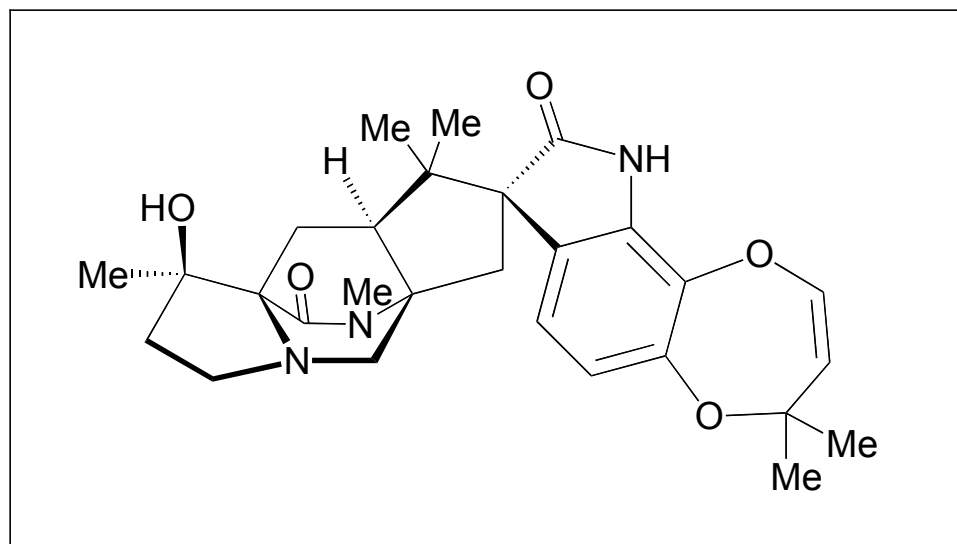
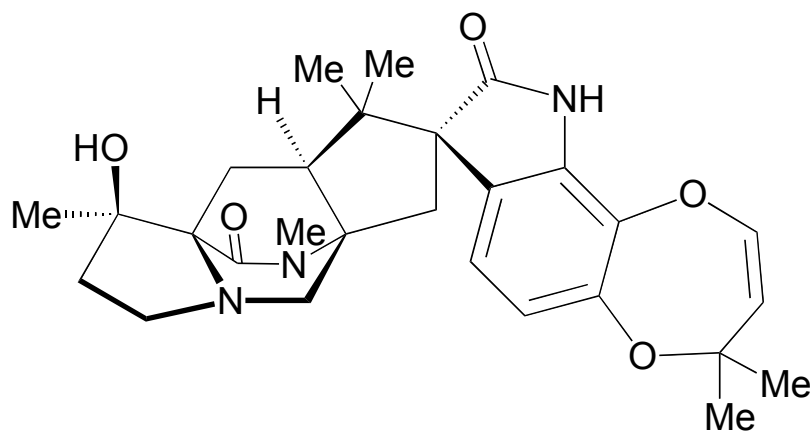


Total Synthesis of Paraherquamide A



Introduction

Paraherquamide A

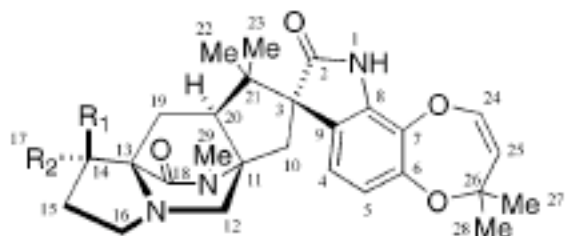


- Potent Anthelmintic Compound
- Isolation: From *Penicillium Paraherquei*,
By Yamazaki, 1981.
- Synthesis: Williams, 2000

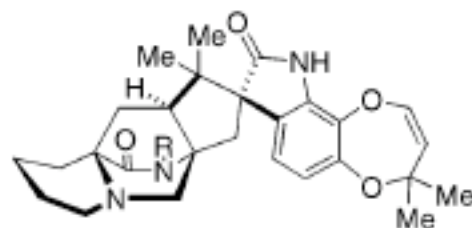
Williams, R. A.; Cao, J.; Tsujishima, H.; Cox, R. J.
Angew. Chem. Int. Ed. **2000**, *39*, 2540-2544

Williams, R. A.; Cao, J.; Tsujishima, H.
J. Am. Chem. Soc. **2003**, *125*, 12172-12178

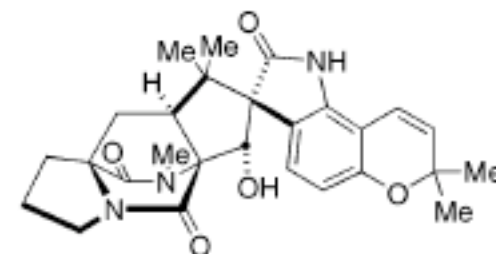
Related Natural Products



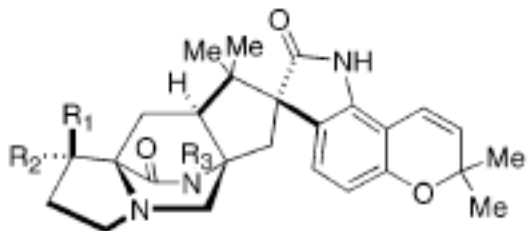
1, paraherquamide A, $R_1 = \text{OH}$, $R_2 = \text{Me}$
 2, paraherquamide B, $R_1 = \text{H}$, $R_2 = \text{H}$



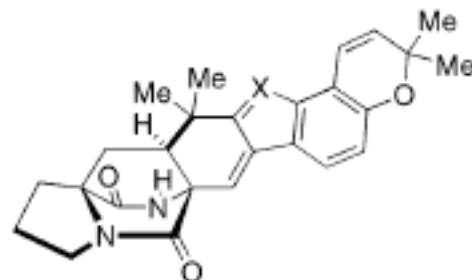
3, marcfortine A, $R = \text{Me}$
 4, marcfortine B, $R = \text{H}$



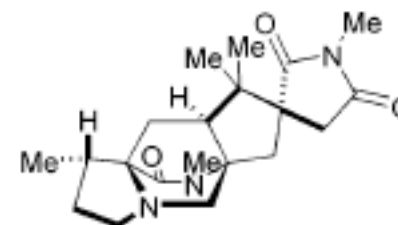
11, sclerotiamide



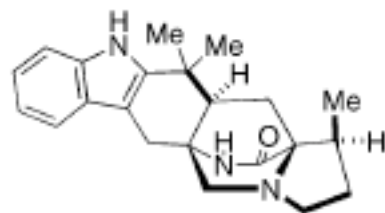
5, paraherquamide F, $R_1 = \text{H}$, $R_2 = \text{Me}$, $R_3 = \text{Me}$
 6, paraherquamide G, $R_1 = \text{OH}$, $R_2 = \text{Me}$, $R_3 = \text{Me}$
 7, VM55595, $R_1 = \text{H}$, $R_2 = \text{Me}$, $R_3 = \text{H}$



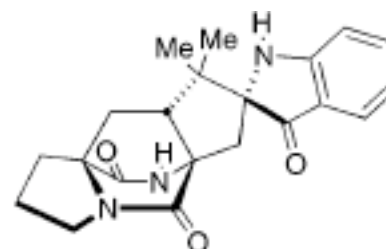
8, aspergamide B, $X = \text{N}^+ \text{-O}^-$
 9, stephacidin A, $X = \text{N}$



13, asperparaline A

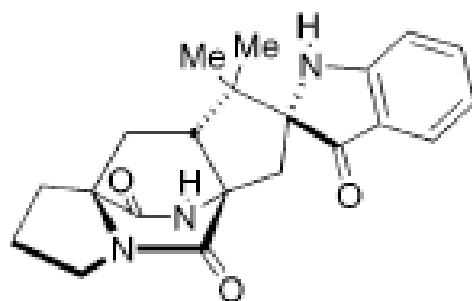


10, VM55599



12, brevianamide B

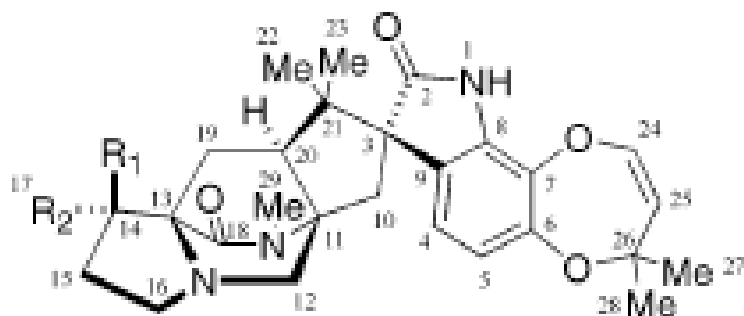
Williams' Work



12, brevianamide B

(-)-Brevianamide B

J. Am. Chem. Soc. **1990**, *112*, 808-821



1, paraherquamide A, $R_1 = \text{OH}$, $R_2 = \text{Me}$

2, paraherquamide B, $R_1 = \text{H}$, $R_2 = \text{H}$

(+)-Paraherquamide B

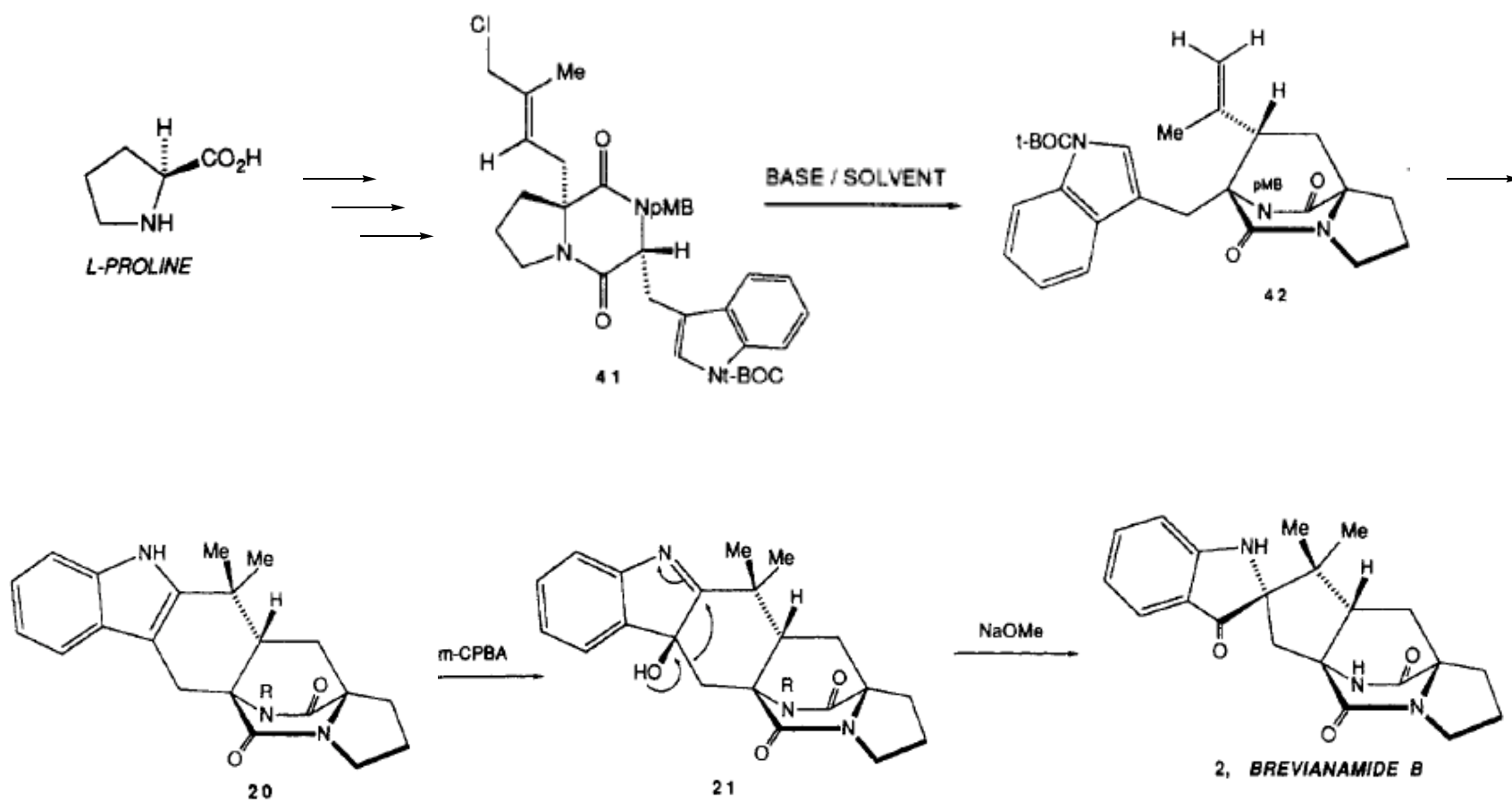
J. Am. Chem. Soc. **1996**, *118*, 557-579

Paraherquamide A

Angew. Chem. Int. Ed. **2000**, *39*, 2540-2544

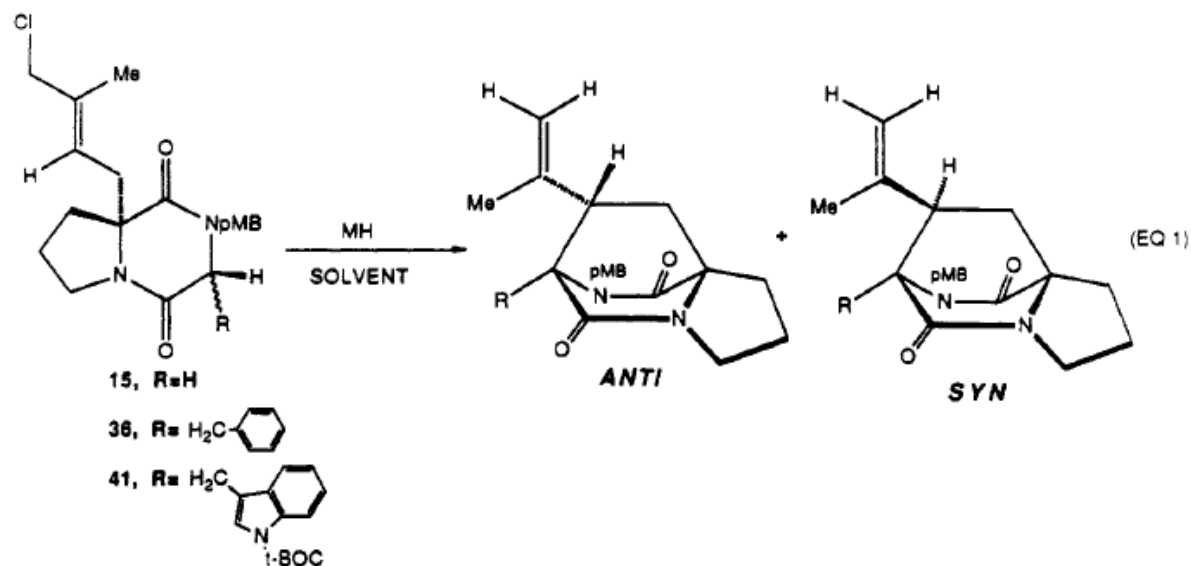
J. Am. Chem. Soc. **2003**, *125*, 12172-12178

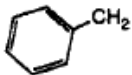
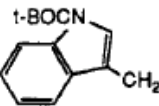
Key Steps in the Total Synthesis of Brevianamide B



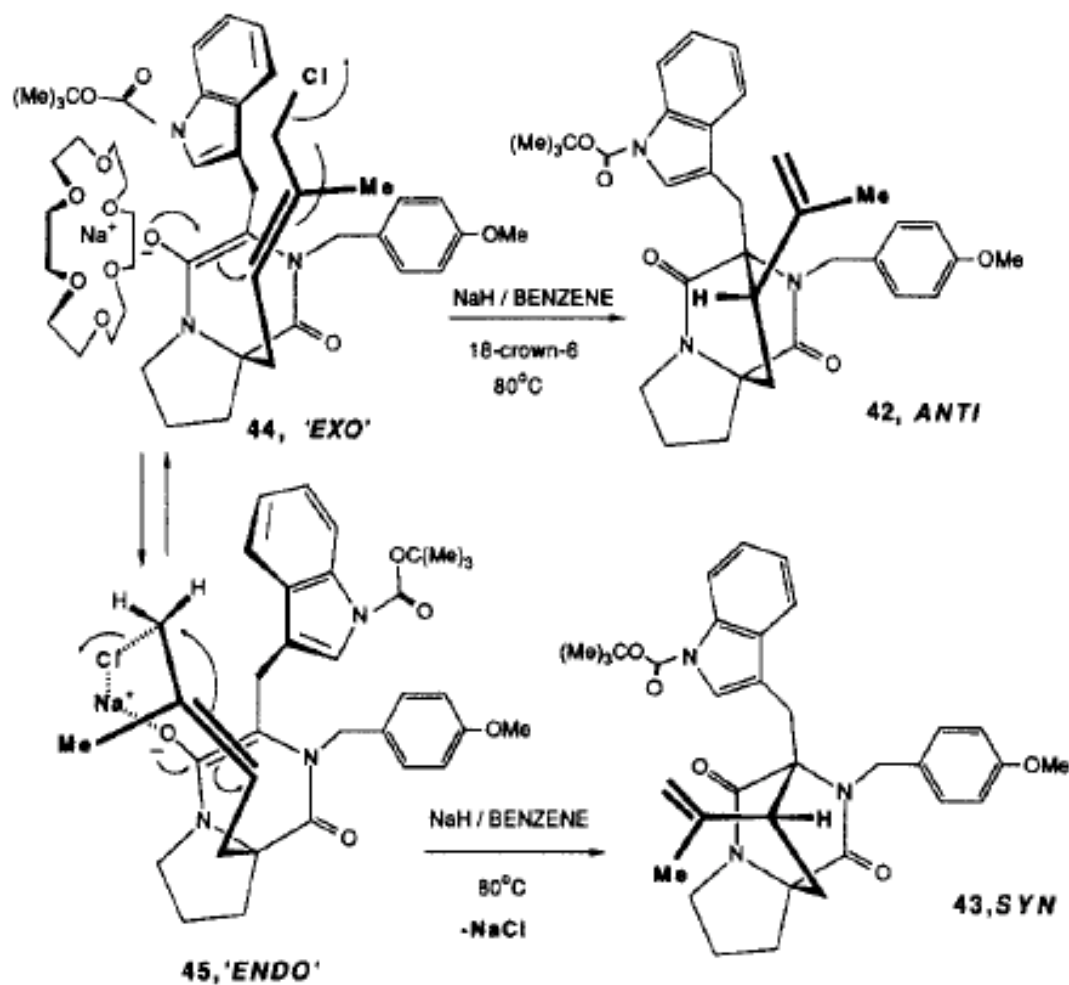
J. Am. Chem. Soc. **1990**, *112*, 808-821

Stereoselectivity in the SN2' Cyclization



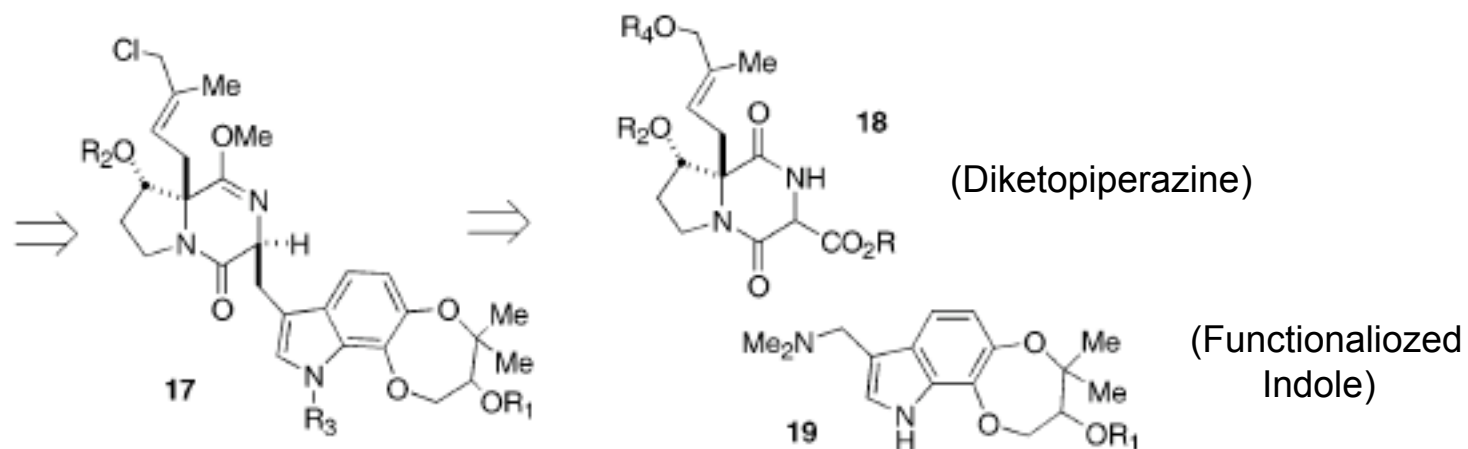
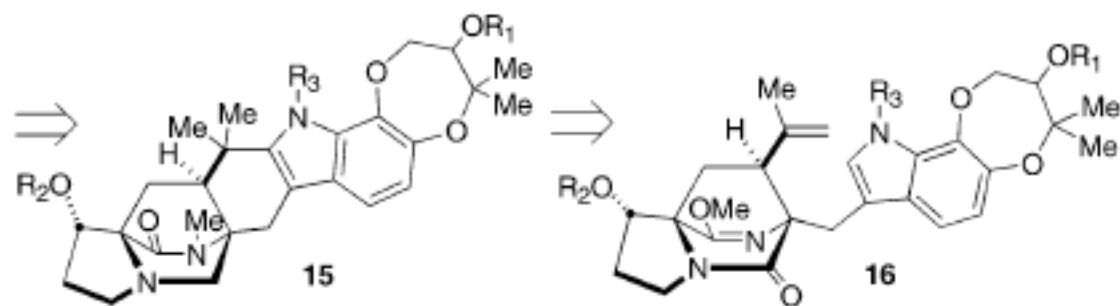
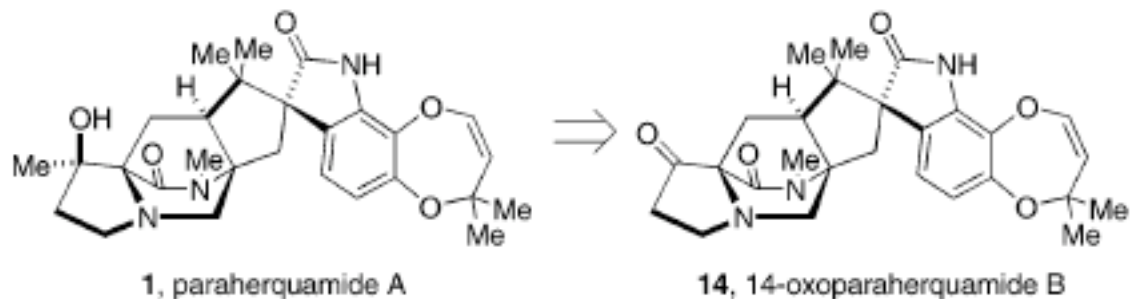
substrate (R)	solvent T, °C		base	ratio (anti:syn)	yield, %
H	DMF	25	NaH	10:1	60
	benzene	80	NaH	~0:1	10
	DMF	25	NaH	2:3	65
	benzene	80	NaH	~0:1	20
	DMF	25	NaH	2:1	63
	benzene	80	NaH	3:97	82
	benzene	80	NaH/18-crown-6	3.9:1	56
	benzene	80	KH/18-crown-6	1.1:1	38
	benzene	80	NaH/15-crown-5	1.42:1	40
	benzene	25	NaH/18-crown-6	6:1	14
	THF	67	NaH/18-crown-6	4.9:1	64

Rational for the Stereoselective SN2'



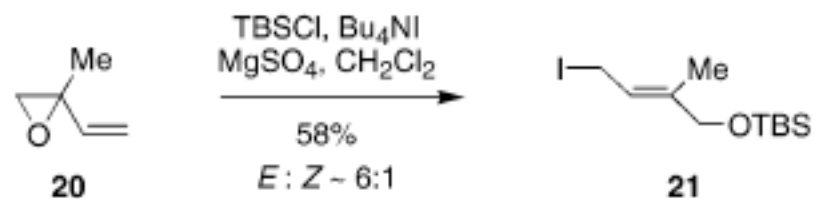
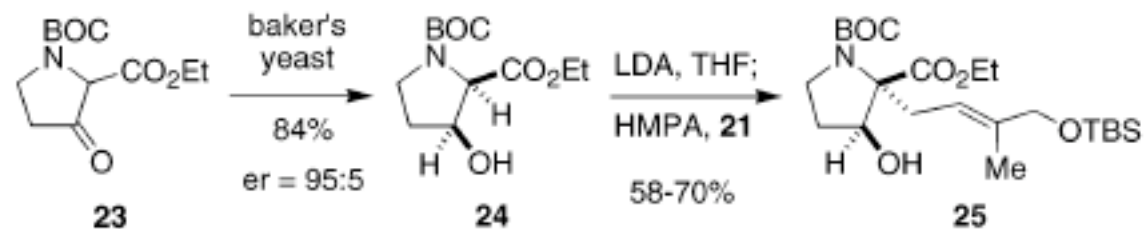
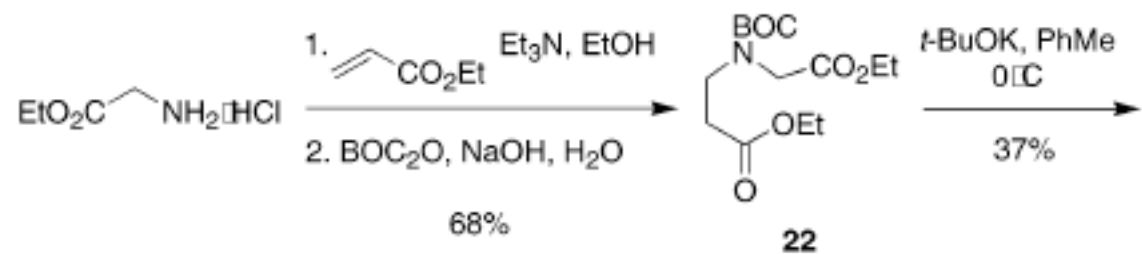
J. Am. Chem. Soc. **1990**, *112*, 808-821

Retrosynthesis of Paraherquamide A

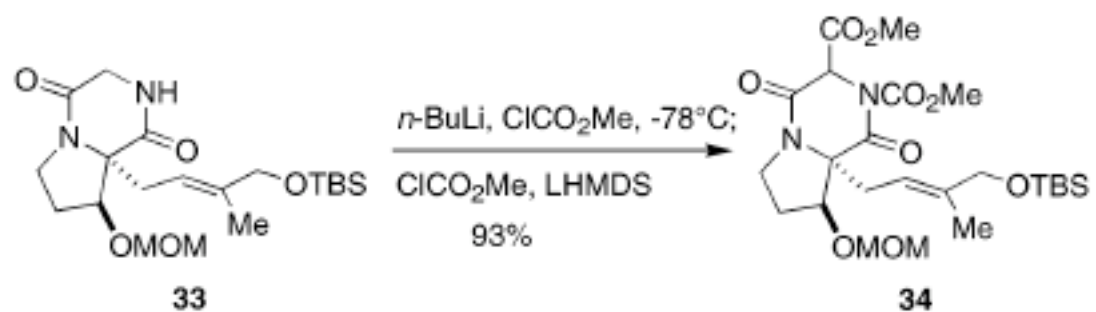
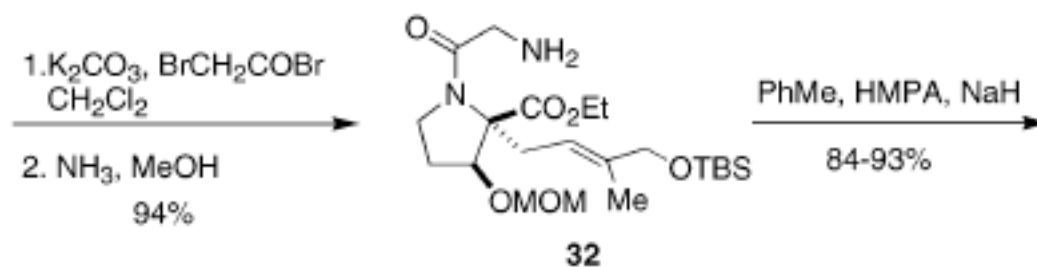
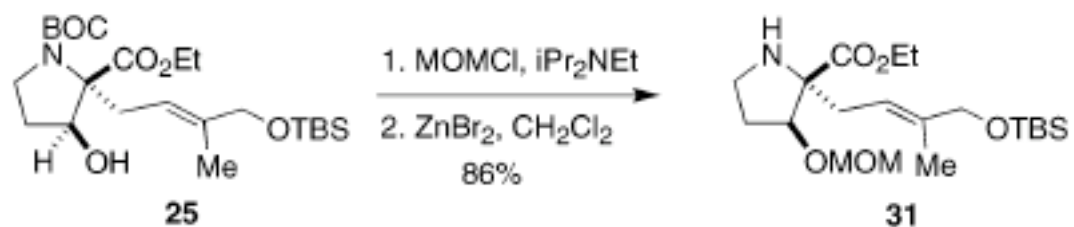


J. Am. Chem. Soc. **2003**, *125*, 12172-12178

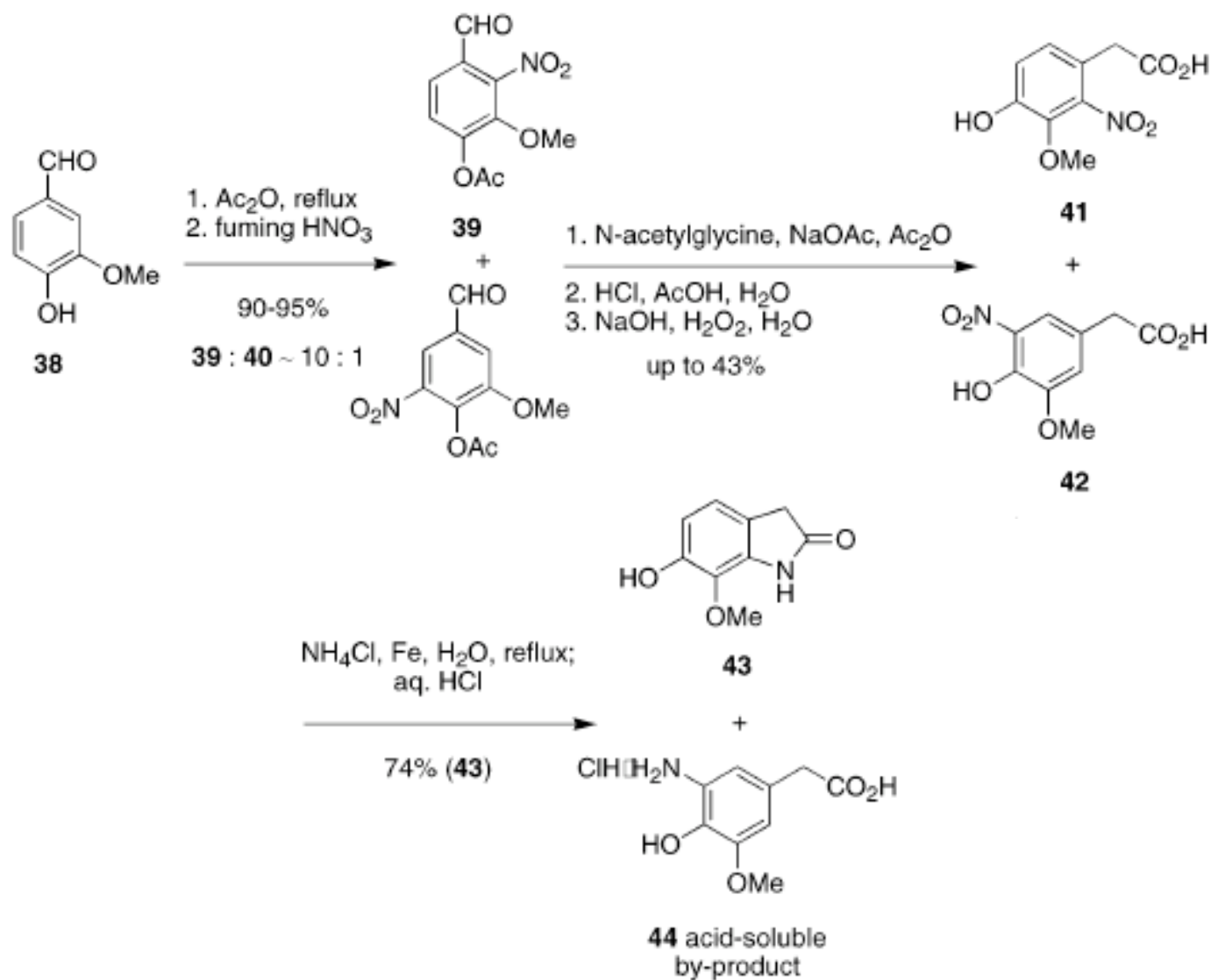
Synthesis of α -alkylated- β -Hydroxyproline **25**



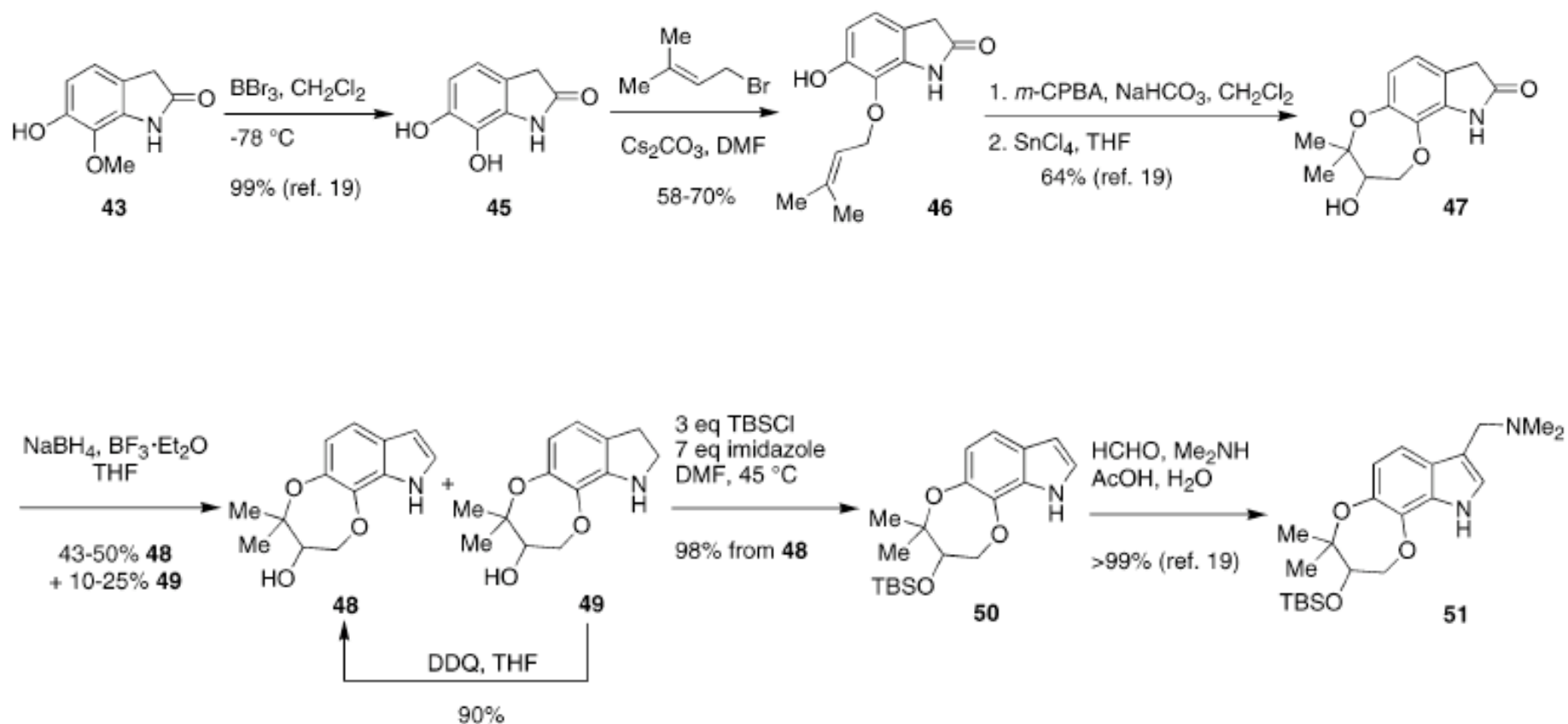
Synthesis of Diketopiperazine **34**



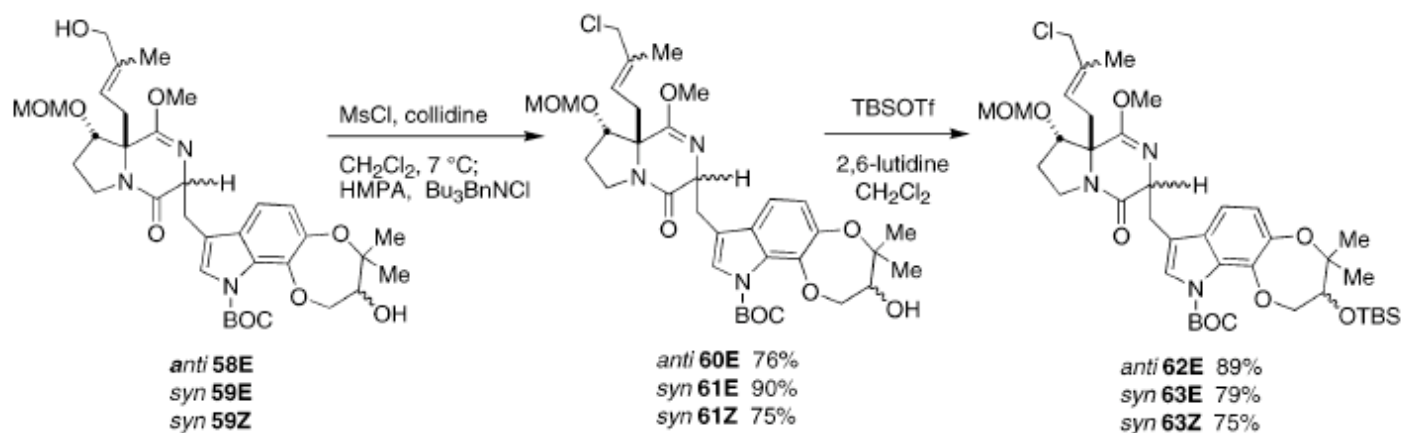
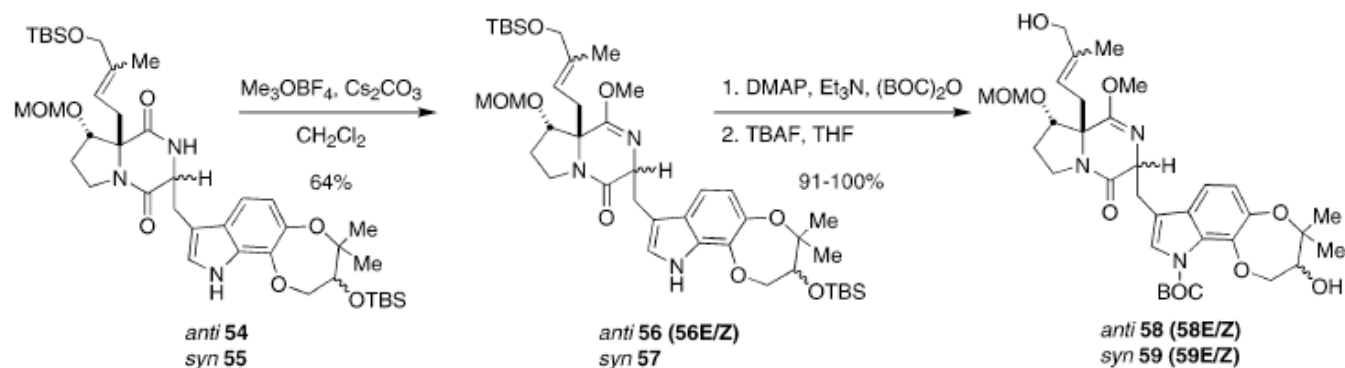
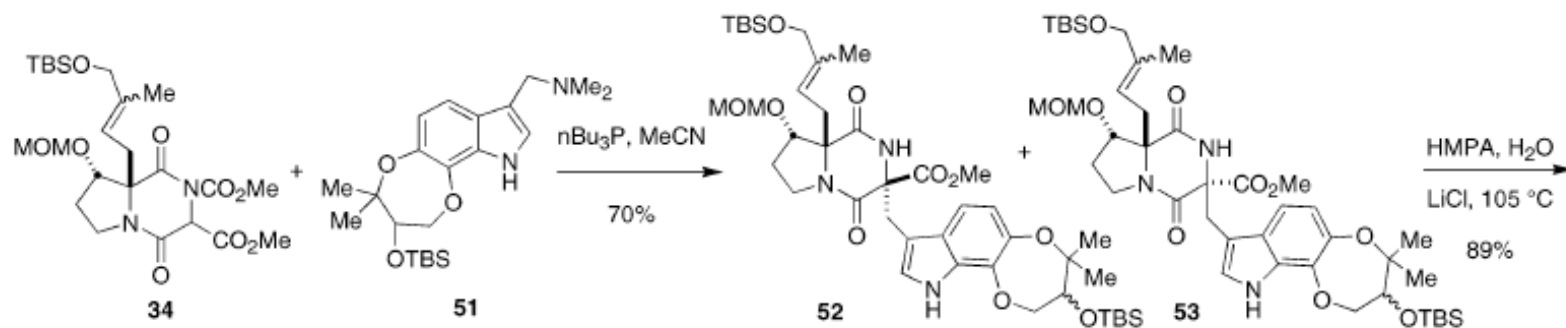
Synthesis of the Functionalized Indole



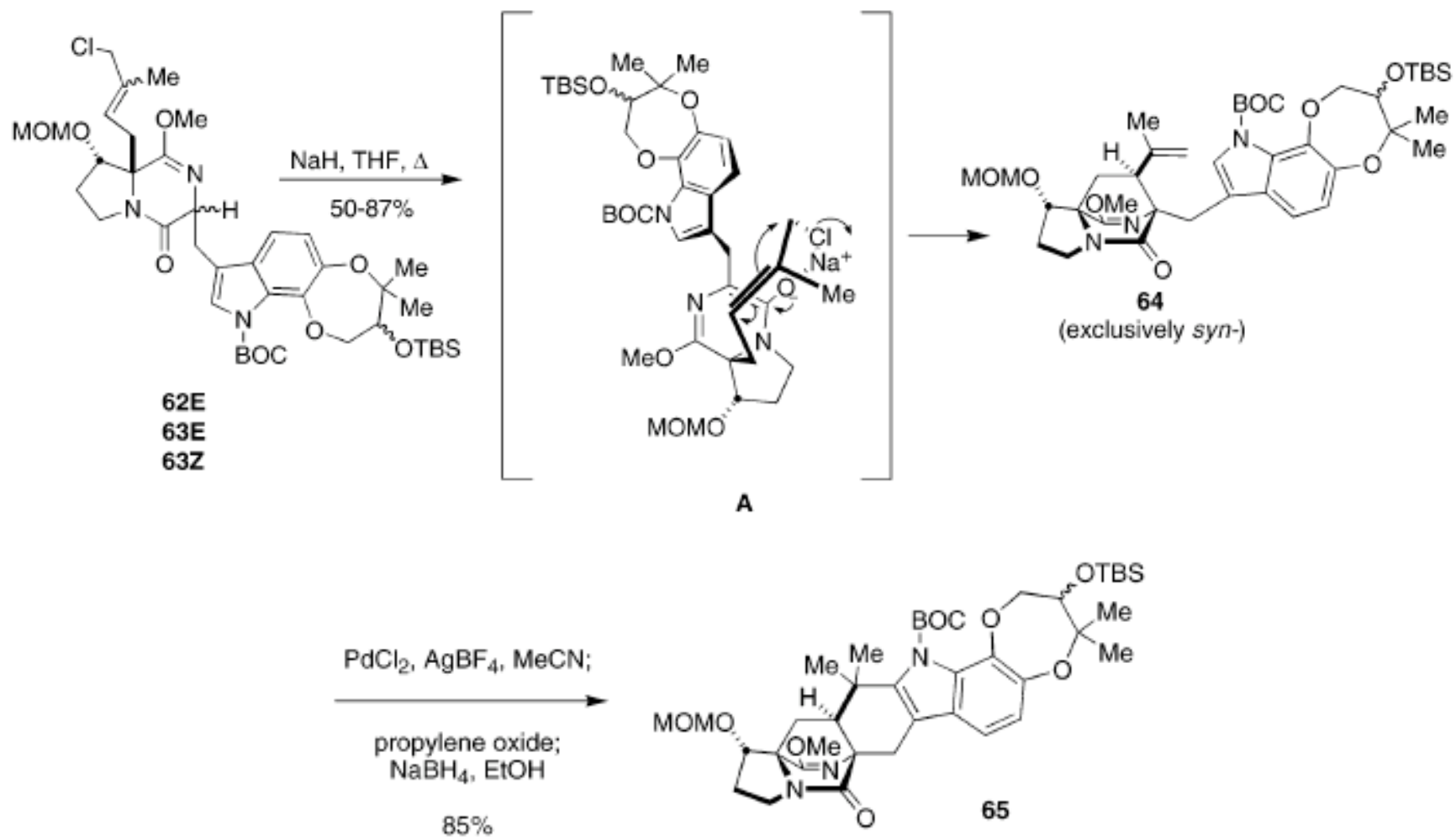
Synthesis of the Functionalized Indole 51



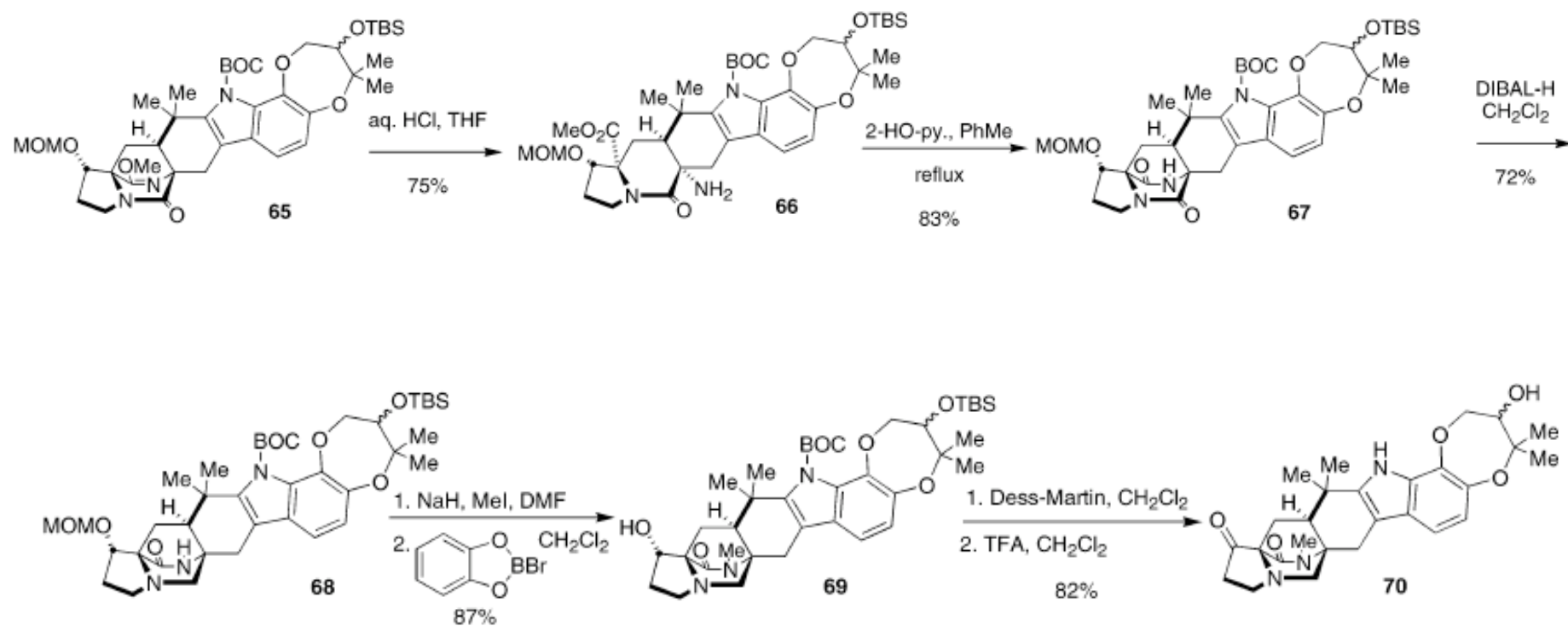
Coupling of the Indole and Diketopiperazine



Key Step 1: Intramolecular SN2'



Manipulation of the Hepacycle prior to Key Step 2



Key Step 2 and Completion

