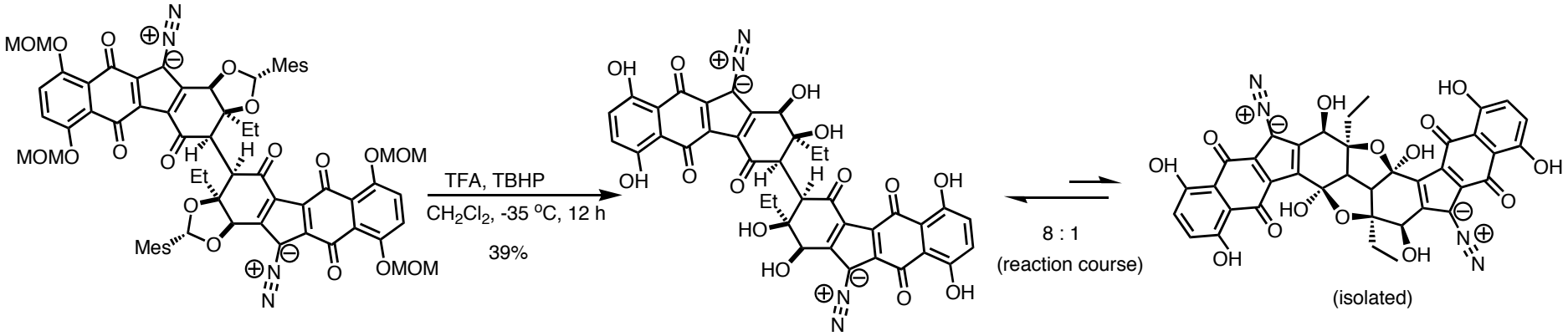
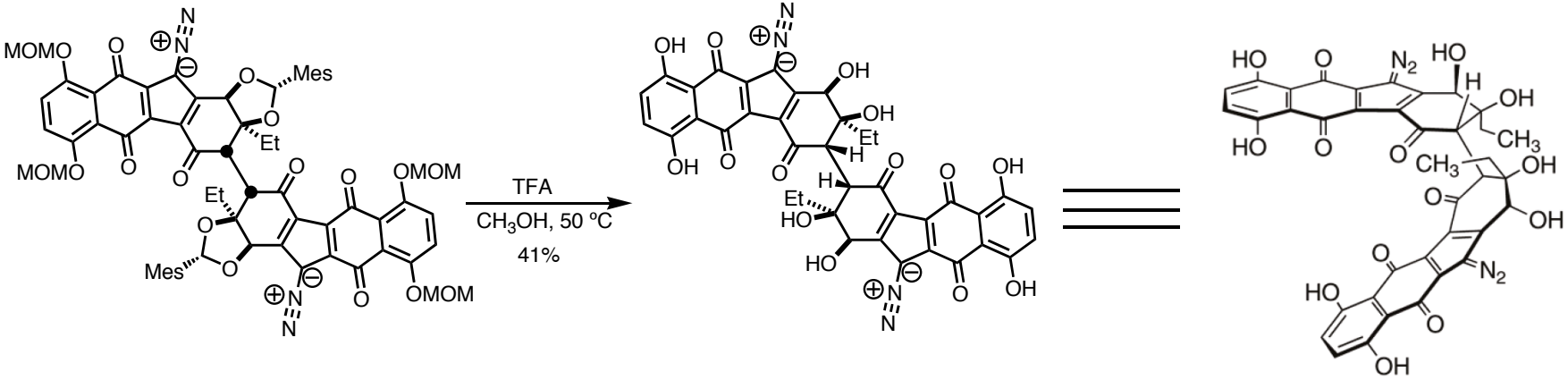
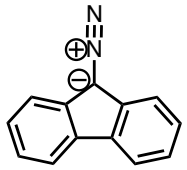
Formation of Lomaiviticin Aglycon





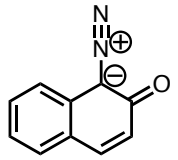
Proposed Mechanism of Action and Diazonium Character



9-diazofluorene

υ = 1906 cm^{-1} (C-N_2)

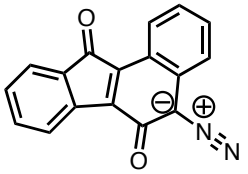
N-N = 1.133 Å



2,1-naphthoquinodiazide

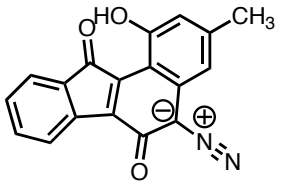
υ = 2056 cm^{-1} (C-N_2)

N-N = 1.111 Å



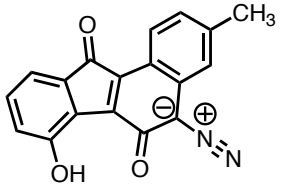
υ = 2087 cm^{-1} (C-N_2)

N-N = 1.108 Å



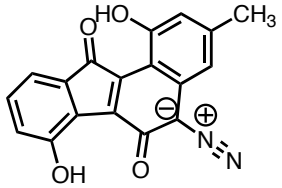
υ = 2101 cm^{-1} (C-N_2)

N-N = 1.107 Å



υ = 2125 cm^{-1} (C-N_2)

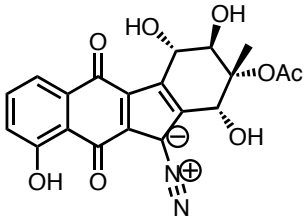
N-N = 1.105 Å



Isoprekinamycin

υ = 2139 cm^{-1} (C-N_2)

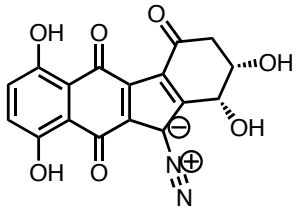
N-N = 1.103 Å



Kinamycin B

υ = 2188 cm^{-1} (C-N_2)

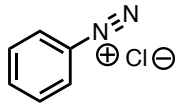
N-N = 1.099 Å



Model for lomaiviticin A

υ = 2212 cm^{-1} (C-N_2)

N-N = 1.097 Å



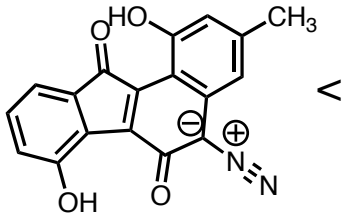
υ = 2212 cm^{-1} (C-N_2)

N-N = 1.100 Å

ab initio calculations at HF theory level using 6-31G and LanL2DZ basis sets.

Laufer, R. S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **2002,** *124,* 1854-1855.

The trend in "diazonium character" parallels the trend in antiobiotic and antitumor activity.



Isoprekinamycin

υ = 2139 cm^{-1} (C-N_2)

N-N = 1.103 Å

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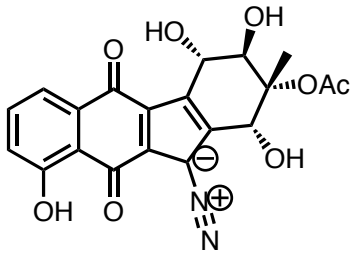

Kinamycin B

υ = 2188 cm^{-1} (C-N_2)

N-N = 1.099 Å

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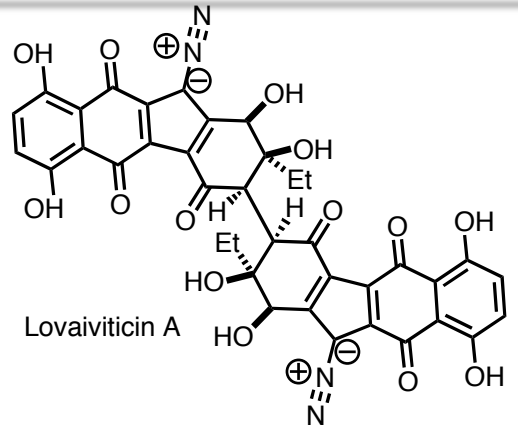
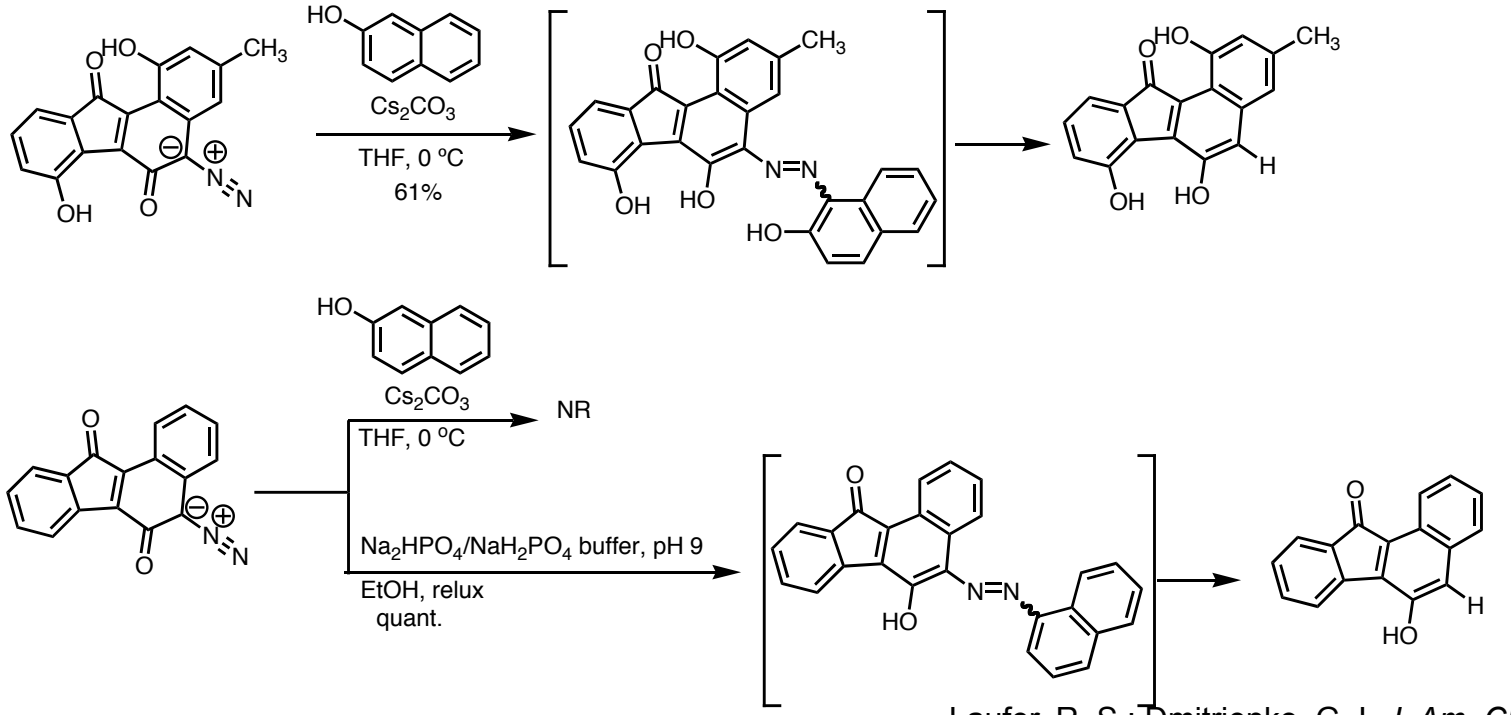


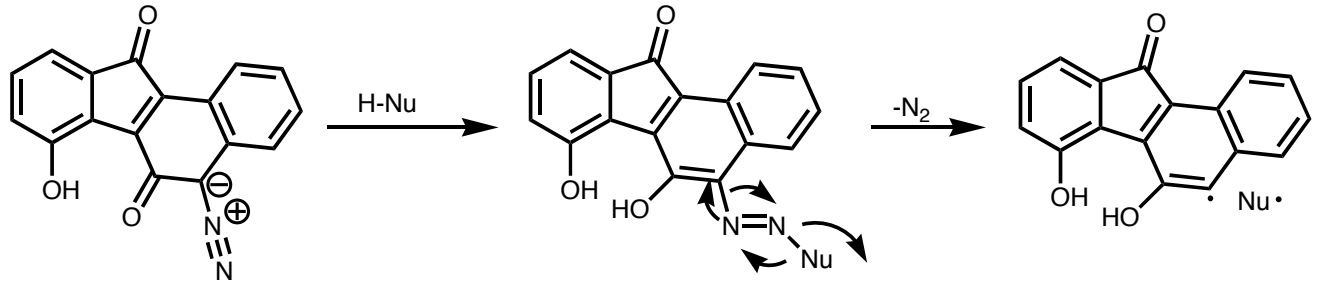
Lovaiviticin A

Proposed Mechanism of Action (Continued)

The authors also provided experimental evidence for relative electrophilicities and a proposal that deazetation by nucleophilic attack followed by H-atom abstraction is a possible MOA.

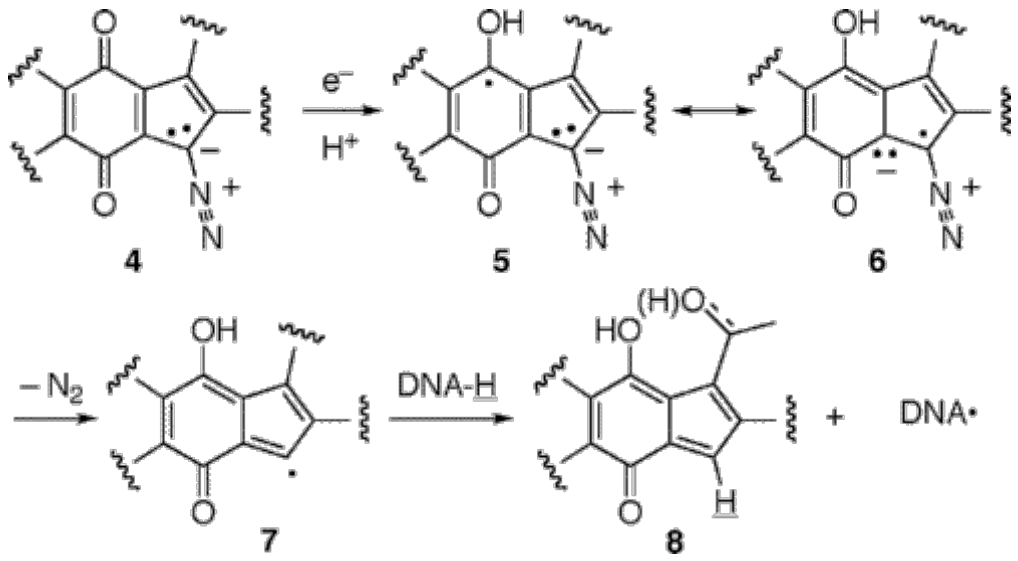


Laufer, R. S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **2002,** *124,* 1854-1855.

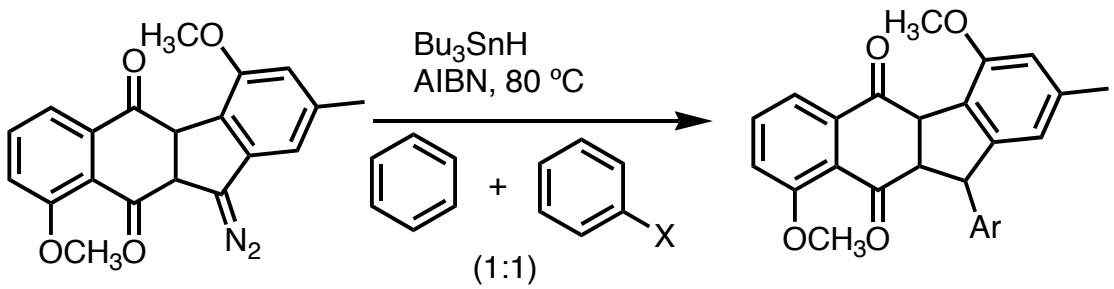


K¨pke, T.; Zaleski, J. M. *Anticancer Agents Med. Chem.* **2008,** *8,* 292-304.

A Second Proposal: 1-electron reduction



An alternative proposal involves 1-e$^-$ reduction followed by H-atom abstraction.



Relative rate (relative to benzene)

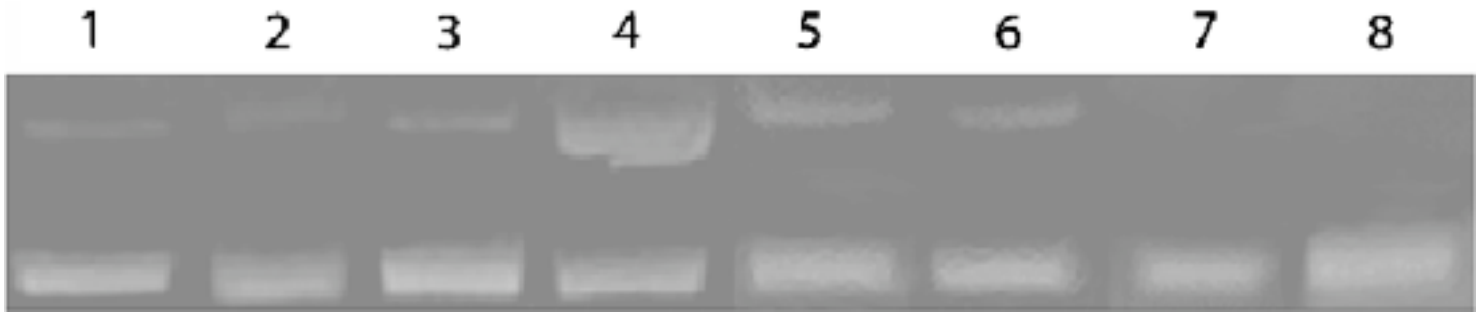
X	CH_3	Cl	CN	OCH_3
rate	2.2	1.5	2.1	3.1

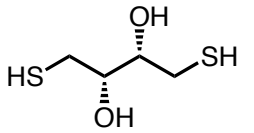
Additionally, yields of solvent incorporation dropped with increasing equivalents of Bu_3SnH.

The authors estimate the rate constant for sp^2 radical addition to the aromatic solvent to be 10^7 M^{-1} s^{-1}. The reported rate constant for addition of phenyl radical to chlorobenzene is ~10^6 M^{-1} s^{-1}..

Feldman, K. S.; Eastman, K. J. *J. Am. Chem. Soc.* **2005,** *127,* 15344-15345.

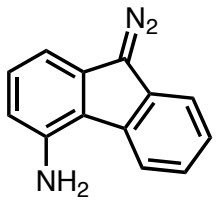
Experimental Evidence of DNA Strand Cleavage



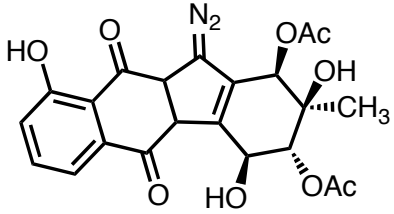


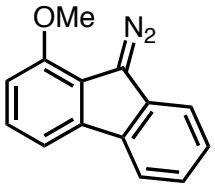
Dithiothreitol (DTT)

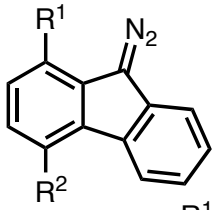
The authors compared the DNA cleavage ability of kinamycin D to a variety of diazoflourene probes.



kinamycin D







R^1 = Cl or NO_2, R^2 = H
R^1 = H, R^2 = Cl or NO_2

% DNA cleavage	18 ± 8 (44 ± 7 with no DTT)	28 ± 7	41 ± 6	< 5%

Melander et al. *Bioorg. Med. Chem. Lett.* **2006,** *16,* 5148-5151.

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Summary and Outlook

- Herzon and coworkers have completed the first synthesis of lomaiviticin aglycon in 11 linear steps. Several operations are amenable to large-scale preparative work. As of the online publication date, the group has synthesized 15 mg of lomaiviticin aglycon.

- After exhaustive screening, the authors demonstrated the feasibility of an oxidative dimerization using $Mn(hfacac)_3$. Their report is the first use of this reagent in an oxidative enoxysilane coupling.

- . Herzon and coworkers previously reported the synthesis of the sugar residues (*Org. Lett.* **2009,** *11,* 4322-4325) and demonstrated formation of the glycosidic bonds on a model system. With the aglycon in hand, elaboration to form usable quantities of the natural products is a possibility.

- The ability to produce useful quantities of the core may lead to analog development and future application to important antibiotics and/or cancer therapeutics.

- Further probing of the lomaiviticins' MOA *via* some of the same assays used to study the kinamycins is also a possibility with synthetic access to the materials.