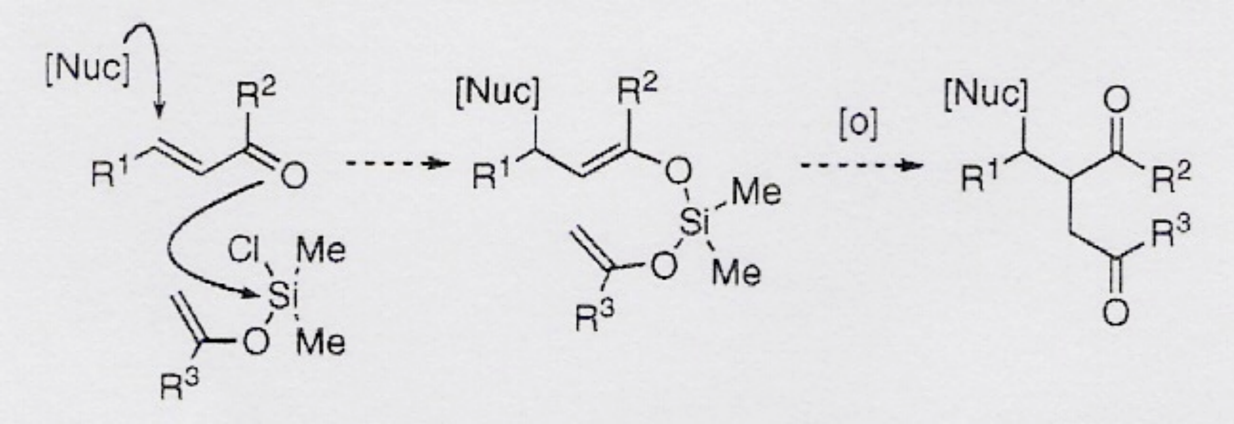
Development of a Merged Conjugate Addition/Oxidative Coupling Sequence. Application to the Enantioselective Total Synthesis of Metacycloprodigiosin and Prodigiosin R1

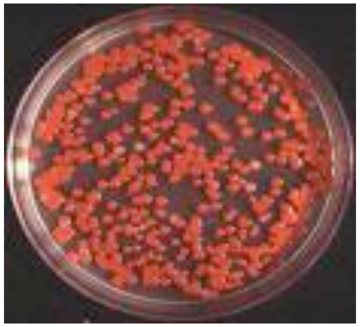
Michael D. Clift and Regan J. Thomson
JACS ASAP, 9/15/09.



Current Literature: David Arnold, 10/3/09

Biological Background: Prodigiosin Natural Products

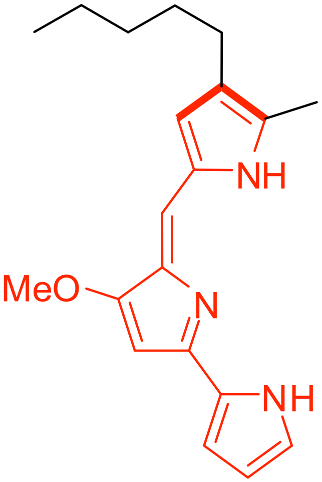
- Prodigiosins are a class of pyrrole alkaloids isolated from the *Serratia* and *Streptomyces* class of bacteria.



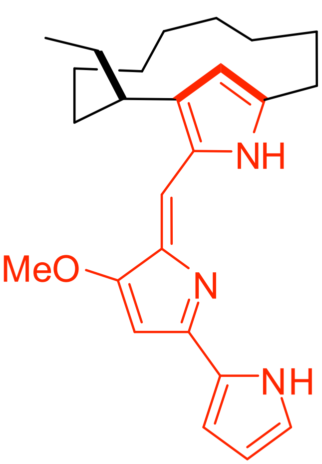
Serrita marcescens
www.gefor.4t.com

- These bacteria have been argued to play an interesting role in history (322 B.C. to 1819) resulting from their propensity to grow on food and give the effect of "bleeding food" due to their deep red colors.... For more information see *Angew. Chem. Int. Ed.* **2003**, *42*, 3582-3603.

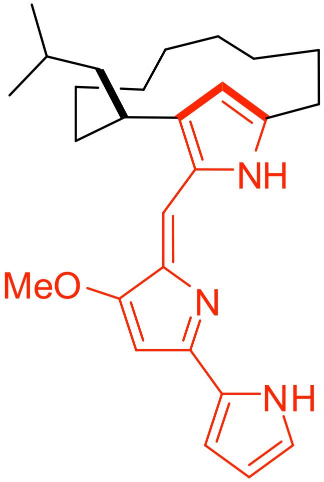
The conserved pyrrolylpyrromethene chromophore marks this class of alkaloids



prodigiosin



metacycloprodigiosin

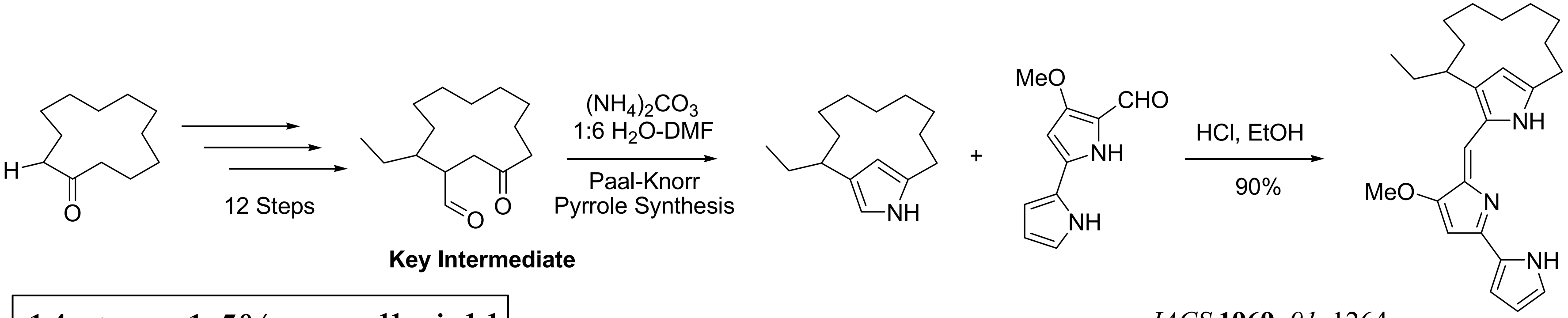


prodigiosin R1

- Biological activities include immunosuppressive and anticancer effects.

Previous Syntheses of Metacycloprodigiosin

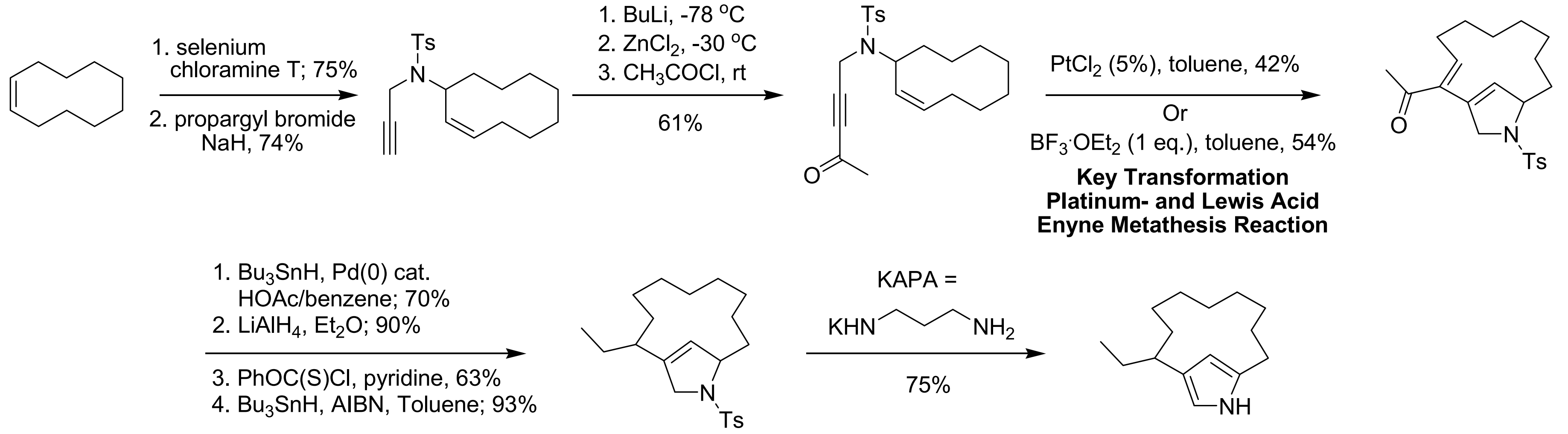
- Original total synthesis of racemic metacycloprodigiosin in 1969 by Wasserman



14 steps, 1.5% overall yield

JACS **1969**, *91*, 1264.
Tetrahedron **1976**, *32*, 1867.

- Formal total synthesis of metacycloprodigiosin by Fürstner in 1998.

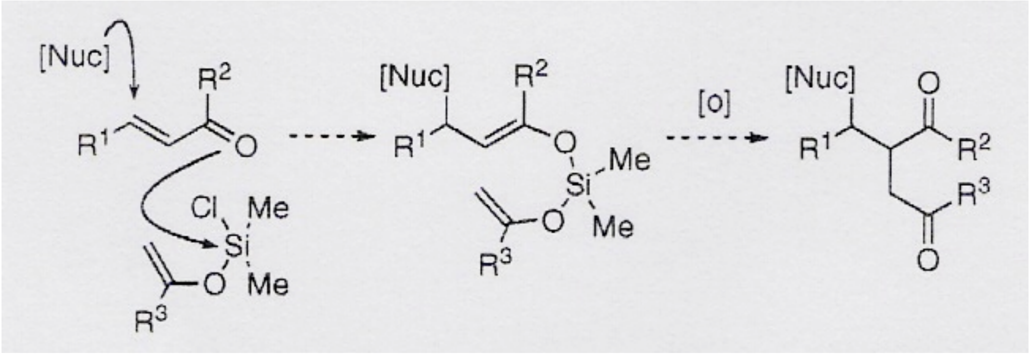


10 steps, 2.1% overall yield

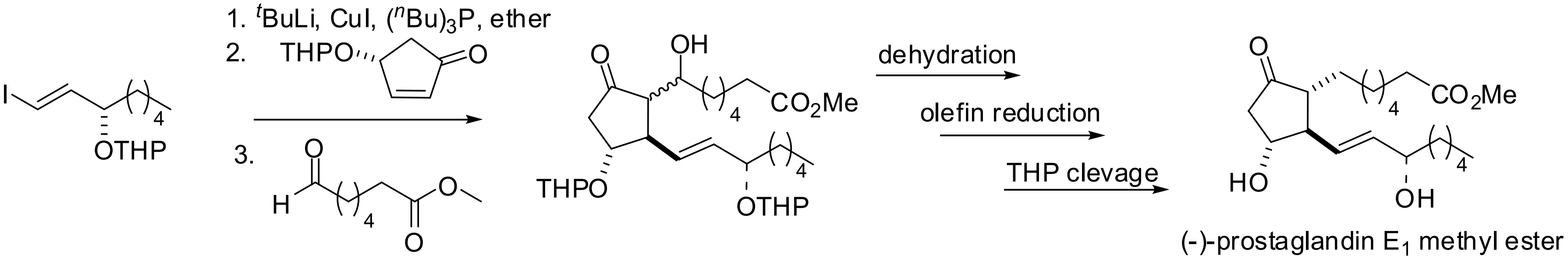
JACS **1998**, *120*, 8305.

Background to the Authors Current Methodology

Tandem conjugate addition/oxidative silyl bis-enol ether coupling strategy
to furnish 1,4-diketones



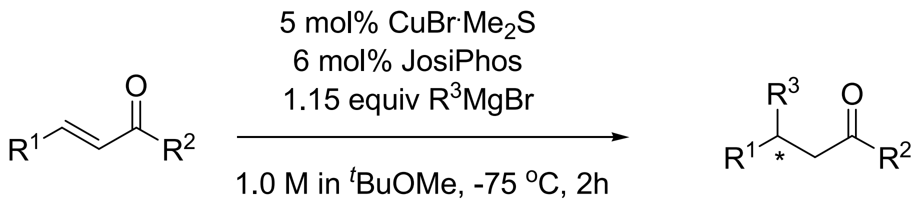
- **Traditional three component couplings:** Noyori's conjugate addition/enolate trapping sequence: synthesis of (-)-prostaglandin E_1 methyl ester



(-)-prostaglandin E_1 methyl ester

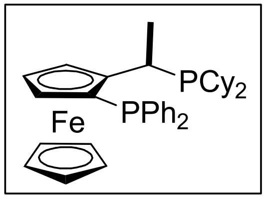
Tetrahedron Letters **1982**, *23*, 4057.

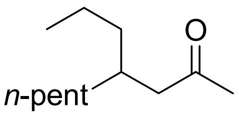
Copper-Catalyzed Enantioselective Conjugate Addition of Grignard Reagents



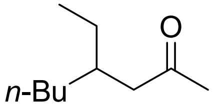
5 mol% $CuBr{\cdot}Me_2S$
6 mol% JosiPhos
1.15 equiv R^3MgBr

1.0 M in ^{t}BuOMe, -75 °C, 2h

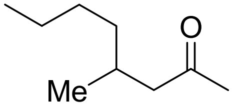




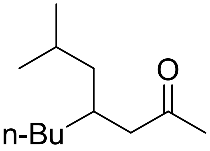
84%, 90% ee



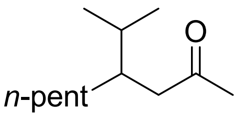
91%, 90% ee



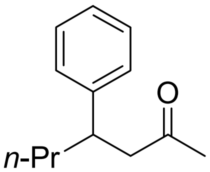
78%, 93% ee



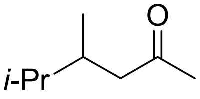
89%, 84% ee



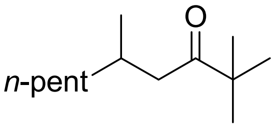
83%, 48% ee



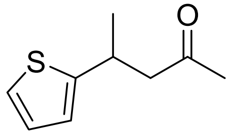
75%, 76% ee



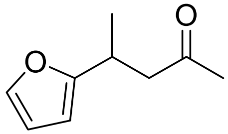
52%, 94% ee



56%, 40% ee



72%, 97% ee

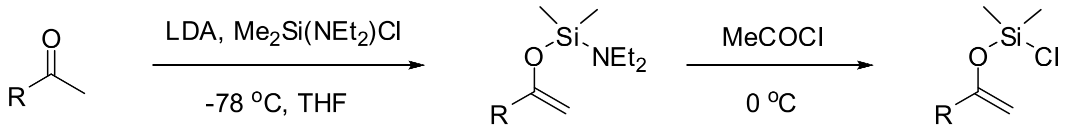


80%, 96% ee

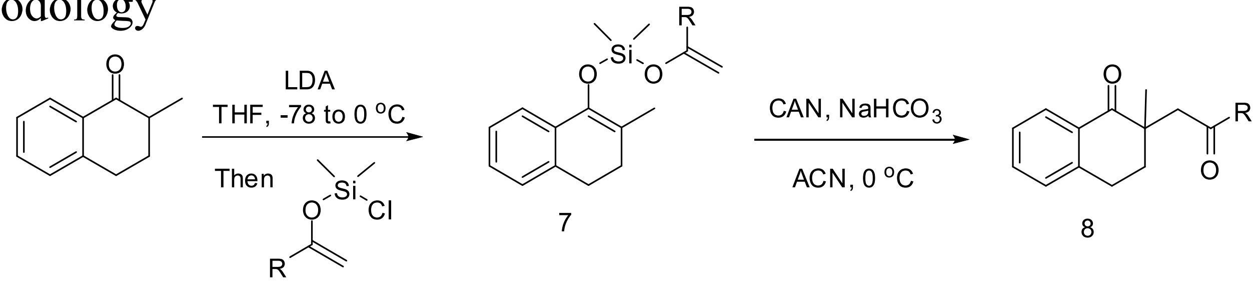
JACS **2004**, *126*, 12784.

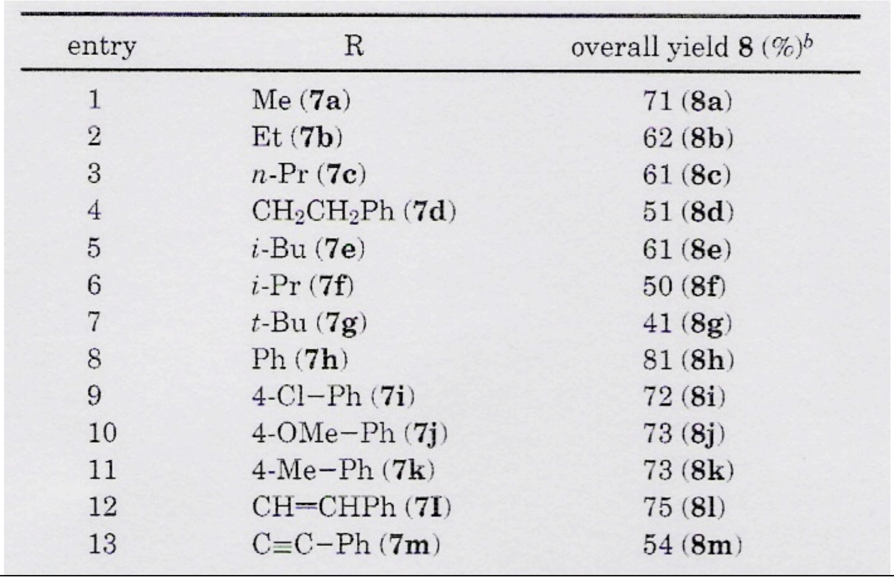
Author's Previous Work on Oxidative Carbon-Carbon Bond Formation via Silyl Bis-enol Ethers

- Formation of enol silyl chlorides:



- Methodology

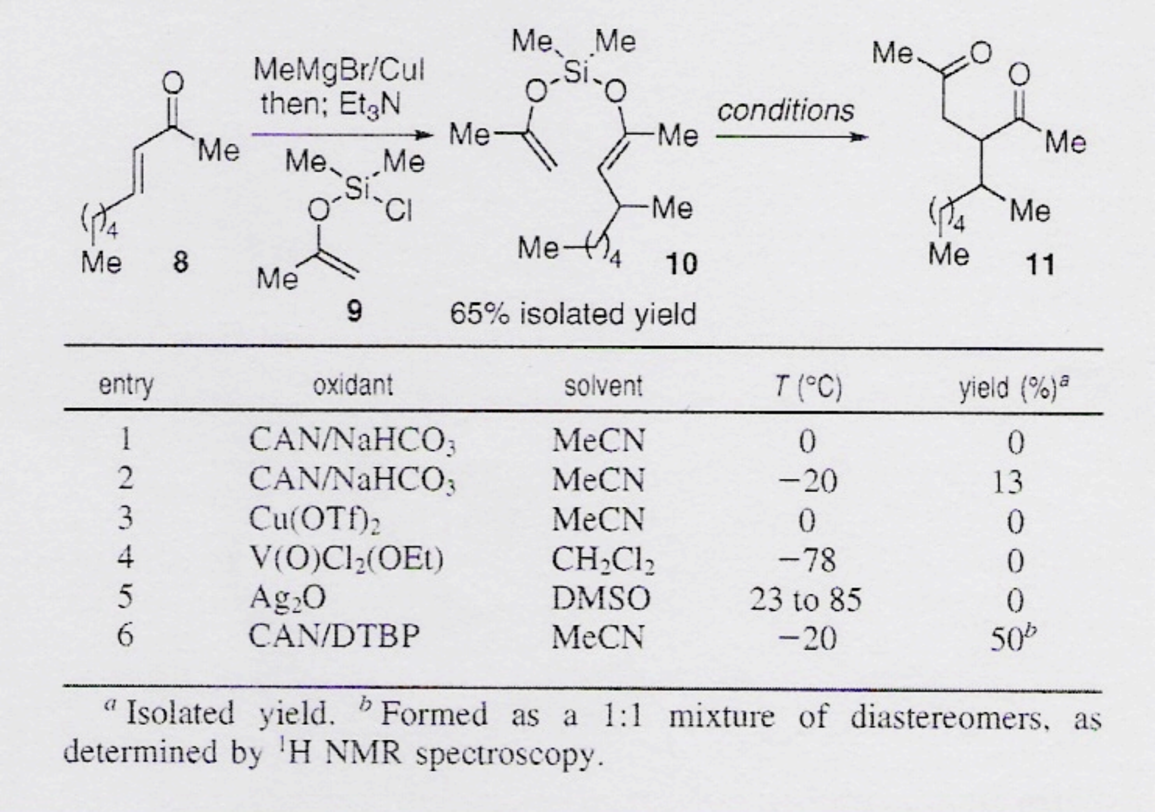




entry	R	overall yield **8** (%)[b]
1	Me (**7a**)	71 (**8a**)
2	Et (**7b**)	62 (**8b**)
3	*n*-Pr (**7c**)	61 (**8c**)
4	CH_2CH_2Ph (**7d**)	51 (**8d**)
5	*i*-Bu (**7e**)	61 (**8e**)
6	*i*-Pr (**7f**)	50 (**8f**)
7	*t*-Bu (**7g**)	41 (**8g**)
8	Ph (**7h**)	81 (**8h**)
9	4-Cl−Ph (**7i**)	72 (**8i**)
10	4-OMe−Ph (**7j**)	73 (**8j**)
11	4-Me−Ph (**7k**)	73 (**8k**)
12	CH=CHPh (**7l**)	75 (**8l**)
13	C≡C−Ph (**7m**)	54 (**8m**)

Org. Lett. **2007**, *9*, 4669.

Title Paper: Development of the Initial Oxidation Conditions for the Oxidative Coupling of Silyl Bis-Enol Ethers

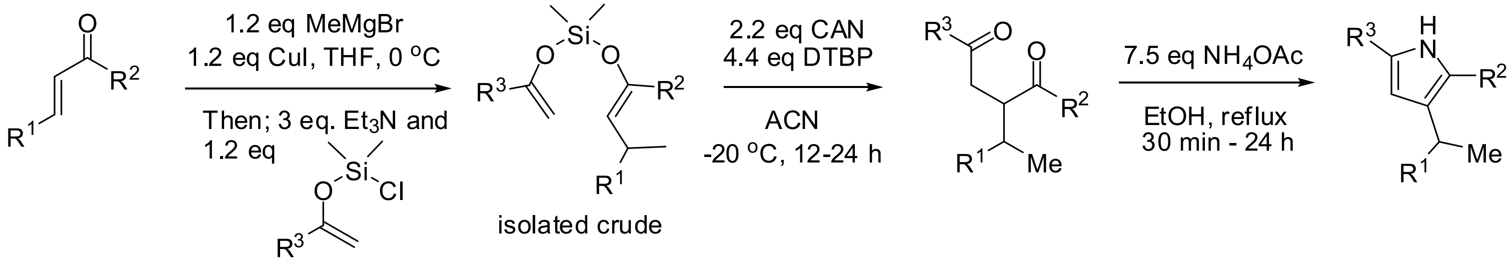


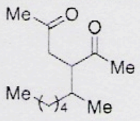
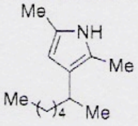
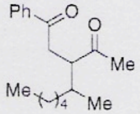
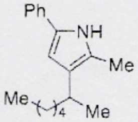
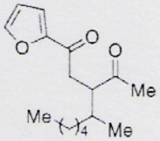
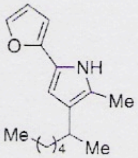
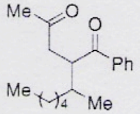
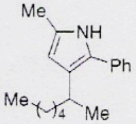
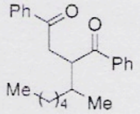
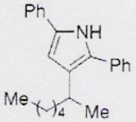
entry	oxidant	solvent	T (°C)	yield (%)[a]
1	CAN/$NaHCO_3$	MeCN	0	0
2	CAN/$NaHCO_3$	MeCN	−20	13
3	$Cu(OTf)_2$	MeCN	0	0
4	$V(O)Cl_2(OEt)$	CH_2Cl_2	−78	0
5	Ag_2O	DMSO	23 to 85	0
6	CAN/DTBP	MeCN	−20	50[b]

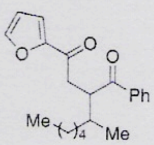
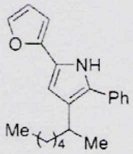
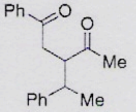
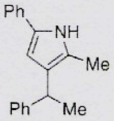
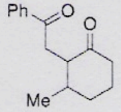
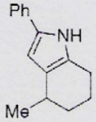
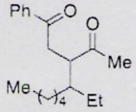
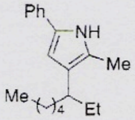
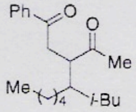
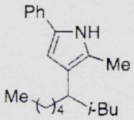
[a] Isolated yield. [b] Formed as a 1:1 mixture of diastereomers, as determined by ^1H NMR spectroscopy.

The optimal oxidation conditions were found to be a mixture of CAN and DTBP in ACN at -20 °C.

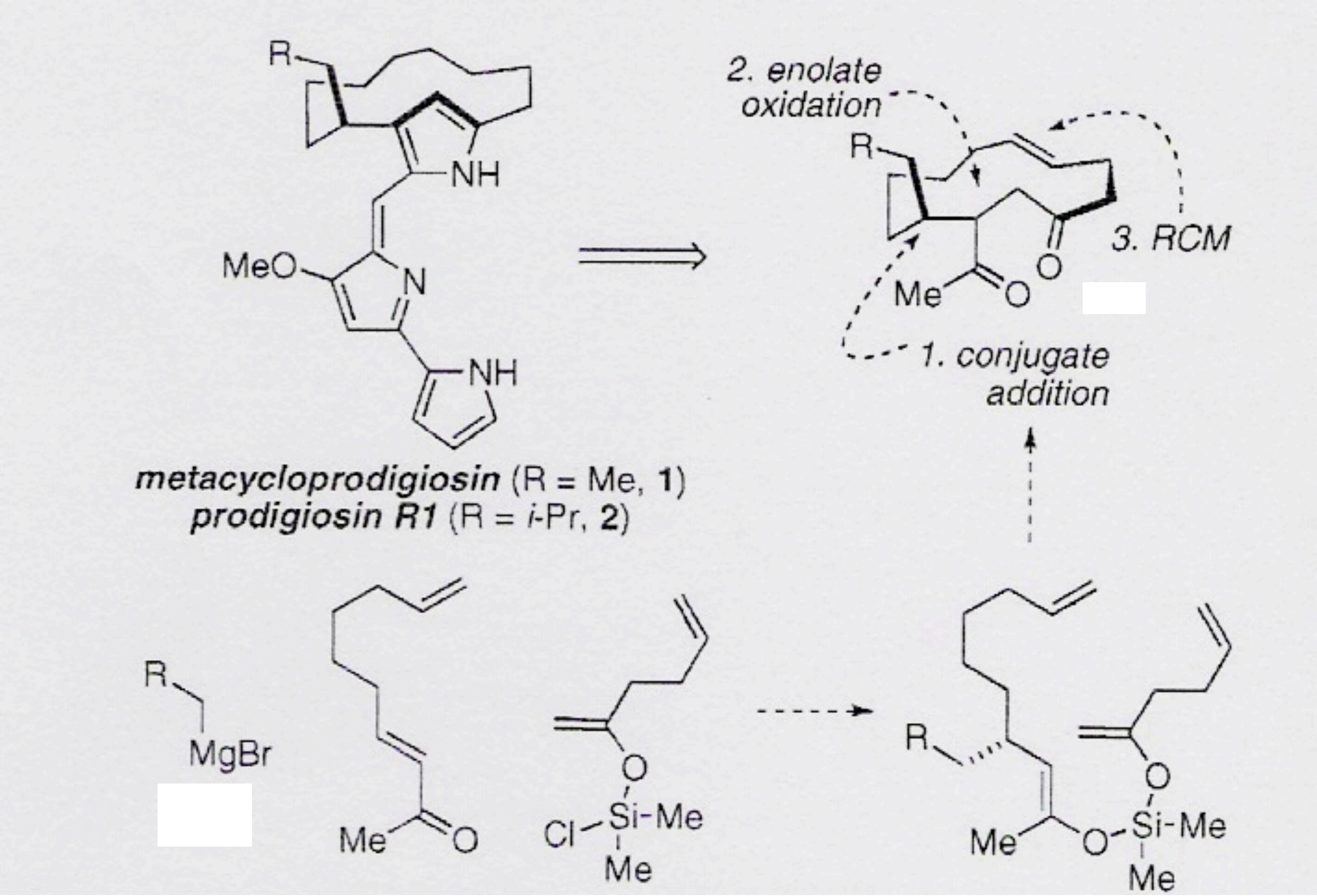
Tandem 1,4-Addition/Oxidative Coupling Sequence Applied to Pyrrole Synthesis



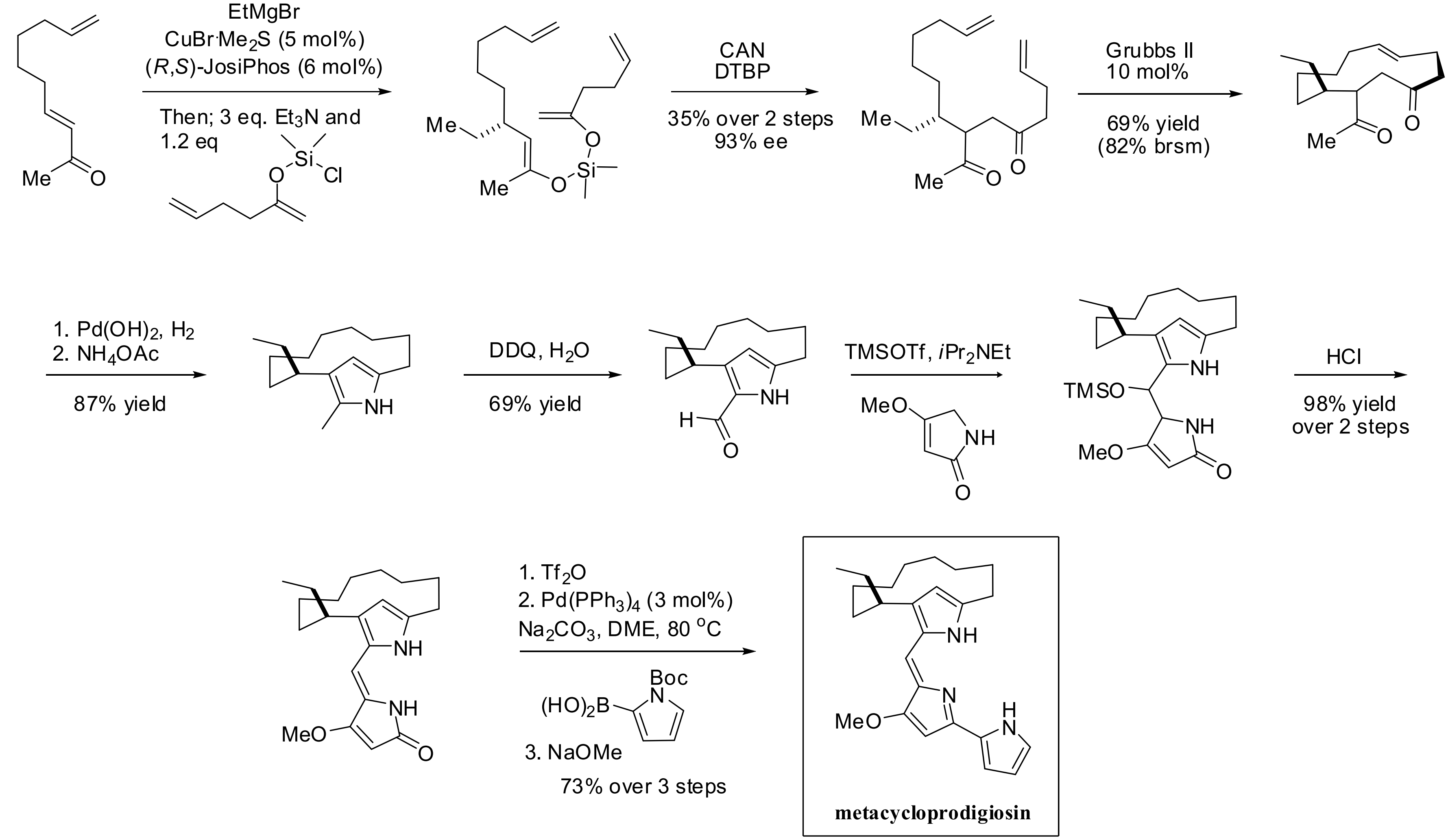
entry	R^1, R^2 R^3	1,4-diketone (**15**)	yield (%)[a] (d.r.)[b]	pyrrole (**16**)	yield (%)[c]
1	C_5H_{11}, Me Me		47 (2:1)		86
2	C_5H_{11}, Me Ph		54 (1.3:1)		92
3	C_5H_{11}, Me 2-furyl		56 (1.7:1)		89
4	C_5H_{11}, Ph Me		51 (1.8:1)		94
5	C_5H_{11}, Ph Ph		51 (2:1)		91

entry	R^1, R^2 R^3	1,4-diketone (**15**)	yield (%)[a] (d.r.)[b]	pyrrole (**16**)	yield (%)[c]
6	C_5H_{11}, Ph 2-furyl		58 (1.6:1)		89
7	Ph, Me Ph		56 (2:1)		87
8	$-(CH_2)_3-$ Ph		54 (1.7:1)		85
9[d]	C_5H_{11}, Me Ph		57 (1:1)		92
10[e]	C_5H_{11}, Me Ph		58 (1:1)		87

Synthetic Strategy for the Enantioselective Total Synthesis of Prodigiosin Alkaloids

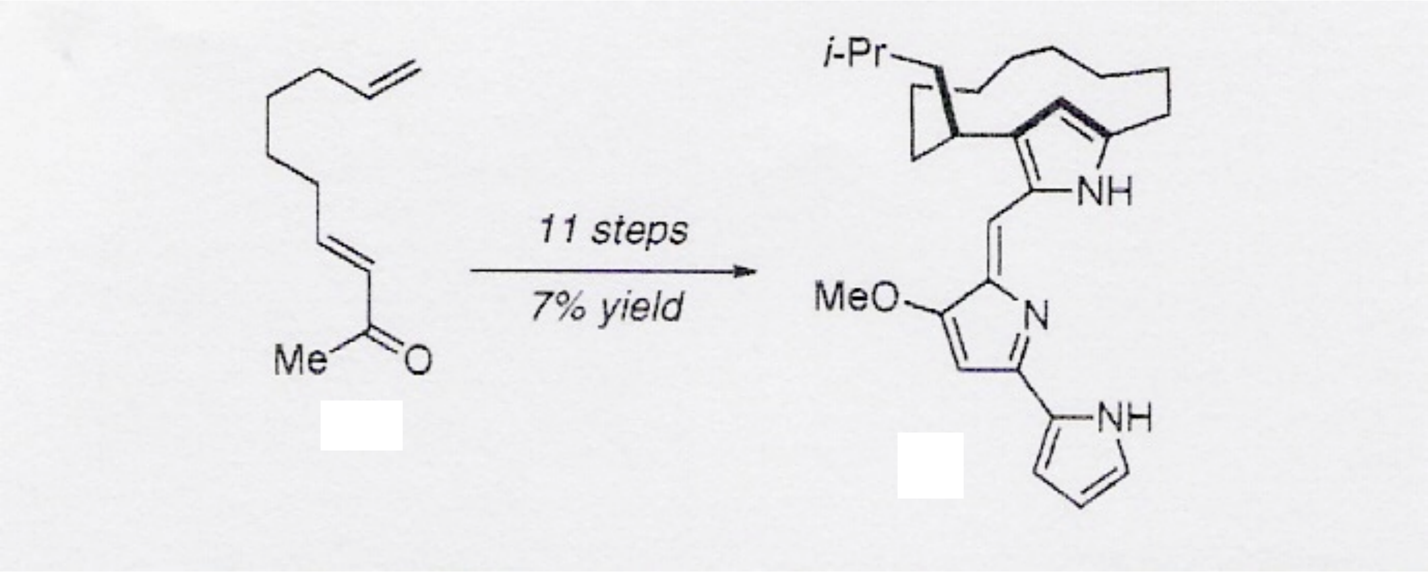


Enantioselective Total Synthesis of Metacycloprodigiosin



The total synthesis was completed in 11 steps in 13% overall yield

First Total Synthesis of Prodigiosin R1



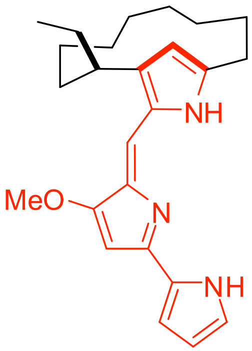
Synthesized by the same reaction sequence as metacycloprodigiosin 92% ee

Conclusion

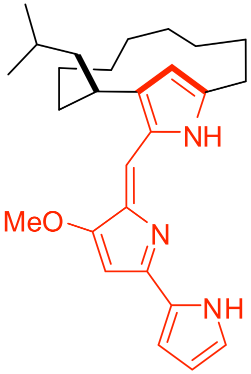
- The authors have demonstrated a tandem conjugate addition and oxidative coupling sequence, of the resulting tethered unsymmetrical silyl bis-enol ethers, to efficiently form 1,4-diketones which could be smoothly converted into the corresponding trisubstituted pyrroles.

- This methodology has been applied to the first enantiomeric total syntheses of metacycloprodigiosin and prodigiosin R1.

- The development of this methodology allows for the construction and easy derivatization of enantiopure prodigiosin alkaloids: a class of pyrrole based alkaloids demonstrated to have promising biological activities.



metacycloprodigiosin



prodigiosin R1