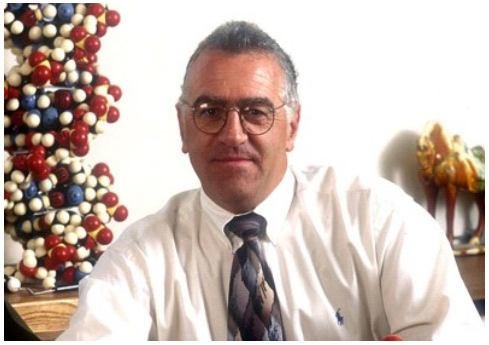
Robert M. Williams

Robert Demoret

Biography



DOB: February 8, 1953
New York

May, 1975: B.A., Chemistry, Syracuse University
Advisor: Professor Ei-ichi Negishi (synthesis)

1975-1979: Ph.D., Chemistry, Massachusetts Institute of Technology
Advisor: Dr. W. H. Rastetter (Epidithiapiperazinedione syntheses)

1979-1980: Postdoc, Harvard University
Advisor: Professor Y. Kishi (Total synthesis of erythromycin A)

Independent Career:

1980-1985: Assistant Professor, Colorado State University

1985-1988: Associate Professor, Colorado State University

1988-2002: Full Professor, Colorado State University

1994-present: Member, Editorial Board "*Chemistry and Biology*"

2002-present: University Distinguished Professor, Colorado State University

2012-present: Director for the Colorado Center of Drug Discovery (C2D2)

Current Group: 2 postdocs; 6 graduate students

Alumni: 78 former postdocs and 56 graduate students; 25 in academia

Primary Research Areas:
- Unnatural Amino Acid Synthesis
- Secondary Metabolite Total Synthesis
- Biosynthesis

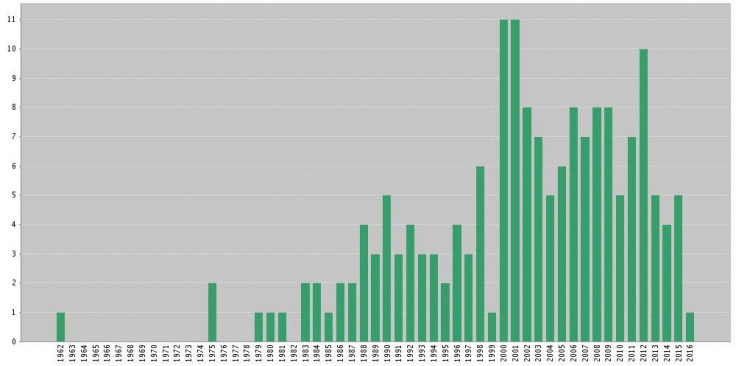
Awards

- Ernest Guenther Award in the Chemistry of Natural Products, American Chemical Society (2011)
- Multiple Myeloma Research Foundation Senior Award (2009-2011)
- University Distinguished Professor, Colorado State University (2002)
- Arthur C. Cope Scholar Award, American Chemical Society (2002)
- Japanese Society for the Promotion of Science (JSPS) Fellowship (1999)
- Merck & Co. Academic Development Award (1991-93)
- Fellow of the Alfred P. Sloan Foundation (1986-88)
- Eli Lilly Young Investigator Grantee (1986-88)
- NIH Research Career Development Awardee (1984-89)

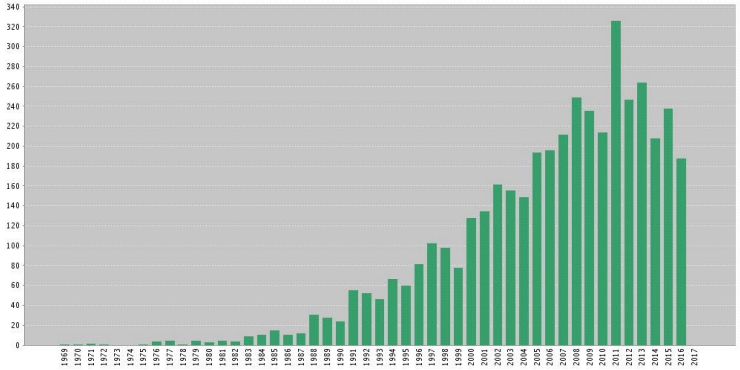
Research Impact

(from Web of Science)

Published Items in Each Year 311 total publications



Citations in Each Year Times Cited: 4138



Top 5 cited papers:
1. Biosynthesis of prenylated alkaloids derived from tryptophan. *Top. Curr. Chem.* **2000**, *209*, 97–174
2. Concise, asymmetric total synthesis of spirotryprostatin A. *Org. Lett.*, **2003**, 5 (17), 3135–3137
3. Asymetric synthesis of 2,6-diaminopimelic acids. *J. Org. Chem.*, **1992**, 57 (24), 6519–6527
4. A concise formal total synthesis of TMC-95A/B proteasome inhibitors *Org. Lett.*, **2003**, 5 (2), 197–200
5. Asymmetric total synthesis of (+) and (−) spirotryprostatin B *Tetrahedron,* **2002**, 58**,** 6311–6322

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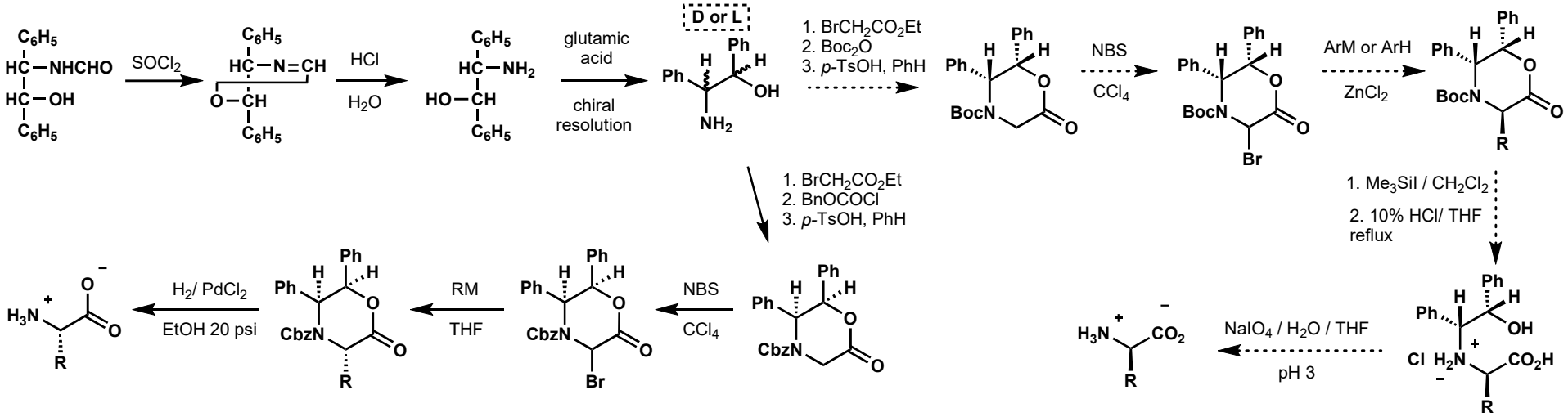
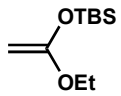
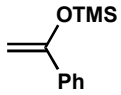
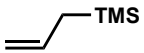
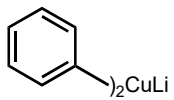
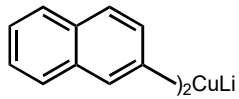
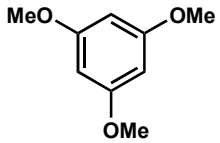
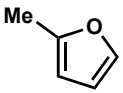
Electrophilic Glycinates (diphenyloxazinones)



RM	Reaction Condition	Yield	Amino Acid	% ee
	$ZnCl_2$ (1.2 eq), THF, rt, 1hr	71%	D-β-ethylaspartate**	96.6
	$ZnCl_2$ (1.2 eq), THF, rt, 1hr	54 %	L-homophenylalanine	96.9
	$ZnCl_2$ (2 eq), THF, rt, 3 days	68%	L-norvaline, L-allylglycine	98.3
MeZnCl	THF, rt, 1 hr	46%	L-alanine	96.8
$Me_2CuCNLi_2$	THF, -78 °C, 0.5 hr	28%		
$Bu_2CuCNLi_2$	THF, -78 °C, 0.5 hr	48%	L-norleucine	99.5

RM	Reaction Condition	% Yield (UAA)	% ee
	Et_2O/THF, -78 °C, 1hr	52	82
	Et_2O/THF, -78 °C, 1.5 hr	29	94
	$ZnCl_2$, THF, 25 °C, 4.5hr	62	91
	$ZnCl_2$, THF, 25 °C, 5.5hr 4 Å M.S.	26	90
	$ZnCl_2$, MeCN, 25 °C, 4hr 4 Å M.S.	73	93

J. Am. Chem. Soc. **1951**,73, 1216, *J. Am. Chem. Soc., **1986,** 1*08 (5),1103–1104

J. Org. Chem. **1990**,55, 3723-3728

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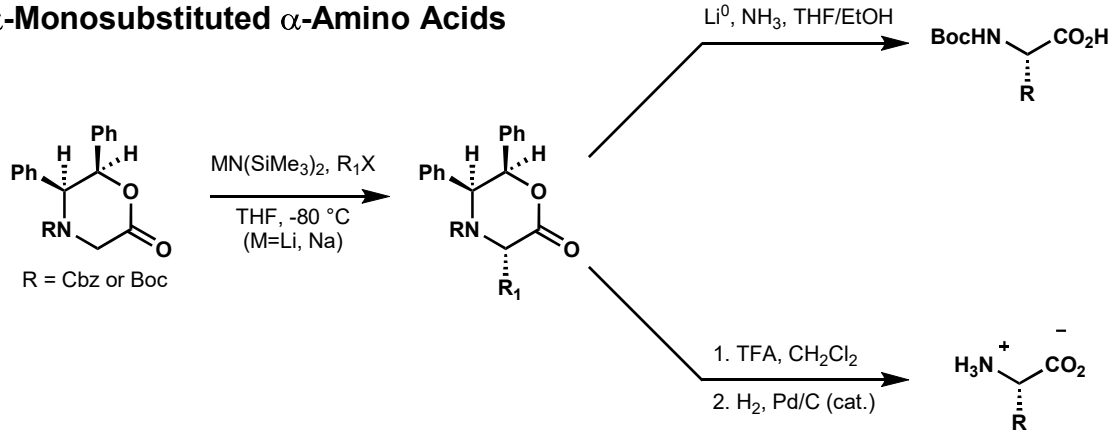
α-Monosubstituted α-Amino Acids



R = Cbz or Boc

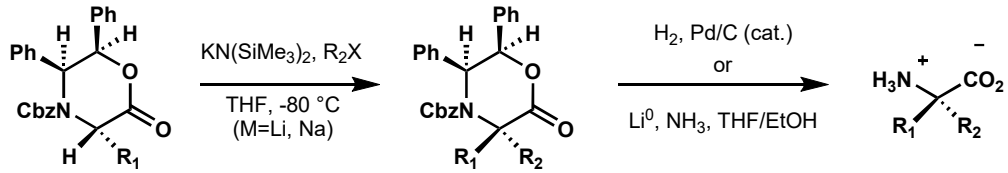
R_1X	Base (eq.)	% yield
$H_2C{=}CHCH_2I$	$LiN(SiMe_3)_2$ (1.2)	82
CH_3I	$NaN(SiMe_3)_2$ (1.1)	88
$PhCH_2Br$	$NaN(SiMe_3)_2$ (1.2)	77
$Me_2C{=}CHCH_2Br$	$NaN(SiMe_3)_2$ (1.1)	84
$BrCH_2CO_2Et$	$NaN(SiMe_3)_2$ (1.1)	64*
n-C_3H_7I	$NaN(SiMe_3)_2$ (1.5)	76

Important Notes:

1. The base should be added to a stirring solution of the oxazinone and the electrophile at -80°C in order to prevent double alkylation (This is more pertinent for unactivated electrophiles).
   - It was noted that the addition of HMPA greatly increased the yields, likely through the prevention of aggregate formation.

2. KHMDS appears to be too reactive and tends to generate dialkylated products.
   - LDA, *n-BuLi,* t-BuLi, and NaH showed no "satisfactory" alkylation

α,α-Disubstituted Amino Acids

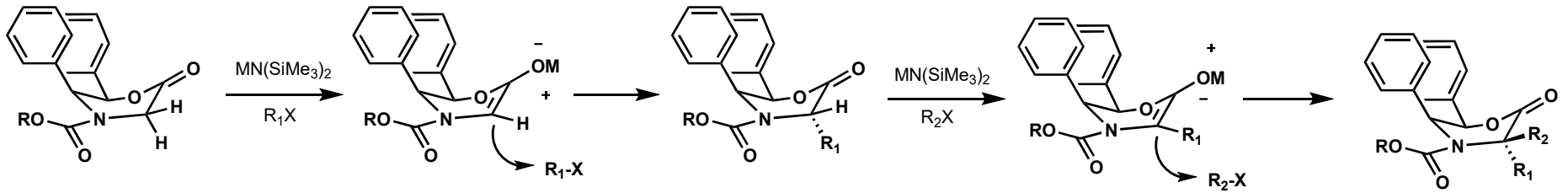


R_1	R_2X	$KN(SiMe_3)_2$ equiv.	% yield
Me	$PhCH_2Br$	2	84
n-C_3H_7	$PhCH_2Br$	2	0
n-C_3H_7	$PhCH_2Br$	5	85
allyl	$PhCH_2Br$	3	84

Important Notes:

1. The same protocol for monosubstituted amino acids had to be used however KHMDS was the only base that proved successful under the reaction conditions.
   - HMPA as an additive led to lower yields (It is presumed that the employment of HMPA for the more reactive potassium enolates only promotes decomposition).

Mechanistic Rationale



J. Am. Chem. Soc., **1991**, 113 (24), 9276–9286

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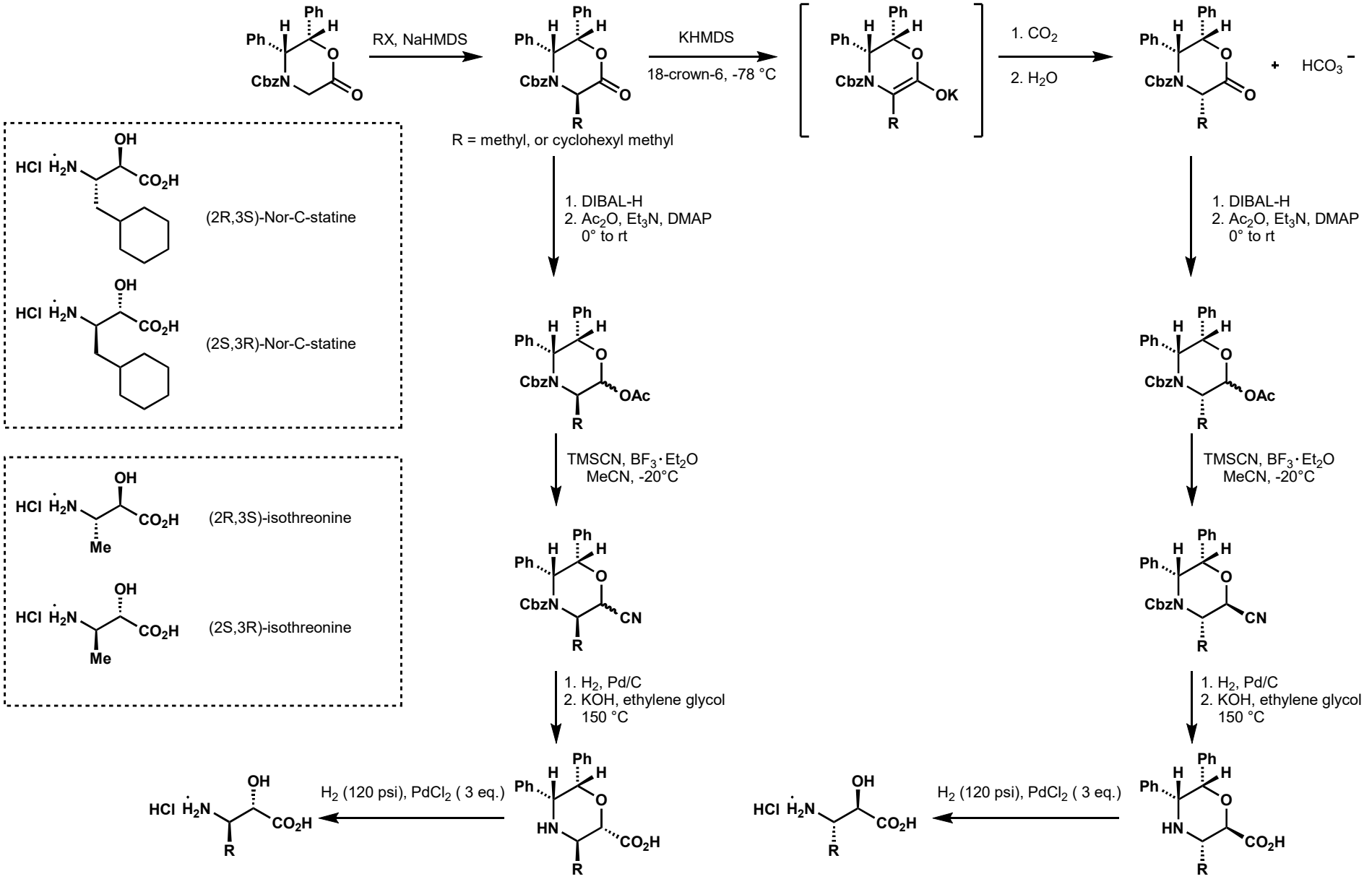
Synthesis of α-Hydroxy-β-amino Acids



J. Am. Chem. Soc., **2001**, 123, 3472–3477

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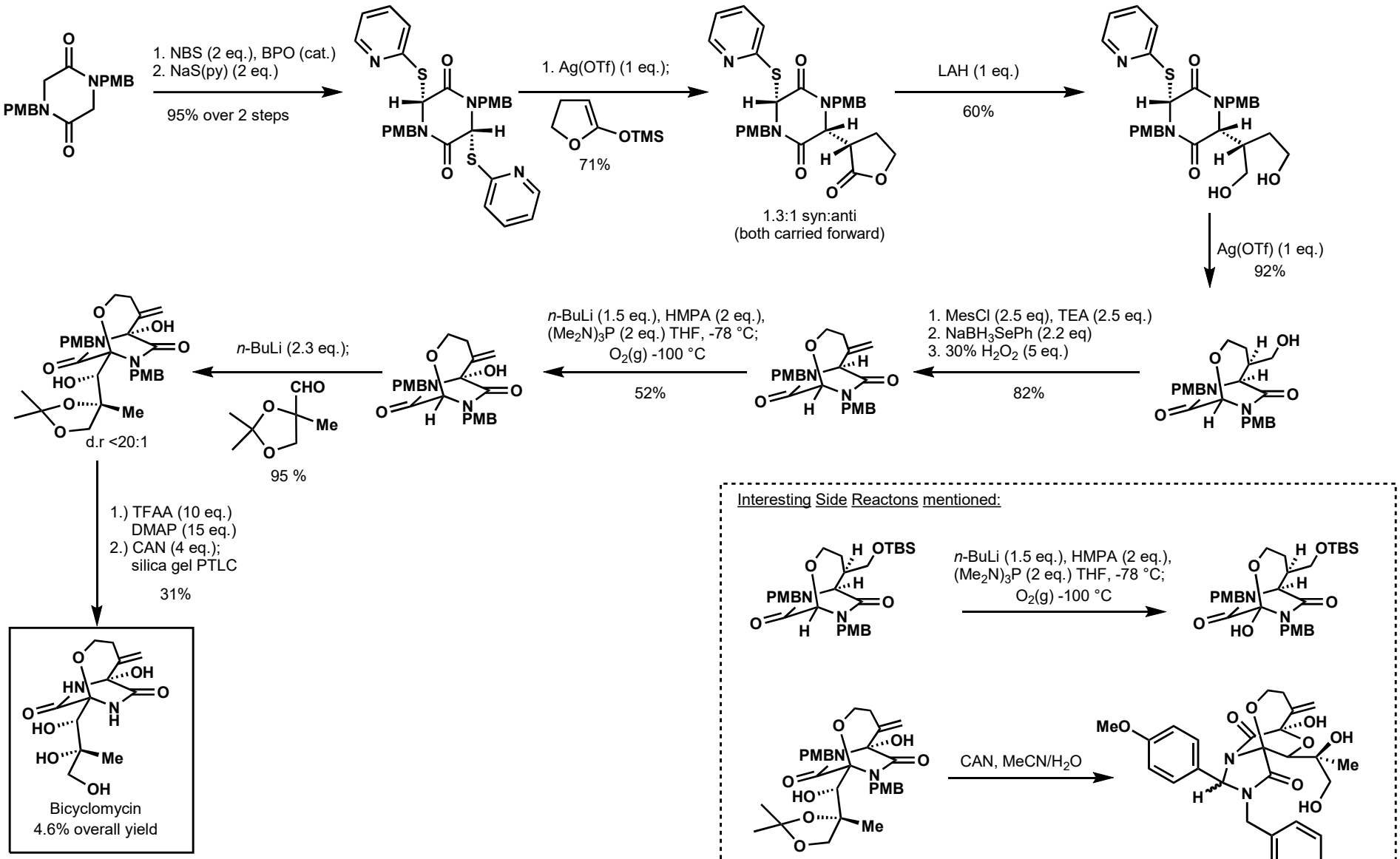
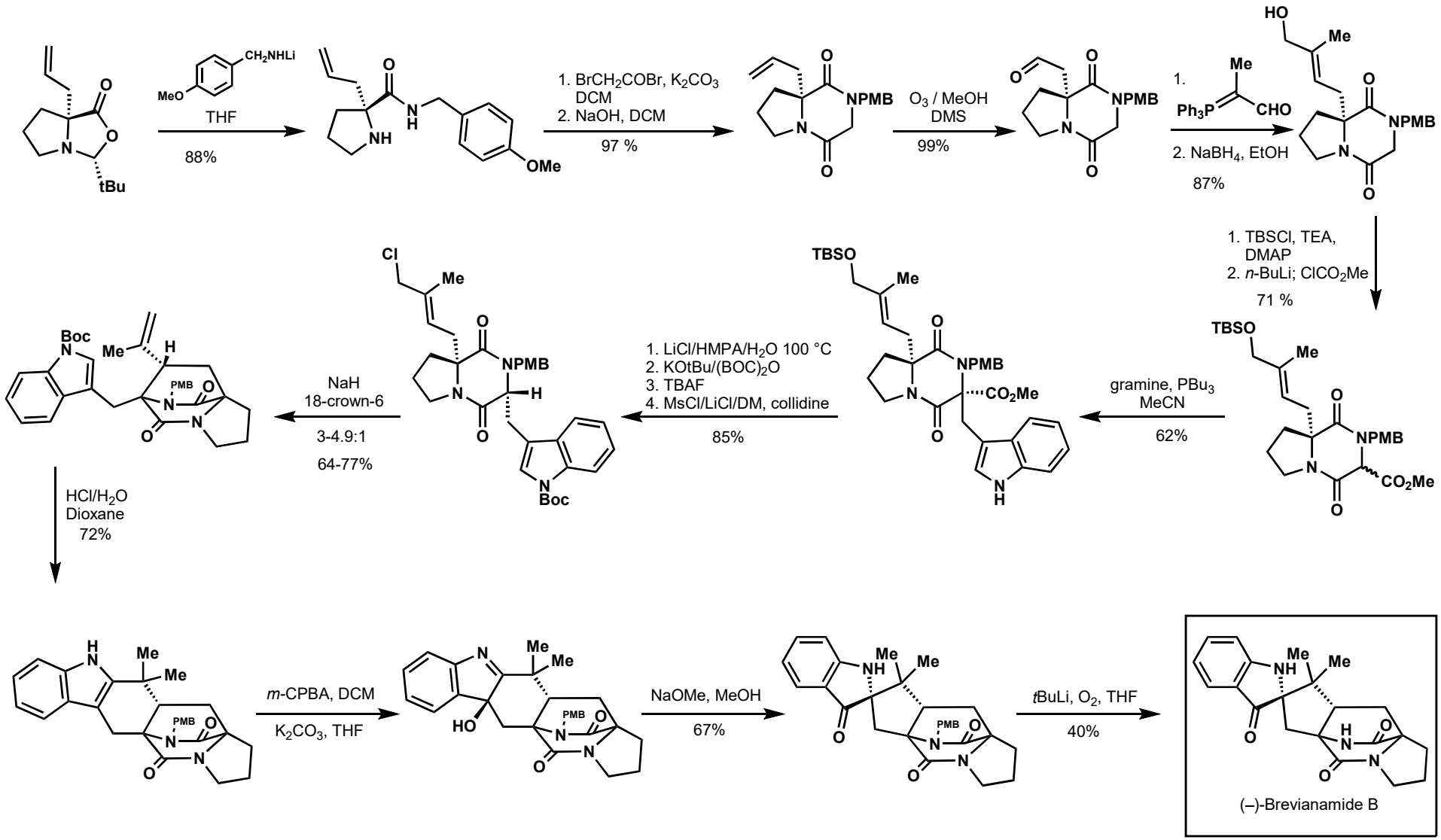
Total Synthesis of (±) and (+) Bicyclomycin:



Interesting Side Reactons mentioned:

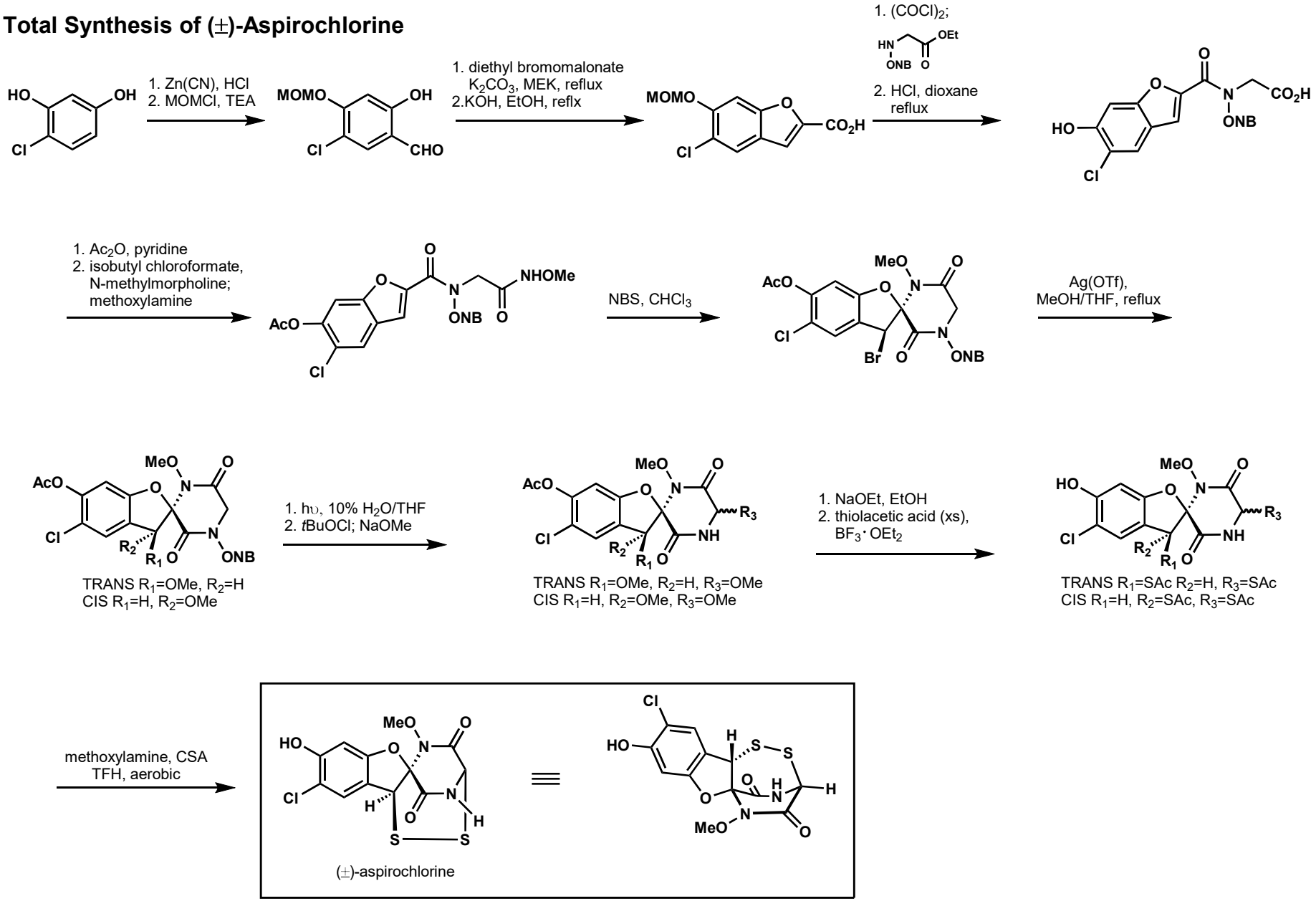
J. Am. Chem. Soc., **1984**, 106, 5748-5750, *J. Am. Chem. Soc.*, **1985**, 107, 3253-3266

Total Synthesis of (–)-Brevianamide B



J. Am. Chem. Soc., **1988**, 110, 5927-5929 *J. Am. Chem. Soc.*, **1990**, 112, 808-821

Total Synthesis of (±)-Aspirochlorine



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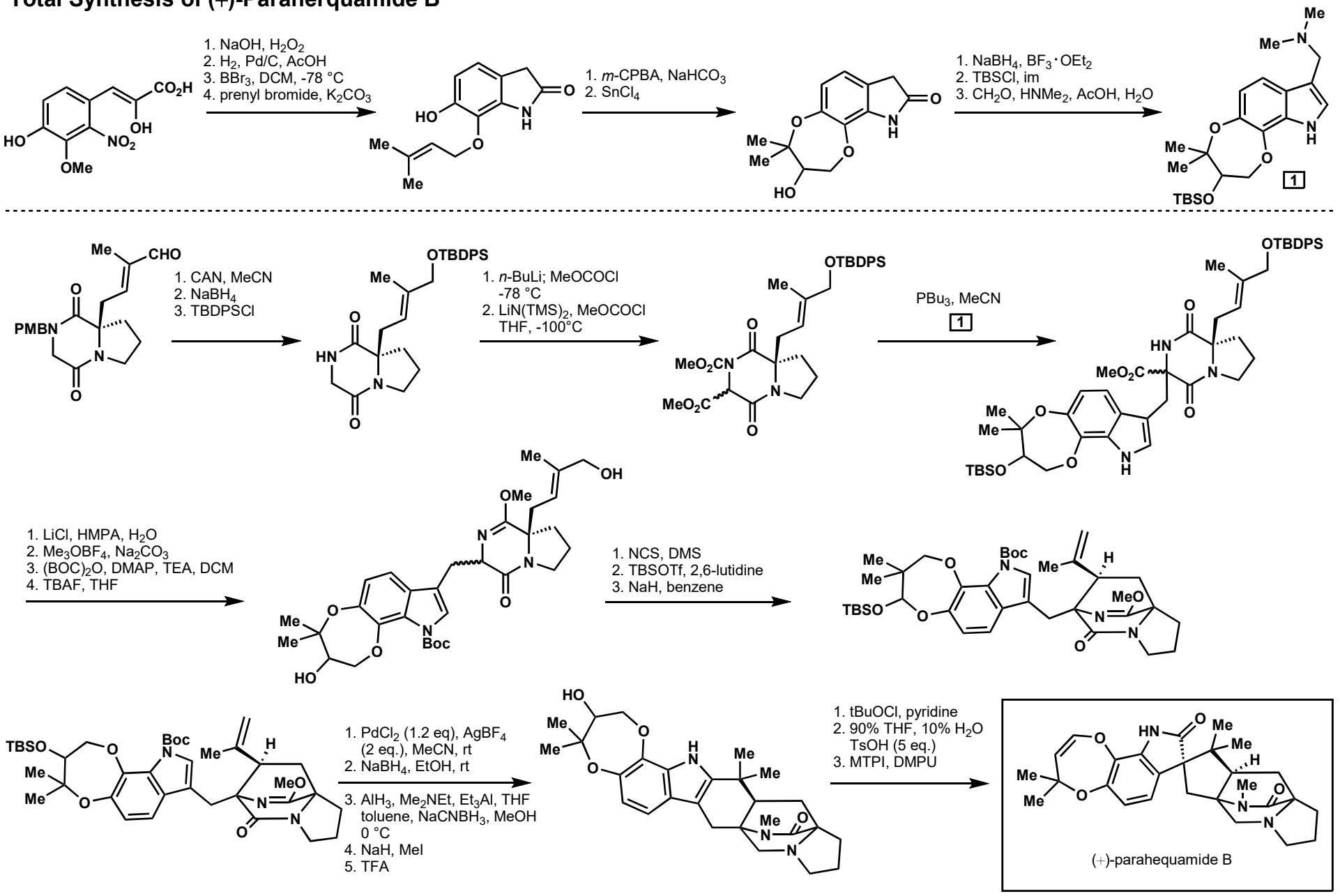
Total Synthesis of (+)-Paraherquamide B



J. Am. Chem. Soc. **1993**, 115, 9323-9324, *J. Am. Chem. Soc.* **1996**, 118, 557-579

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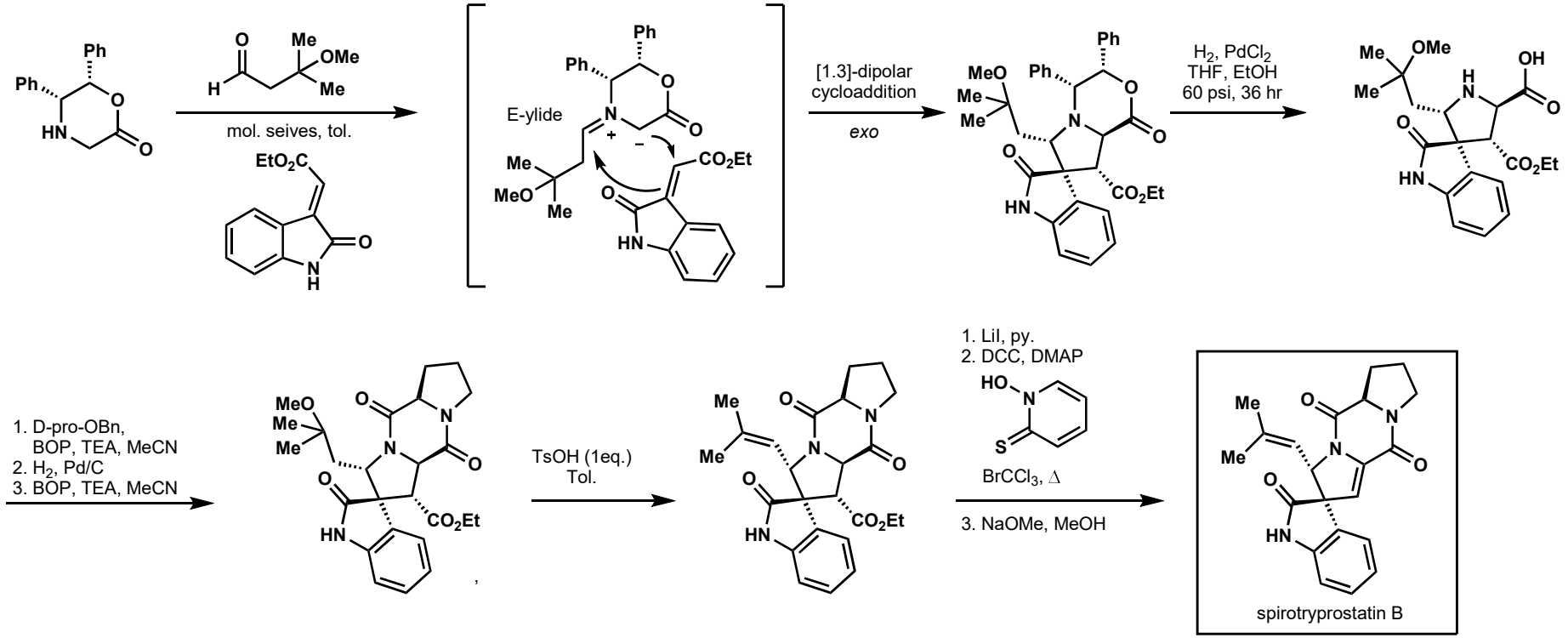
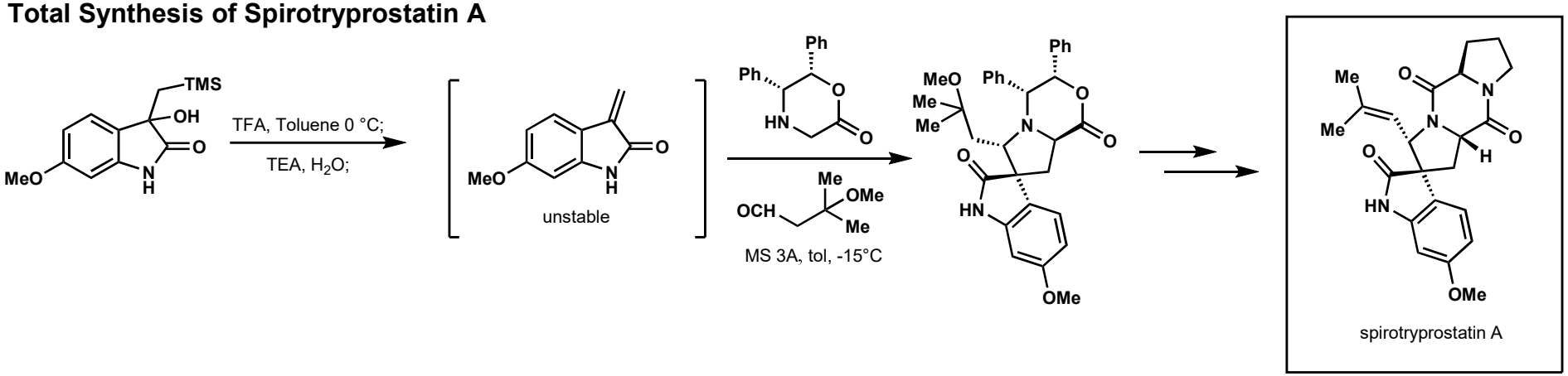
Total Synthesis of (+),(–)-Spirotryprostatin B

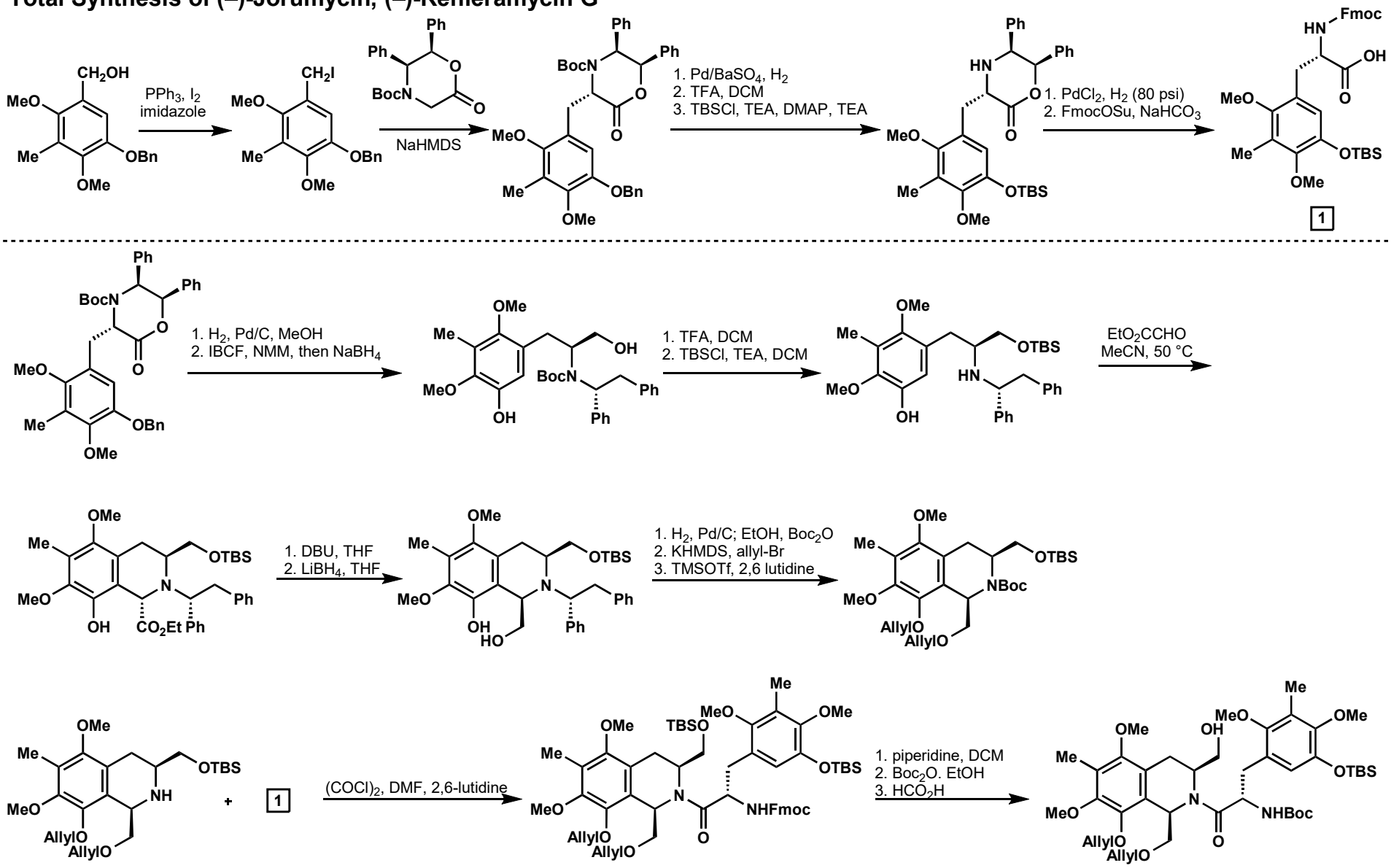


Total Synthesis of Spirotryprostatin A



J. Am. Chem. Soc., **2000**,122 (23),5666-5667, *Org. Lett.*, **2003**, 5 (17), 3135–3137

Total Synthesis of (–)-Jorumycin, (–)-Renieramycin G



J. Am. Chem. Soc., **2005**, 127 (36), pp 12684–12690

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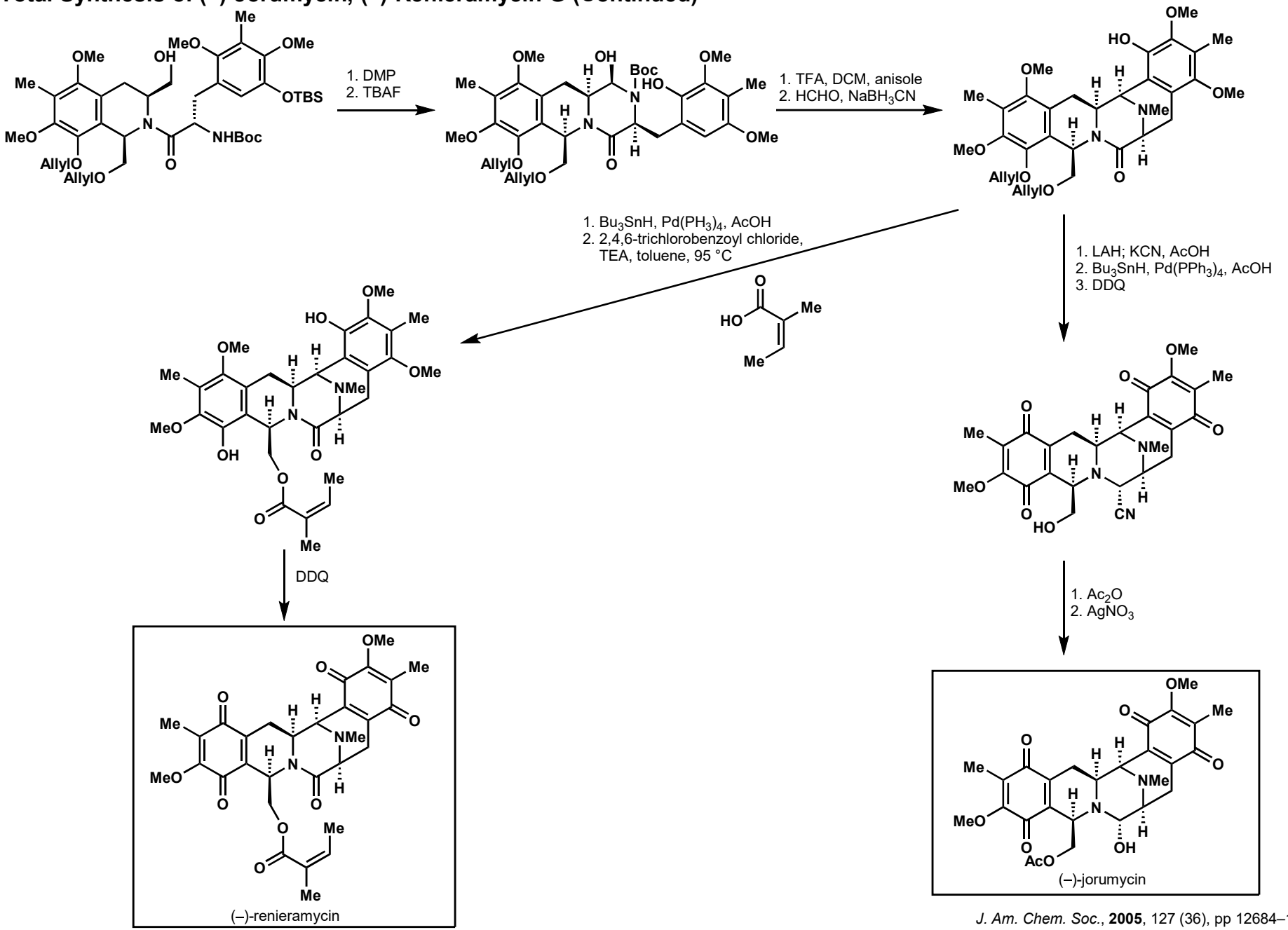
Total Synthesis of (–)-Jorumycin, (–)-Renieramycin G (Continued)



J. Am. Chem. Soc., **2005**, 127 (36), pp 12684–12690

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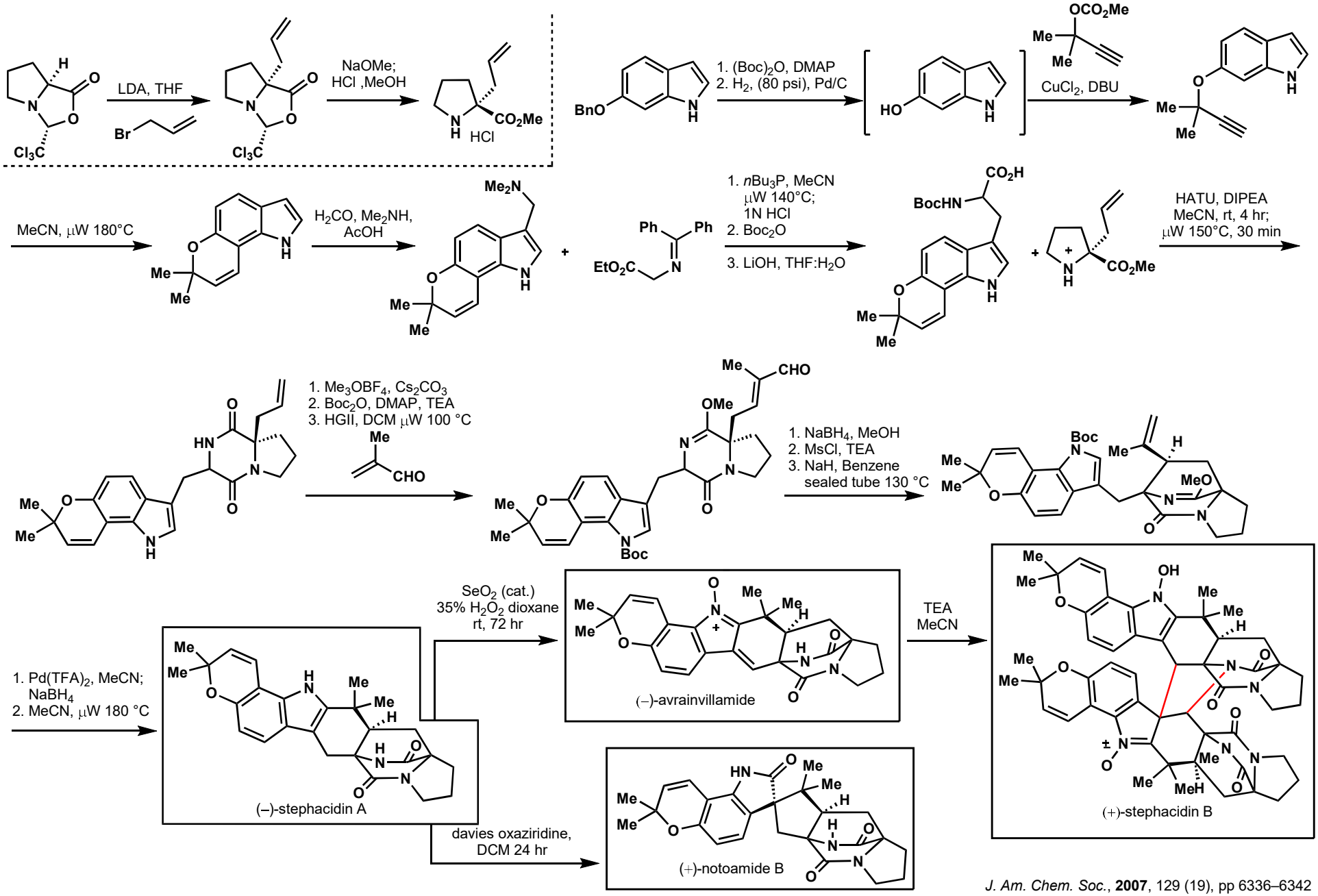
Total Synthesis of Stephacidins A, B and Notoamide B



J. Am. Chem. Soc., **2007**, 129 (19), pp 6336–6342

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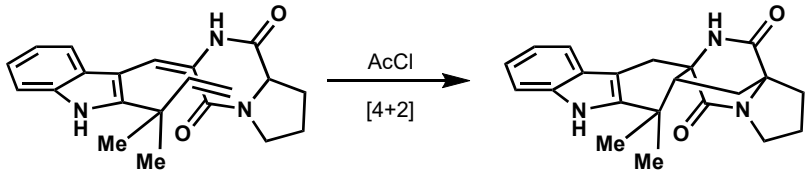
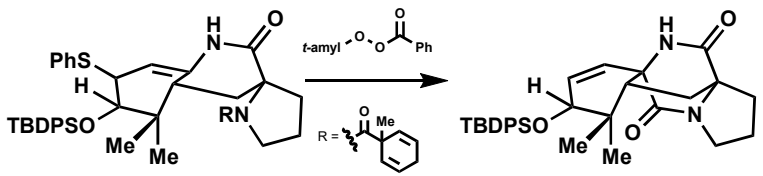
Approaches to construct the bicyclo[2.2.2]diazaoctane nucleus

Williams

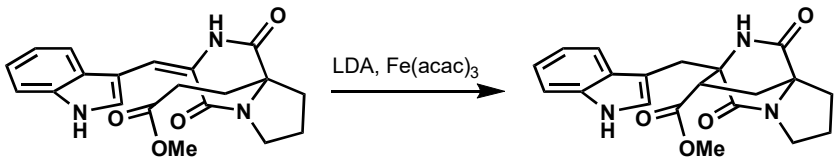
Liebscher

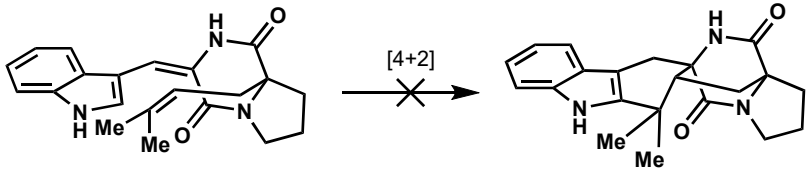


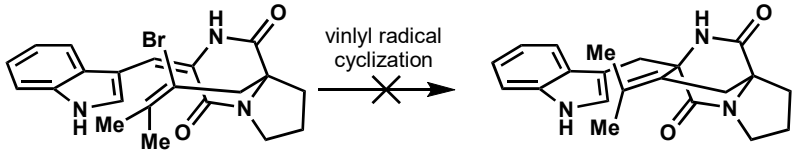
Myers



Baran

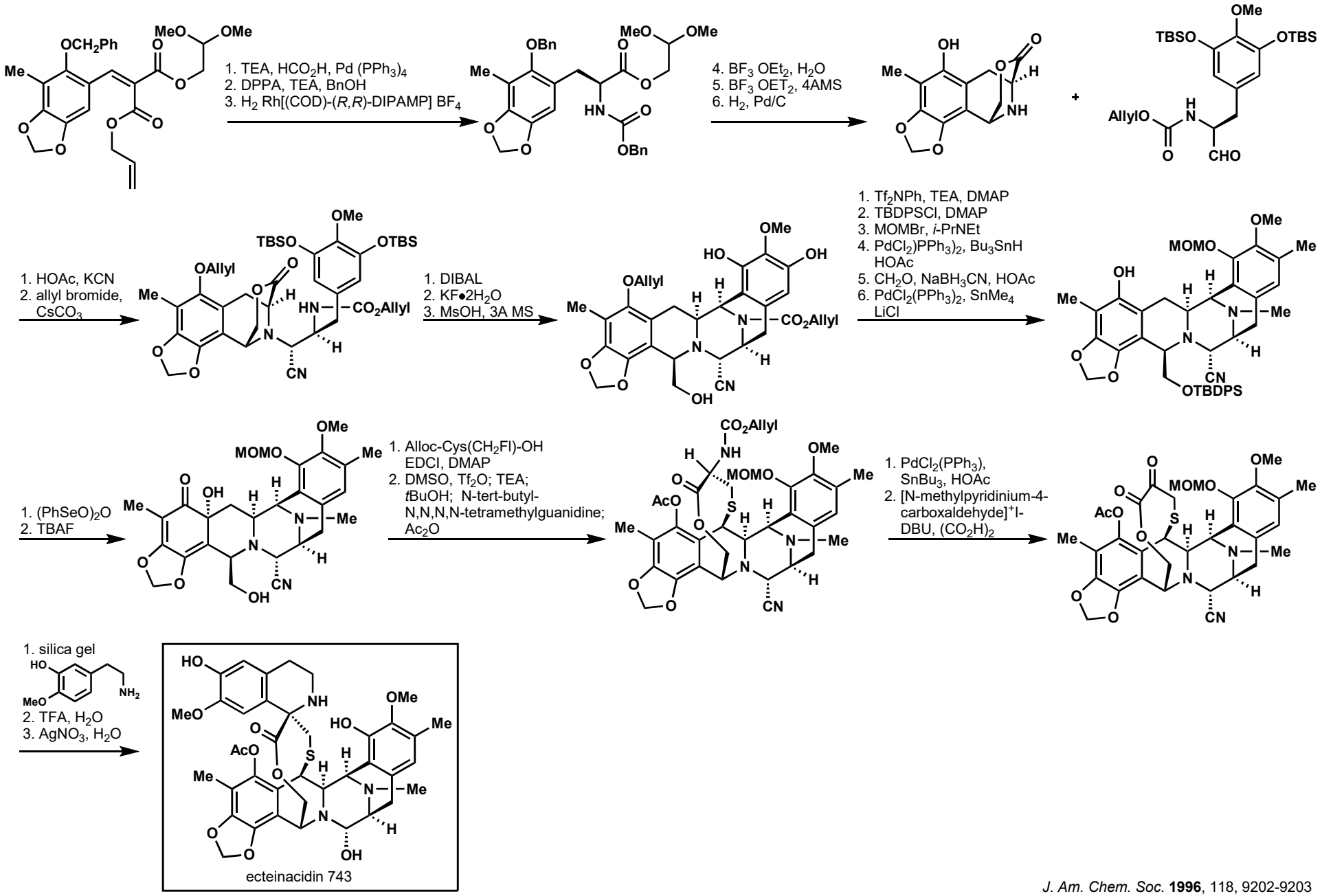






J. Am. Chem. Soc., **2006**, 128 (26), pp 8678–8693

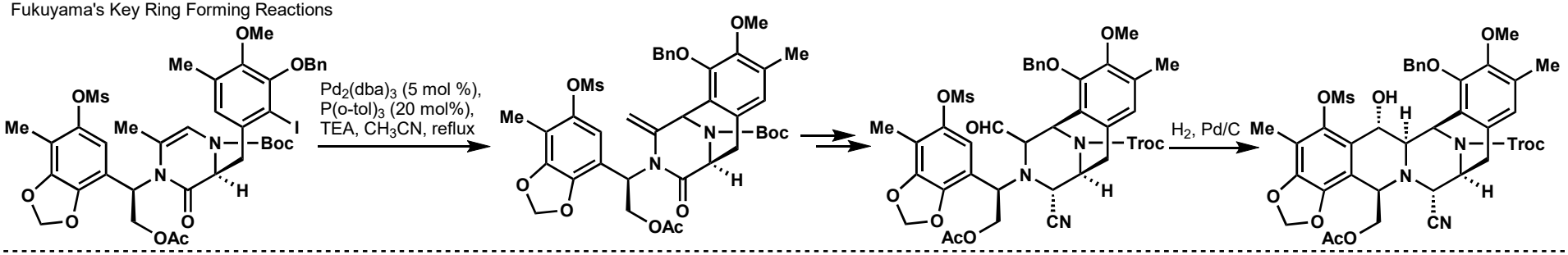
Total Synthesis of Ecteinascidin 743 (E.J. Corey)



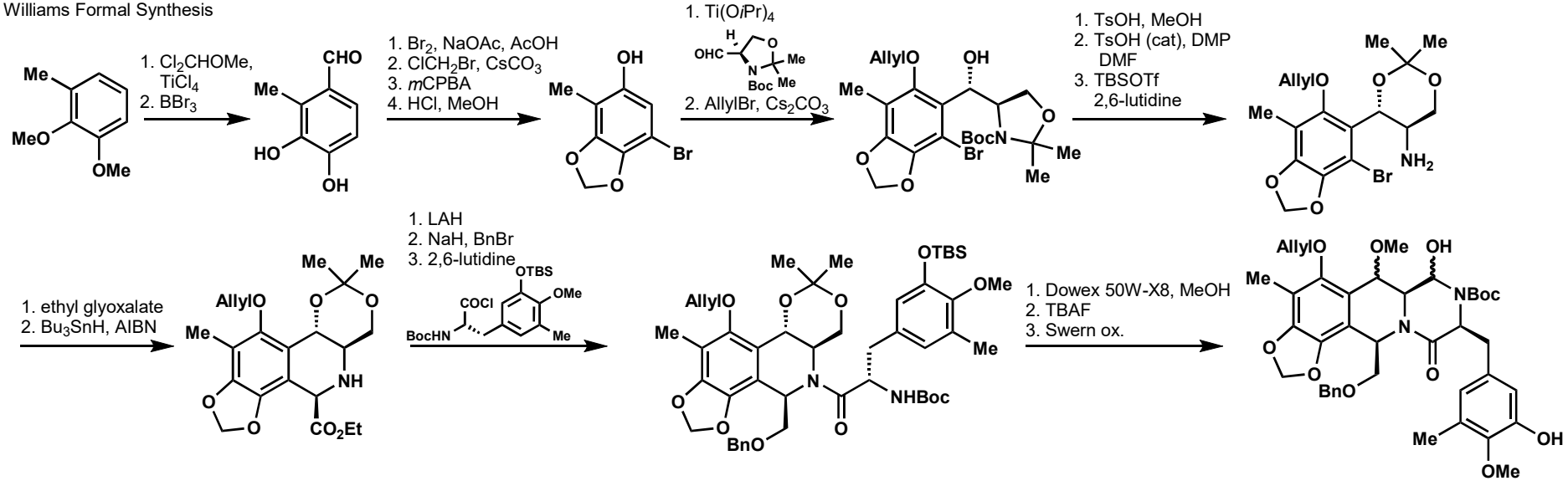
J. Am. Chem. Soc. **1996**, 118, 9202-9203

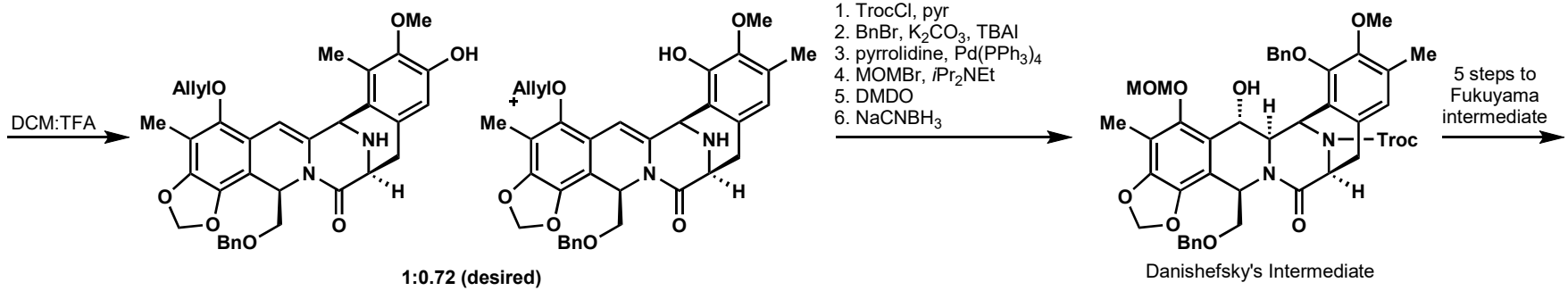
Williams Formal Synthesis of Ecteinascidin 743

Fukuyama's Key Ring Forming Reactions



Williams Formal Synthesis



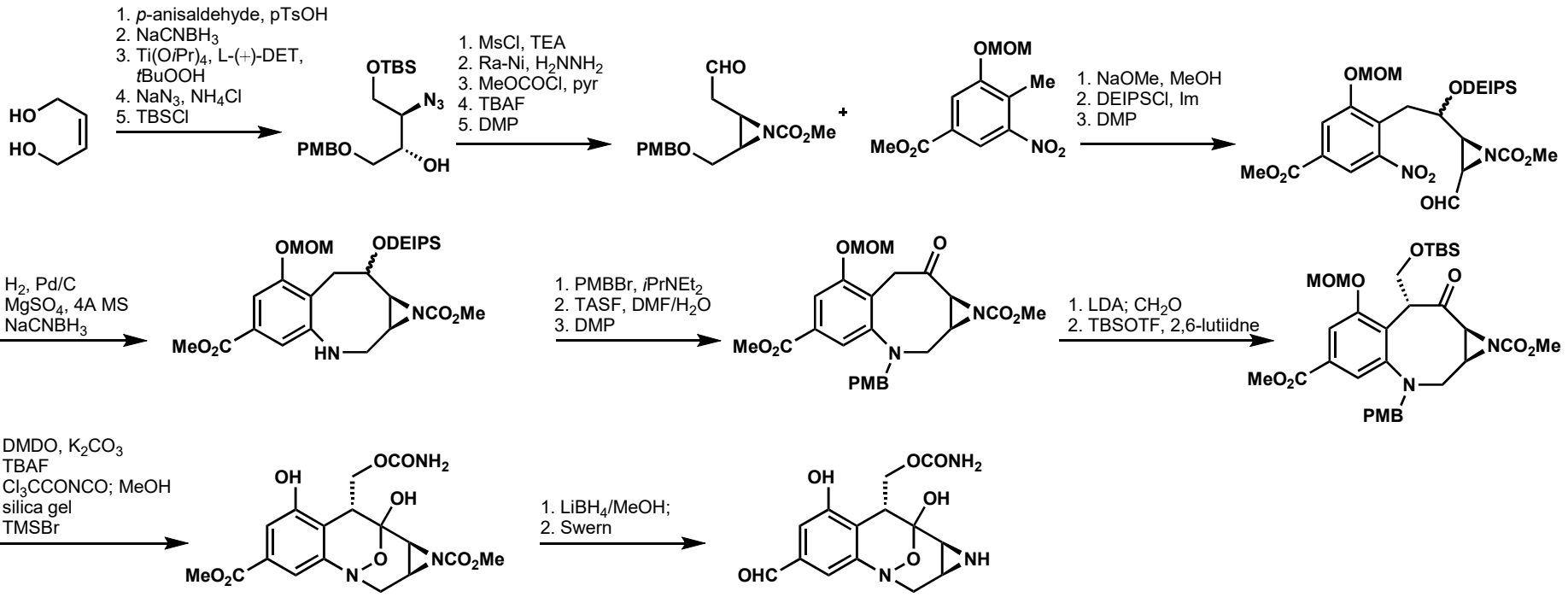


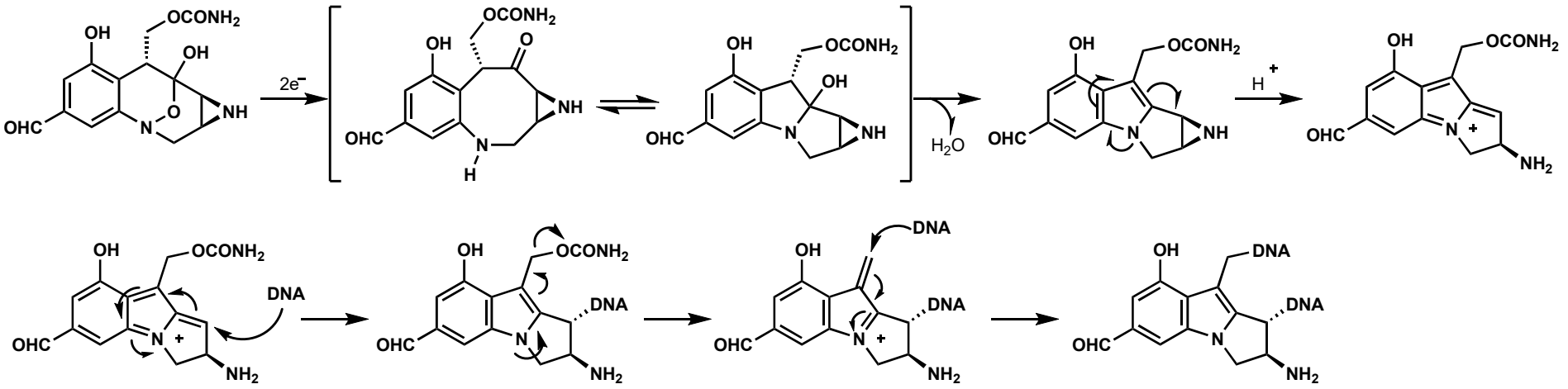
1:0.72 (desired)

Danishefsky's Intermediate

J. Am. Chem Soc. **2002**, 124, 6552-6554; *J. Org. Chem.* ***2008****, 73, 9594–9600*

Total Synthesis of (+)-FR66979 and (+)-FR900482





Angew. Chem. Int. Ed. **2002**, 41, 4683-4685; *Tetrahedron*, **2000**, 56, 521-532; *Chem. Rev.* **2013**, 113, 6816-6863