Total Synthesis of TMC-95A and -B via a New Reaction Leading to Z-Enamides.

Songnian Lin, Zhi-Qiang Yang, Benjamin H. B. Kwok, Michael Koldobskiy, Craig M. Crews, and Samuel J. Danishefsky*

J. Am. Chem. Soc. **2004**, *126*, 6347-6355

Related References:

Early works:

Angew. Chem. Int. Ed. **2001**, *40*, 1967 (core synthesis)

Angew. Chem. Int. Ed. **2002**, *41*, 512 (total synthesis)

J. Am. Chem. Soc. **2003**, *125*, 5111 (computation)

Other finished synthesis:

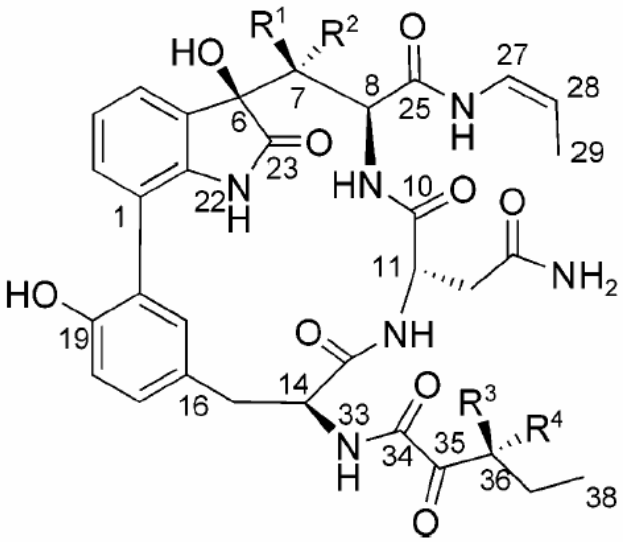
Hirama, Masahiro et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 2654

Williams, Robert et al. *Org. Lett*. **2003**, *5*, 197

Yu Zhang

August 26, 2004

Introduction to TMC-95 Family



TMC-95	R^1	R^2	R^3	R^4
A (1a)	H	OH	Me	H
B (1b)	H	OH	H	Me
C (1c)	OH	H	Me	H
D (1d)	OH	H	H	Me

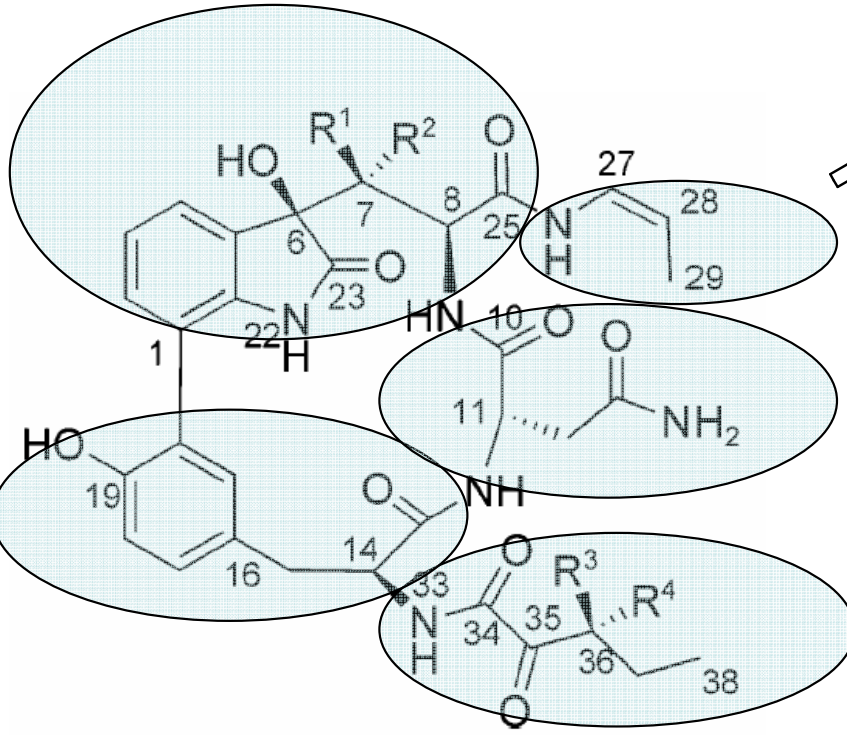
Figure 1. Structures of TMC-95A-D.

- Isolation: Isolated as fermentation products of *Apoispora Montagnei* in 2000.
- Biological Activity: TMC-95A inhibited the chymotrypsin-like, trypsin-like, and post-glutamyl peptide hydrolytic activities of proteasome with IC_{50} of 5.4, 200 and 60 nM. Also showed cytotoxic activities against human cancer cells HCT-116 & HL-60 with IC_{50} of 4.4 and 9.8μM.

Komatsubara, S. *J. Antibiot*. **2000**, *53*, 105.

Structural Characteristics of TMC-95A

Highly oxidized L-tryptophan moiety



Z-Enamide

L-asparagine

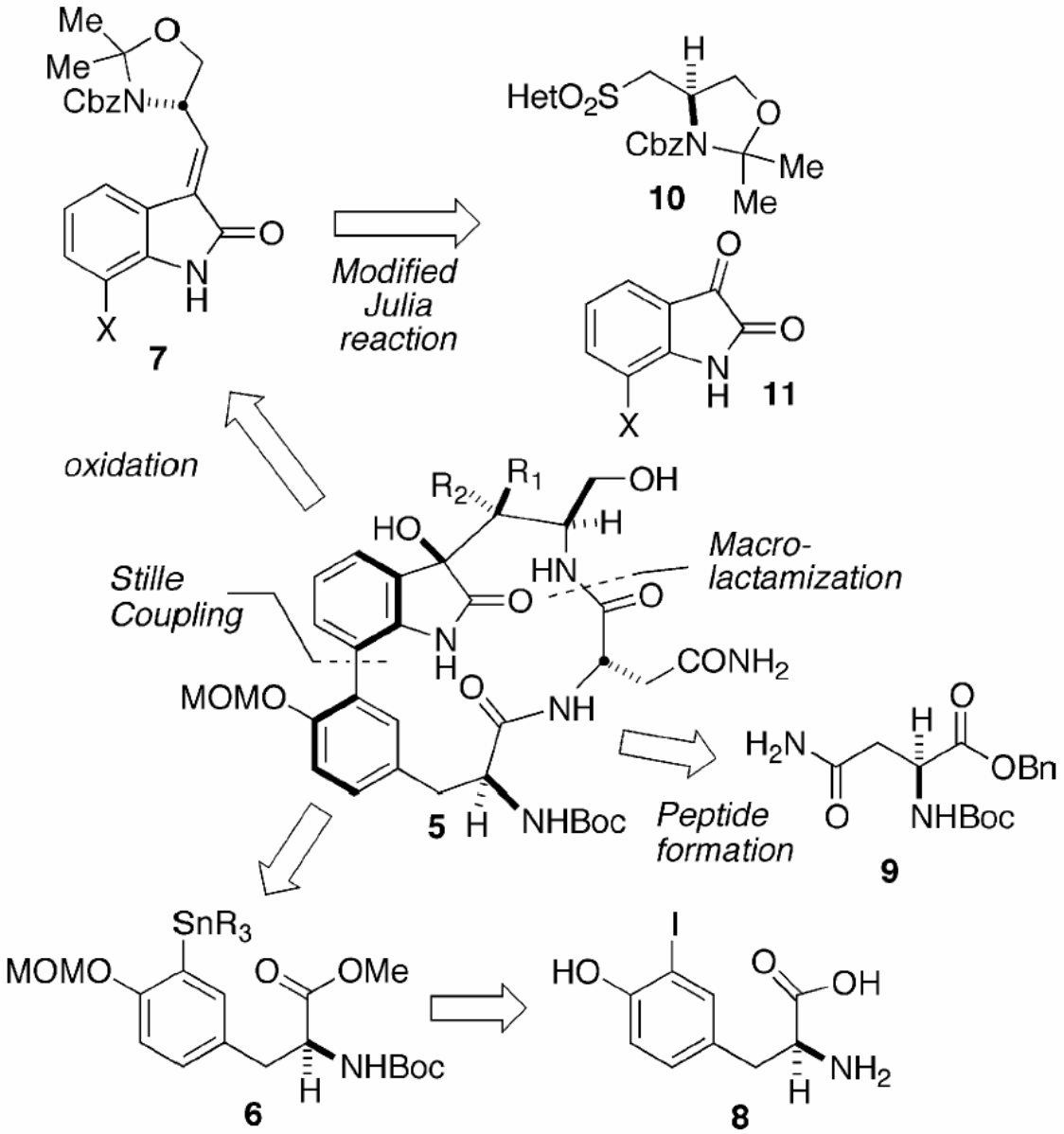
L-Tyrosine

TMC-95	R^1	R^2	R^3	R^4
A (1a)	H	OH	Me	H

3-methyl-2-oxopentanoic acid

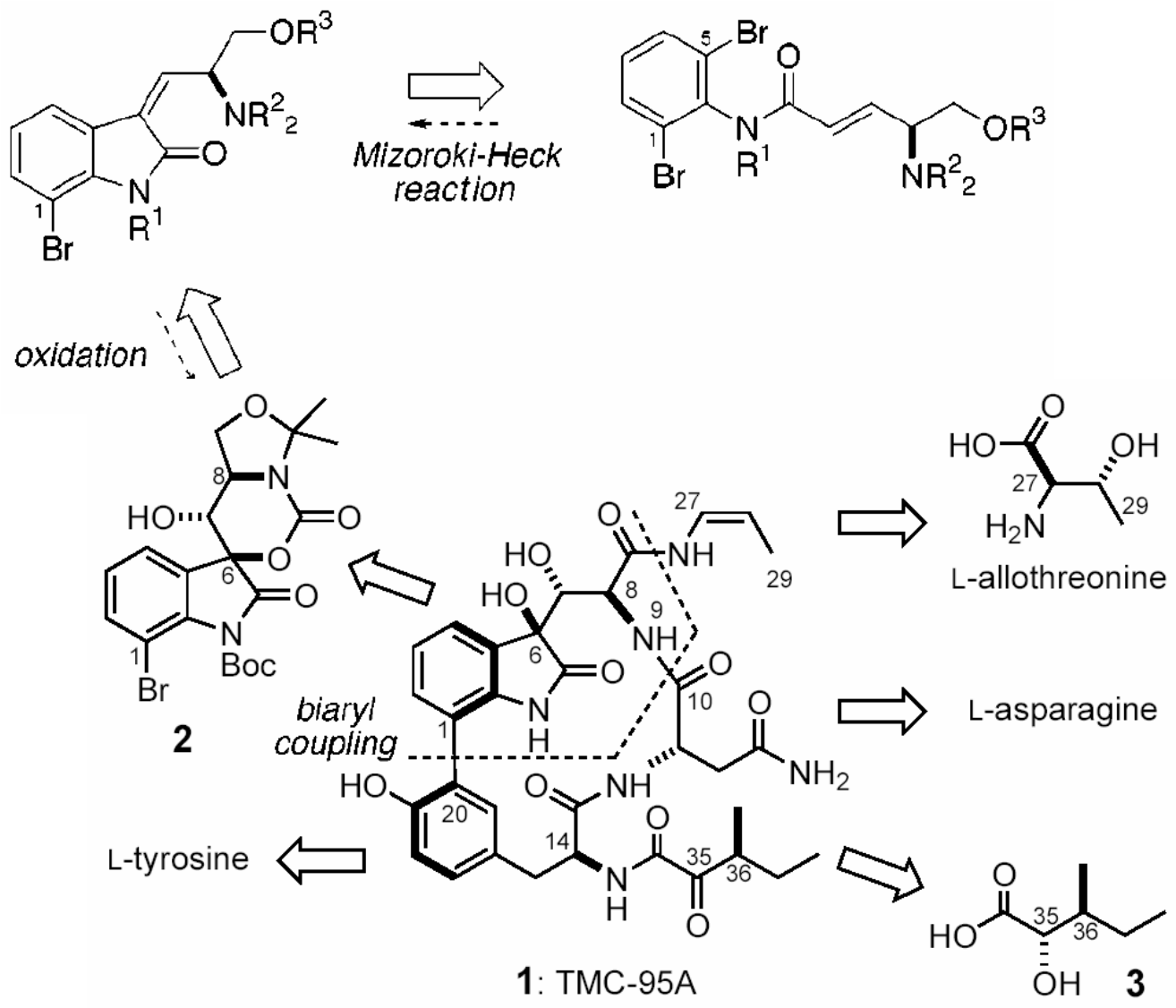
Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

William's Synthetic Strategy



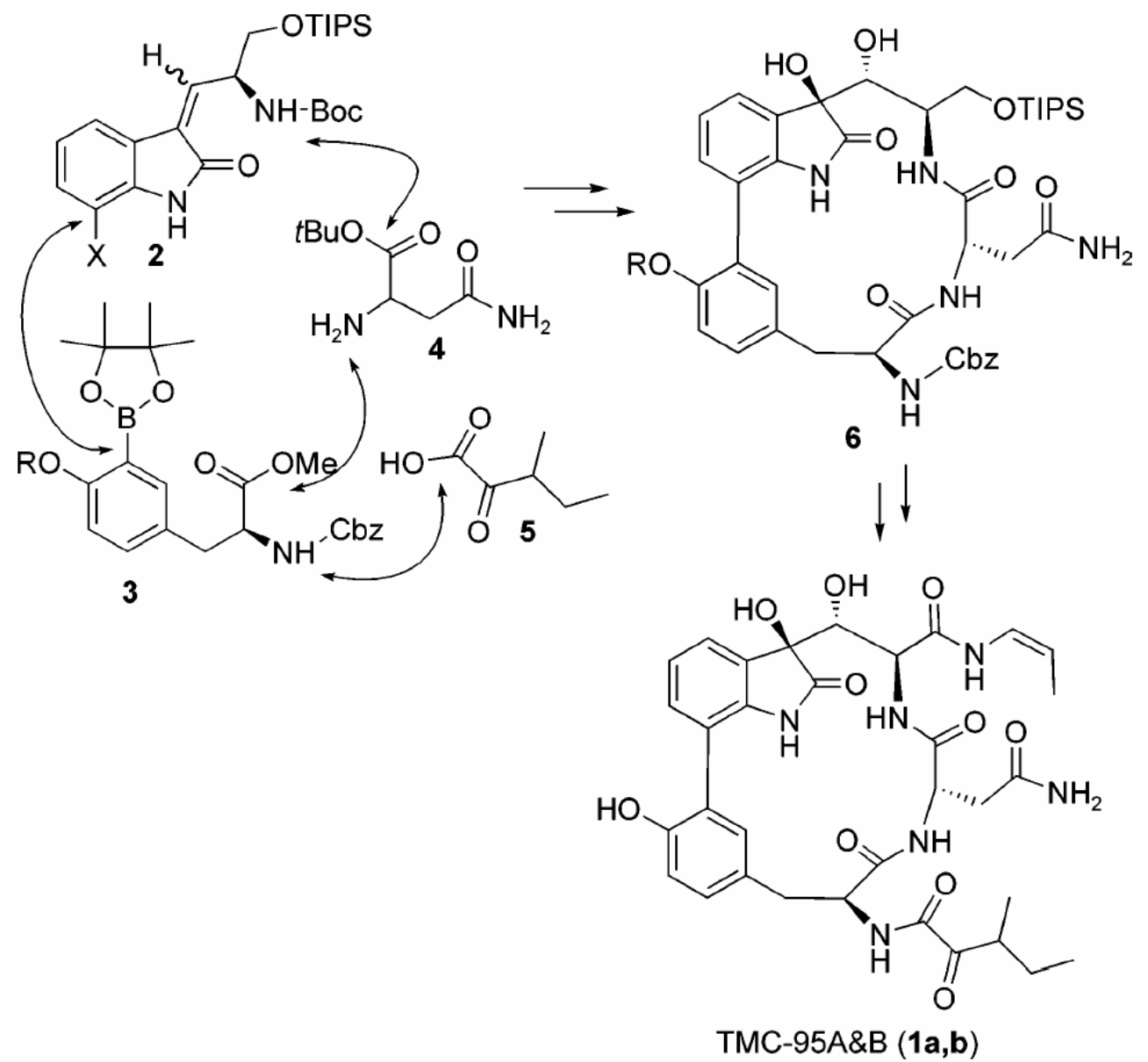
Williams, Robert et al. *Org. Lett*. **2003**, *5*, 197

Hirama's Synthetic Strategy



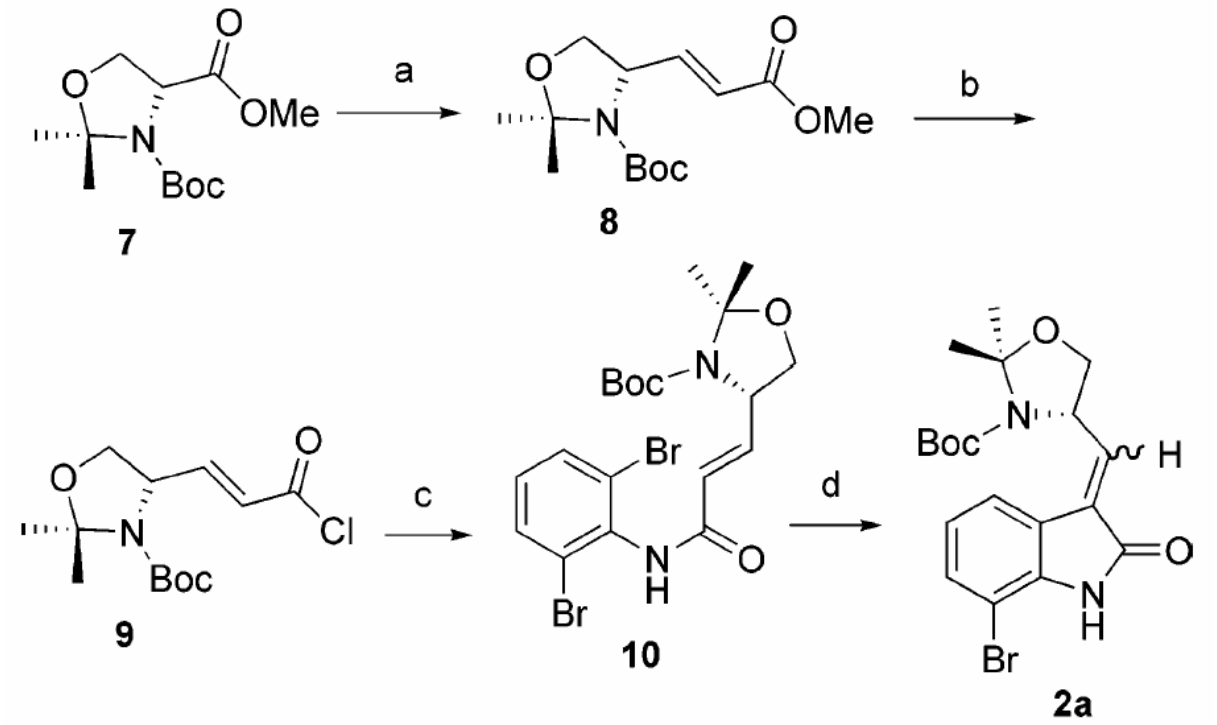
Hirama, Masahiro et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 2654.

Danishefsky's Synthetic Strategy



Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

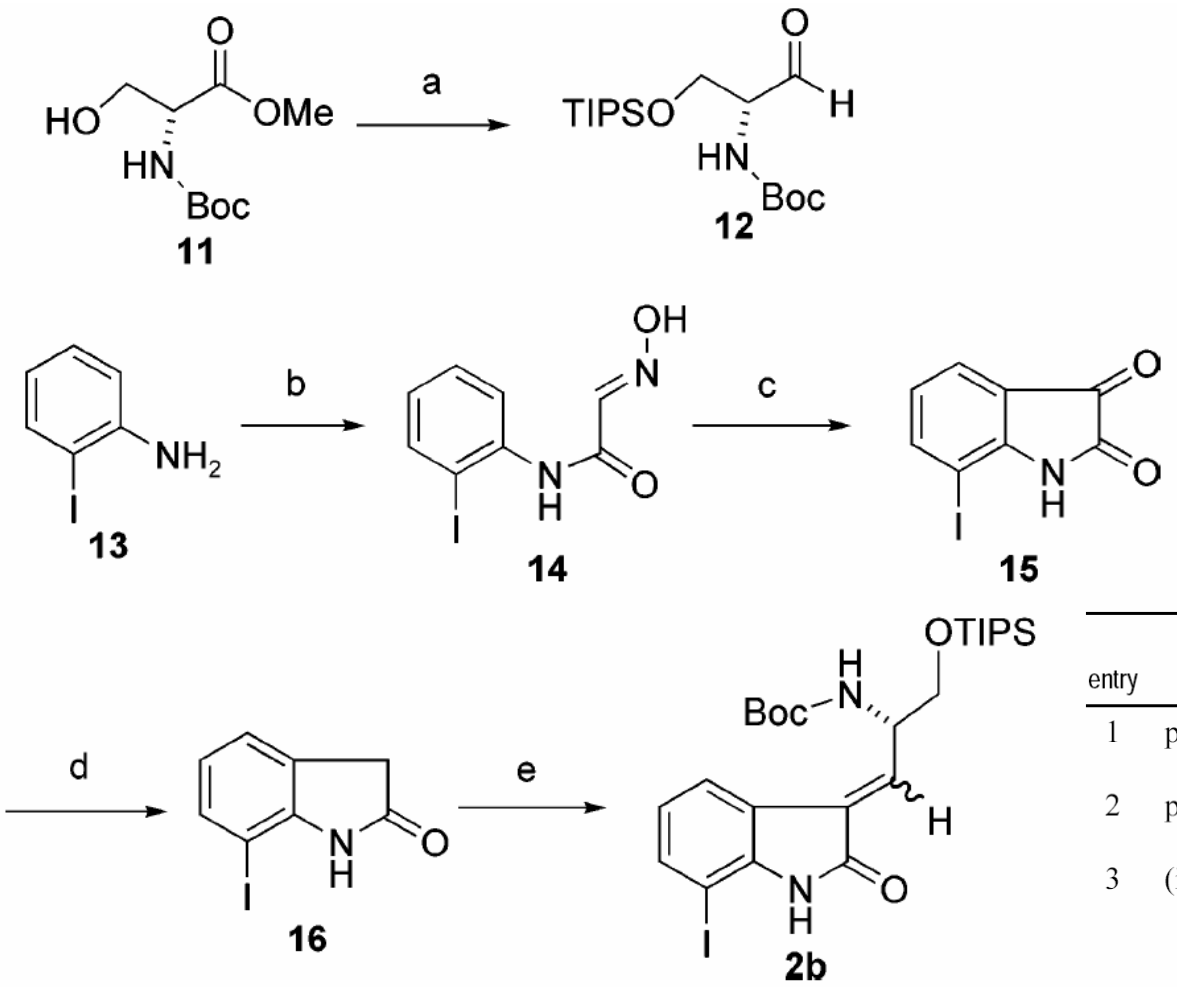
Attempted Synthesis of 7-Bromooxindole **2a**



Conditions:
(a) (1) DIBAL/toluene, -78^{o}C, 1 h; (2) methyl (triphenylphosphoranylidine)acetate, CH_2Cl_2, rt, 88%;
(b) (1)LiOH , THF/MeOH/H_2O, (2) TBSCl, Et_3N/DMAP, (3) $(COCl)_2$, DMF (cat.);
(c) 2,6-dibromoaniline, NaH, DMF/THF, 75 ^{o}C, 1.5 h, 44%;
(d) $[Pd(PPh_3)_4]$ or $Pd(OAc)_2$, 5-15%.

Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

Synthesis of 7-Iodooxindole **2b**

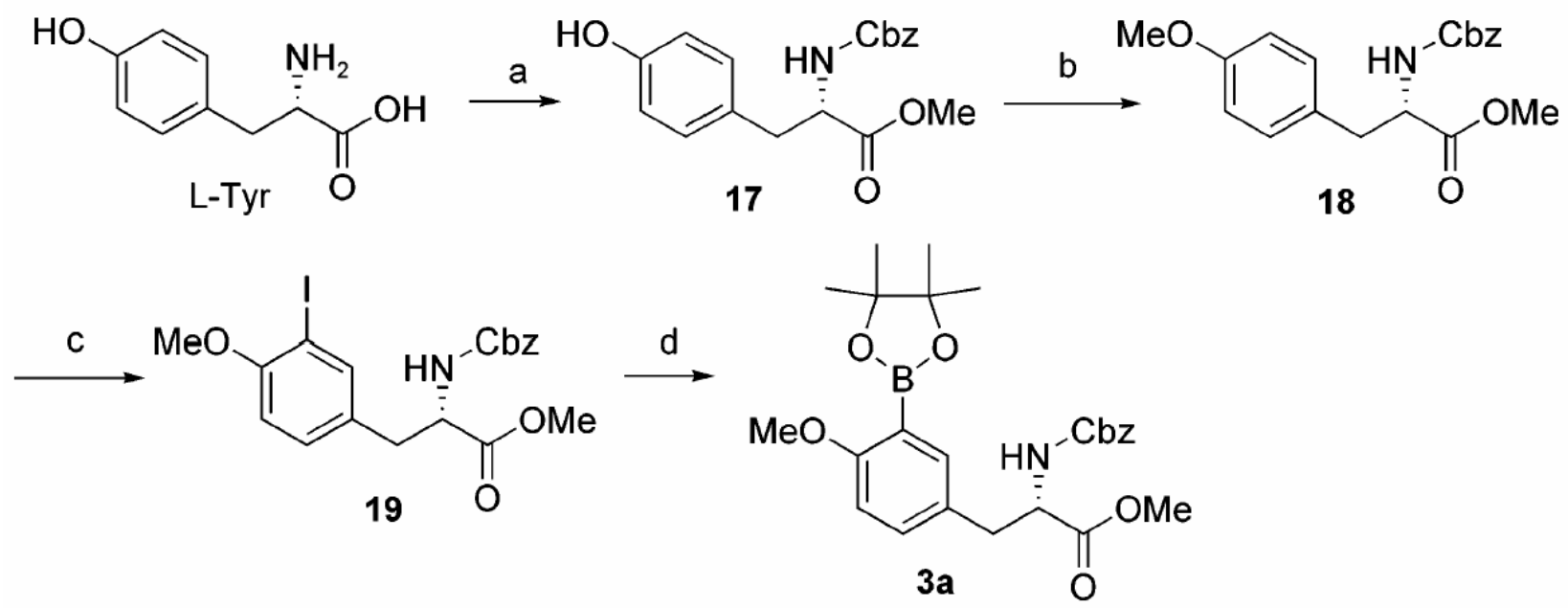


(a) (1)TIPSCl , imidazole, 94%;
DIBAL, -78°C, 96%;
(b) $CCl_3CH(OH)_2$, NH_2OH HCl, Na_2SO_4, H_2O, 45°C, 12 h, 66%;
(c) H_2SO_4, 70°C, 15 min, 88-98%;
(d) (1) $NH_2NH_2 \cdot H_2O$, 125 C, 1 h,
(2) HCl (6 N), 60°C, 2 h, 81% (two steps);
(e) **12**, see Table 1.

entry	conditions	yield[a] (%)	*E*/*Z*[b]	ee[c] (%)
1	piperidine (cat.), MeOH or EtOH, 65 °C, 2−3 h	44−50	2.0/1	0
2	piperidine (cat.), THF, rt, 17−44 h	55	1.7/1	~10
3	(i) LDA (2.1 equiv), THF, −78 °C, **16**, then **12**, 1 h; (ii) TEA (2.5 equiv), MsCl (1.2 equiv), CH_2Cl_2, −60 to −30 °C, 2 h	76	1.3/1	92
4	(i) LDA (2.0 equiv), THF, −78 °C, **16**, then **12**, 1.5 h; (ii) TEA (3 equiv), MsCl (1.5 equiv), CH_2Cl_2, −70 to −50 °C, 1.5 h	74	1.2/1	96

Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

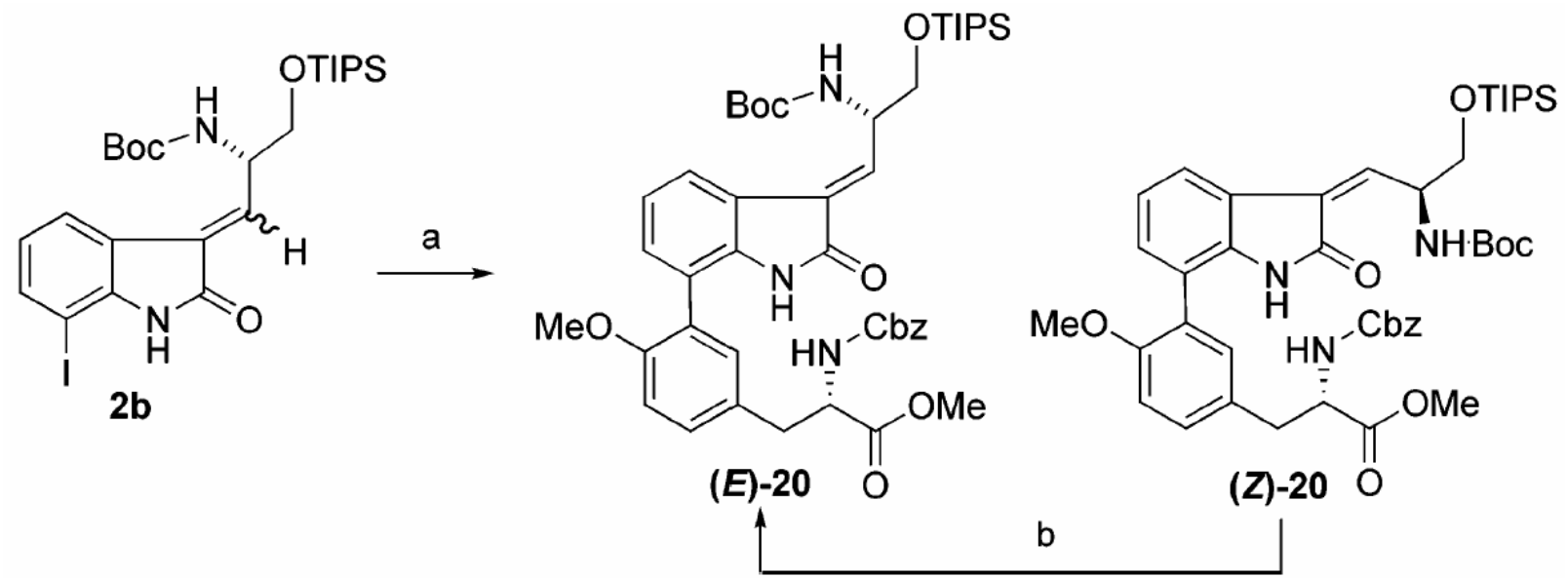
Synthesis of Aryl Borate **3a**



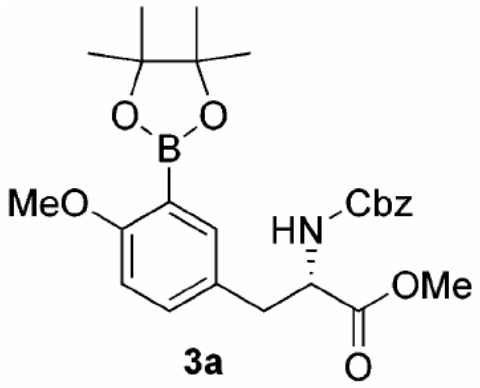
Conditions:
(a) (1) MeOH/$SOCl_2$, (2) CbzCl, K_2CO_3, H_2O/acetone, 96% (two steps);
(b)LiOH , Me_2SO_4, 86%;
(c) I_2, Ag_2SO_4, MeOH, rt, 1.5 h, 93%;
(d)bis(pinacolato)diboron , $[PdCl_2(dppf)]\cdot CH_2Cl_2$, KOAc, DMSO, 80$^oC$, 13 h, 95%

Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

Biaryl Linkage Formation by Suzuki Coupling

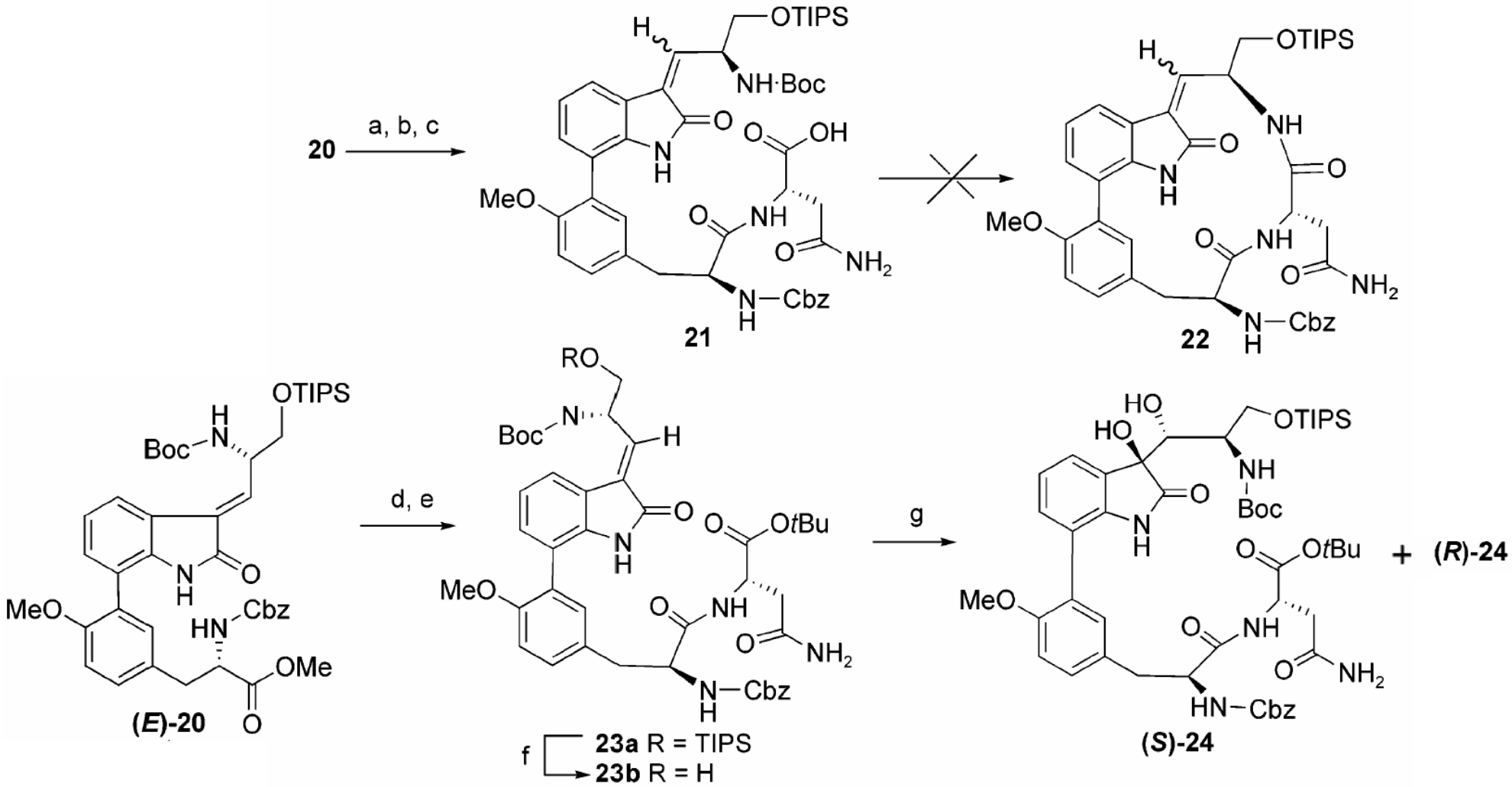


Conditions:
(a)**3a** , $[PdCl_2(dppf)]\cdot CH_2Cl_2$, KOAc, DME, 80°C, 2 h, 72% (*E*/*Z* ~ 2/1);
(b) I_2 (cat.), DME, 80°C, 1 d, 87% (63% conv).



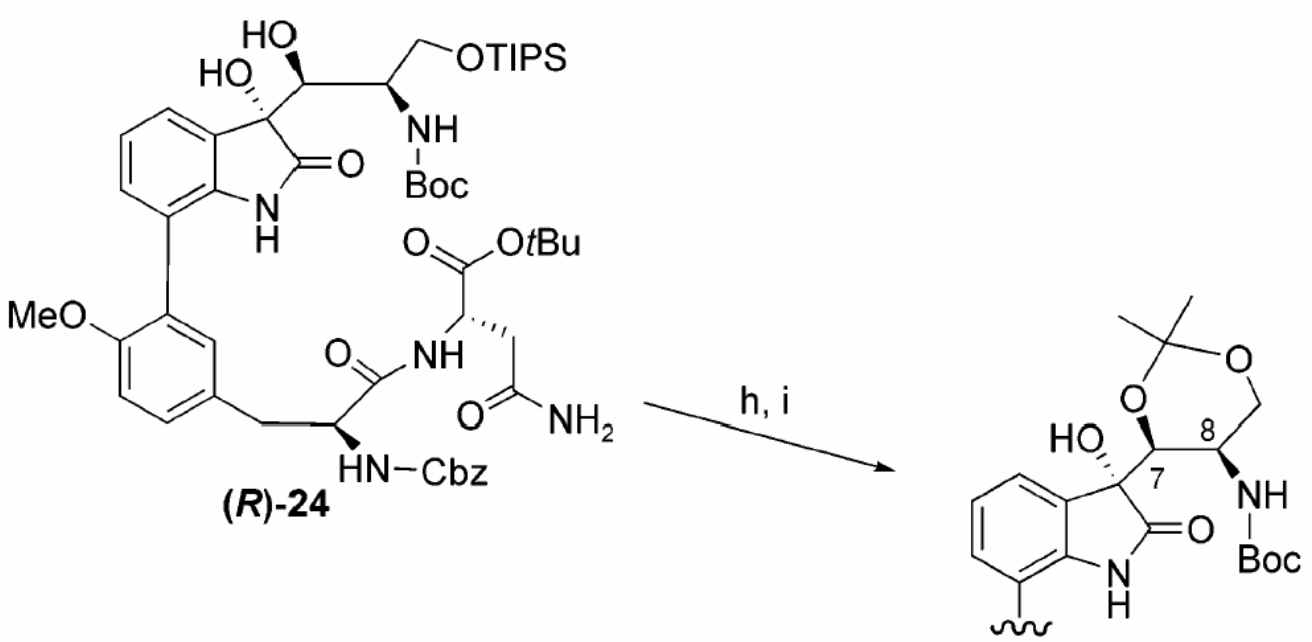
Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

Synthesis of Diols **24**



(a)LiOH , THF/MeOH/H_2O; (b) hydroxysuccinimide, DCC, THF, 55% (two steps);
(c) Ł Asn·H_2O, Et_3N, THF/H_2O, rt, 4 h, 70%;
(d)LiOH , THF/H_2O, 0°C, 1.5 h; (e) H-Asn-O-*t*-Bu, EDC/HOAt, THF, rt, 2 h, 70% (two steps); (f) HF/Py, 84%;
(g) for**23a** : OsO_4/NMO, $(DHQD)_2PHAL$, *t*-BuOH/H_2O, rt, 1 h, 84% (*S*/*R* ~ 1/1.8);
for**23b** : (1) OsO_4/NMO, $(DHQ)_2PHAL$, *t*-BuOH/H_2O, rt, 4 h, (2) TIPSCl, imidazole/DMAP, 5 h, 81% (*S*/*R* ~ 1/1.8);

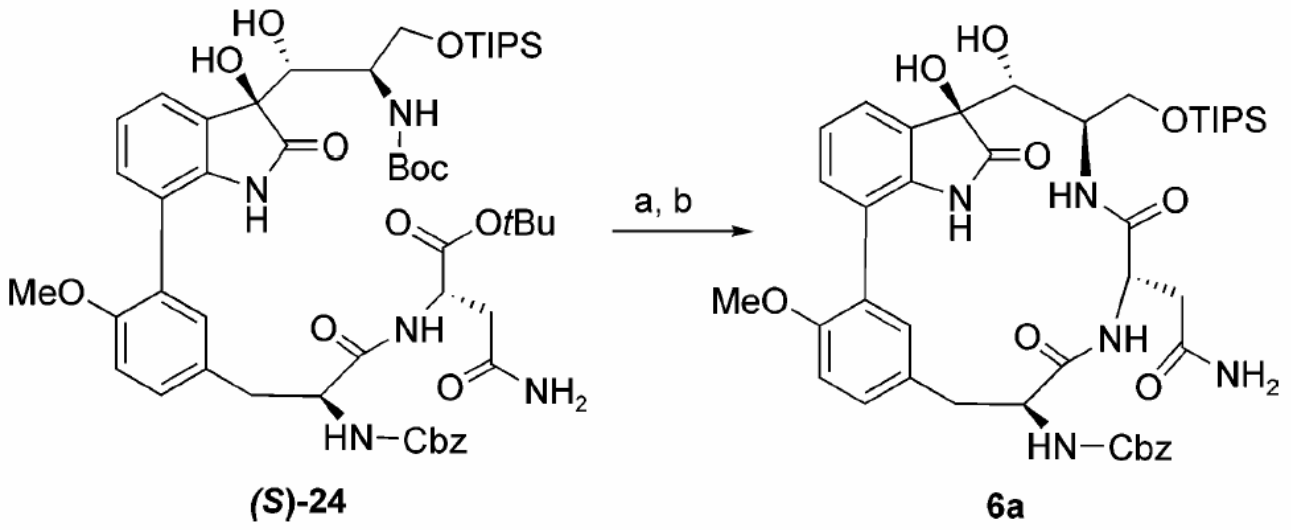
Identification of Absolute Configuration of **24**



(h) HF/Py;
(i) DMP/PPTS, CH_2Cl_2.

Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

Macrolactamization of (*S*)-**24**

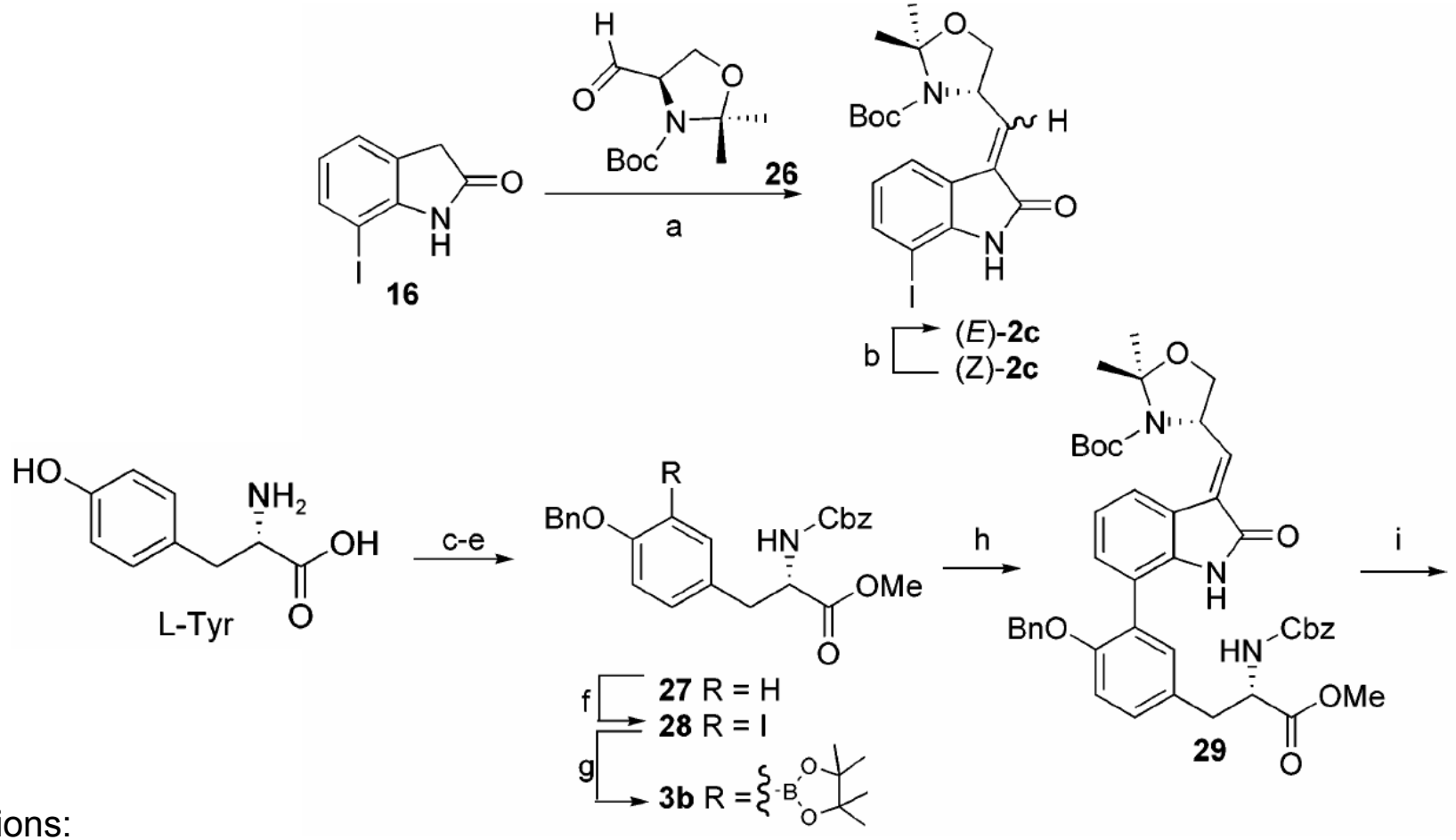


Conditions:
(a) TFA/CH_2Cl_2 (4:1), rt, 2 h;
(b) EDC, HOAT, DIEA, CH_2Cl_2/DMF (4/1, 4 mM), 20 h, 55% (two steps).

♦ Treatment of **24*R*** under same condition did not afford any cyclization product.

Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

Synthesis of Macrolactam **6b**

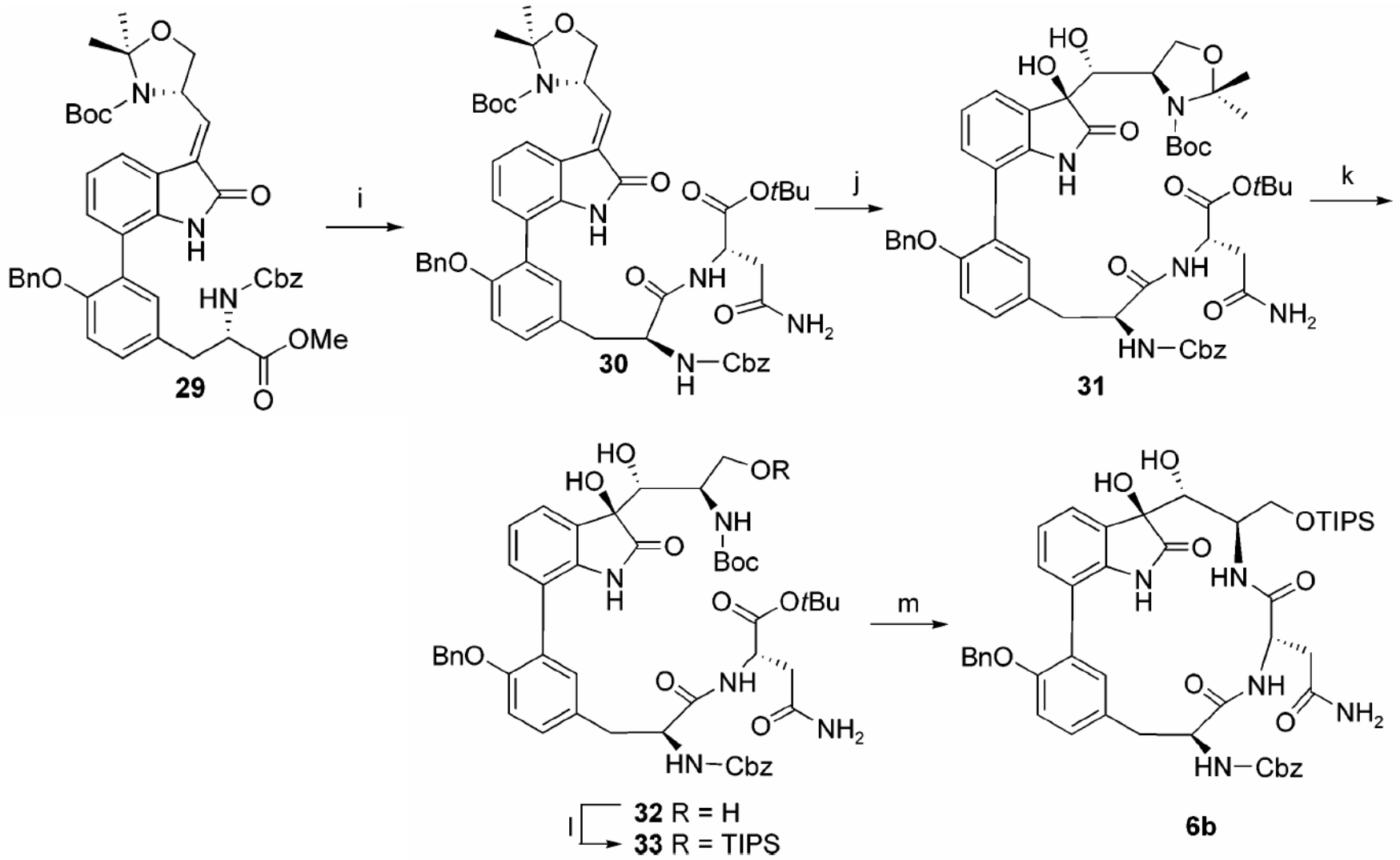


Conditions:

(a) LDA (2.0 equiv), THF, -78°C, 1.5 h; then Et_3N, MsCl, CH_2Cl_2, -70 to -50°C, 1.5 h, 81% (*E*/*Z* = 1.3/1);
(b) I_2 (cat.), benzene, 80°C, 26 h; DMP/PPTS, toluene, 65°C, 5 h; 85% (60% conv);
(c) MeOH/SO_2Cl_2; (d) CbzCl/K_2CO_3; (e) BnBr, Cs_2CO_3, acetone, reflux, 88% (three steps);
(f) Ag_2SO_4/I_2, MeOH, rt, 1 h, 99%;
(g) pinacolatodiborane, [$PdCl_2$(dppf)]CH_2Cl_2, K_2CO_3, DME, 80°C, 10 h, 91%;
(h) (*E*)-**2c**, [$PdCl_2$(dppf)]CH_2Cl_2, K_2CO_3, DME, 80°C, 2 h, 75%;

Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

Synthesis of Macrolactam **6b**

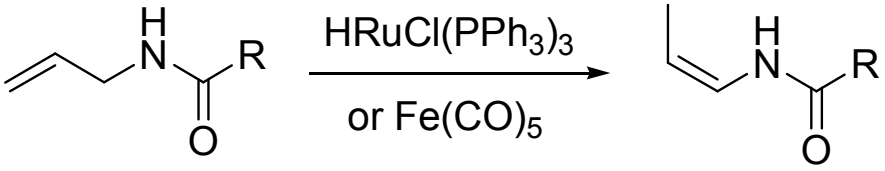


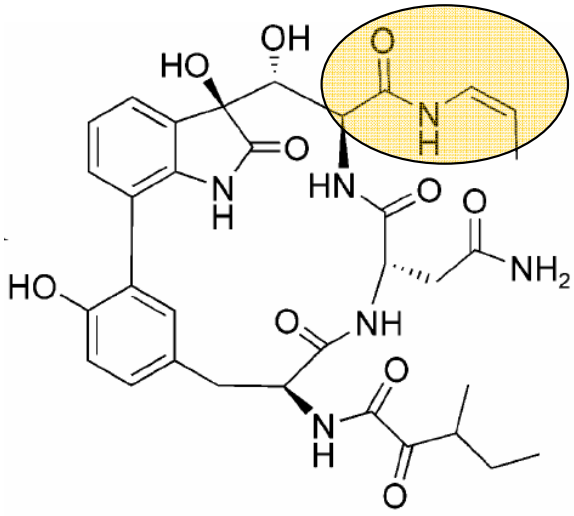
(i) (1) LiOH, THF/H_2O, 0°C, 1.5 h, (2) H-Asn-O-*t*-Bu, EDC/HOAT, THF, rt, 2 h, 85% (two steps);
(j) OsO_4/NMO, $(DHQD)_2PHAL$, *t*-BuOH/H_2O, rt, 12 h, 88% (dr = 5:1);
(k) (1) PPTS/MeOH, reflux, 2 h; (l) TIPSCl, imidazole/DMAP, CH_2Cl_2, rt, 5 h, 88% (two steps);
(m) (1) TFA/CH_2Cl_2 (4:1), rt, 2 h, (2) EDC/HOAT/DIEA, CH_2Cl_2/DMF (2 mM), rt, 24 h, 36%.

Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

Reported *cis*-Enamide Formations

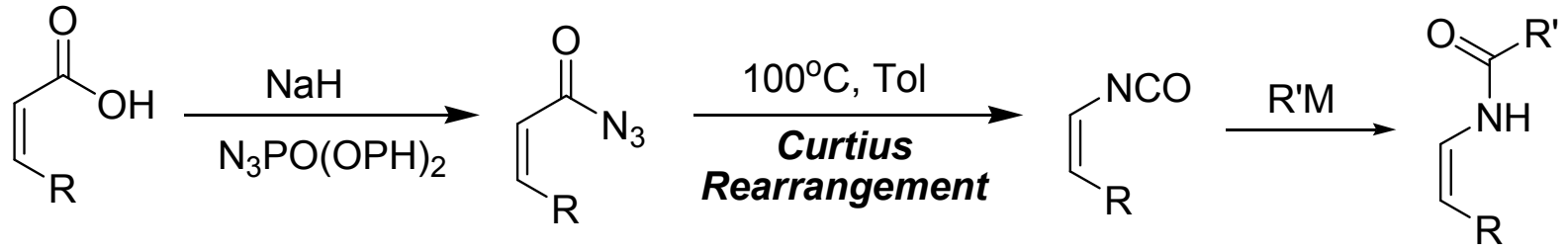
- Isomerization of N-allylamides.
  Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139.





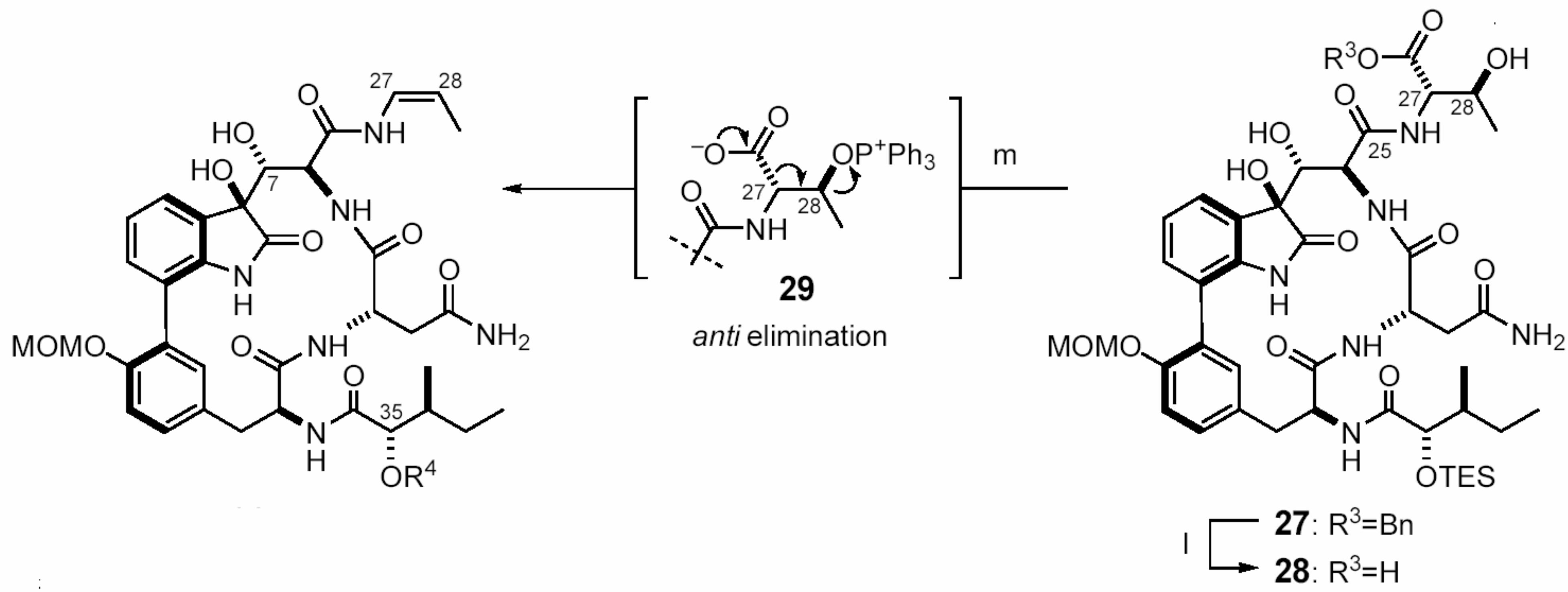
TMC-95A&B (**1a,b**)

- Curtius rearrangement.
  Kitahara, T. et al. *Synlett.* **2000**, *3*, 397.



Reported *cis*-Enamide Formations

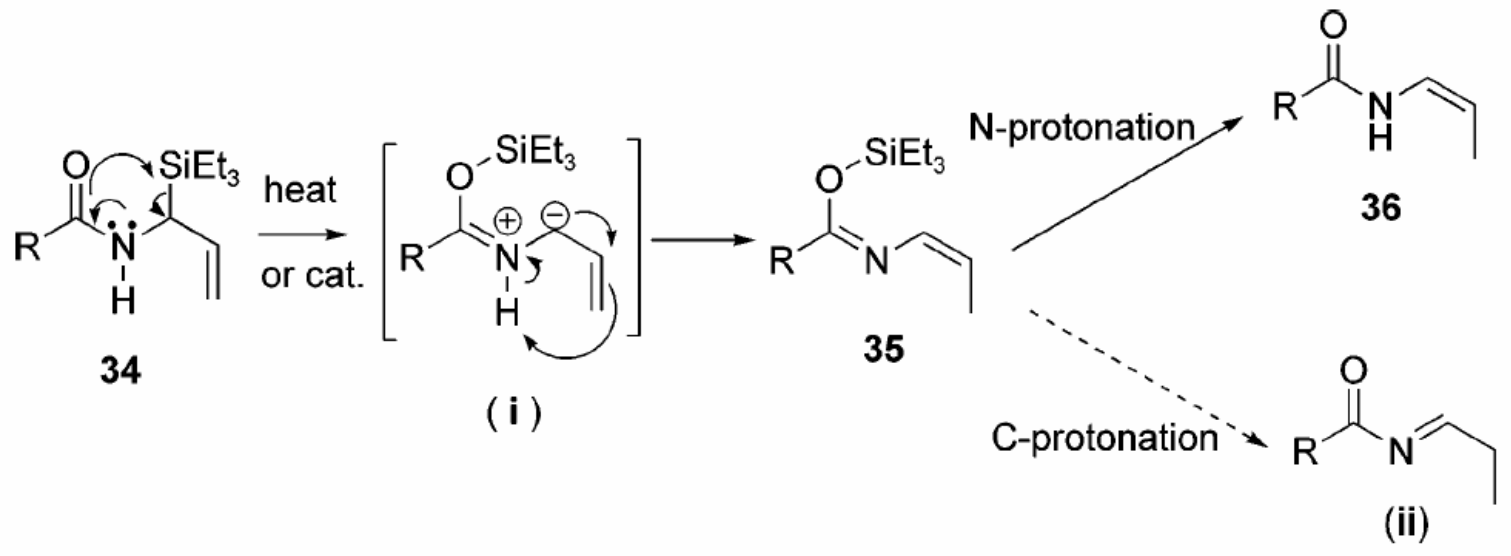
♦ *Anti*-elimination of good leaving group.



l) H_2, $Pd(OH)_2/C$, THF/H_2O (1:2);
m) DEAD, PPh_3, 4-A MS, 0^oC to room temperature, 59% from **27**;

Hirama, M. et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 2654.

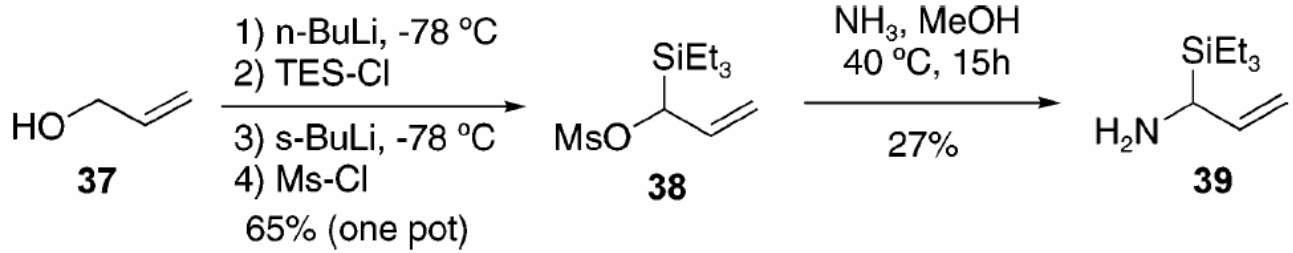
Proposed Strategy for *cis*-Enamide Formations



♦ It was proposed that **34** might undergo concurrent ene- and silatropic-like bond reorganizations that would lead to **35**.

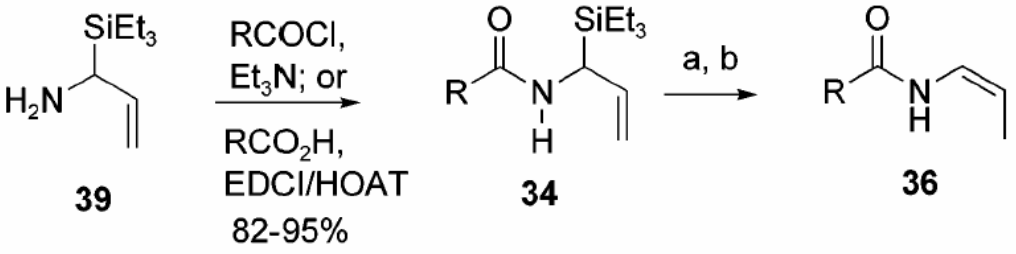
♦ Key step is the transfer of TES from C to O, N-protonation of **35** necessary.

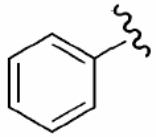
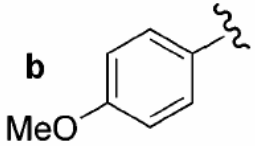
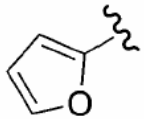
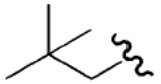
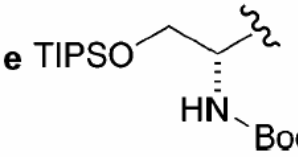
♦ Synthesis of α-silyl Allylamine



Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

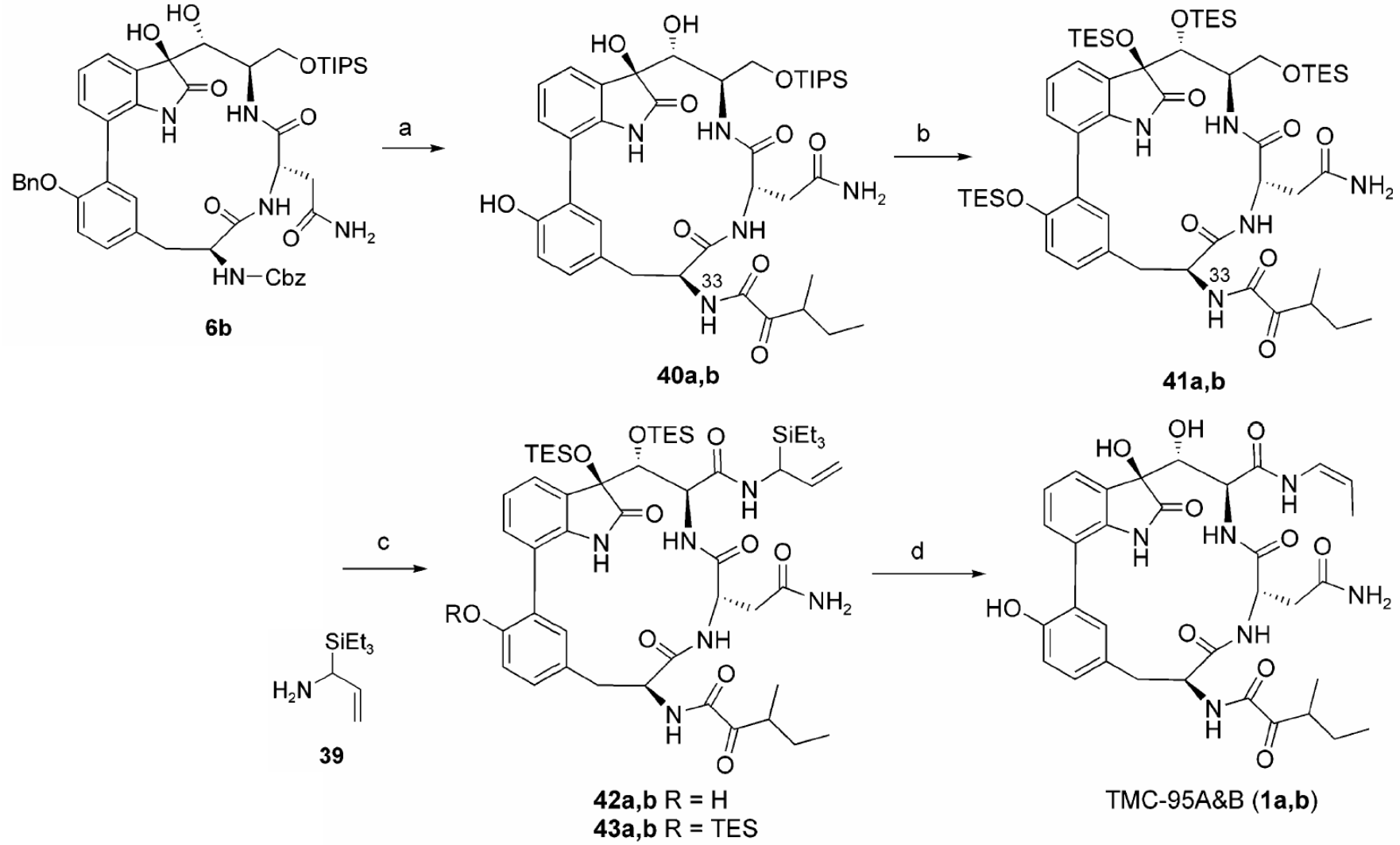
Rearrangement-Hydrolysis of α-Silylallyl Amide **34**



Entry	R =	Conditions	Yield
1	**a** 	a. toluene, 110 °C, 10 h; b. H_2O	81%
2	**b** 	a. toluene, 110 °C, 20 h; b. H_2O	73%
3	**c** 	a. toluene, 110 °C, 27 h; b. H_2O	67%
4	**d** 	a. toluene, 110 °C, 3 d; b. H_2O	72%
5	**e** 	a.*o*-xylene, 110 °C, 4 d; b. H_2O	52%

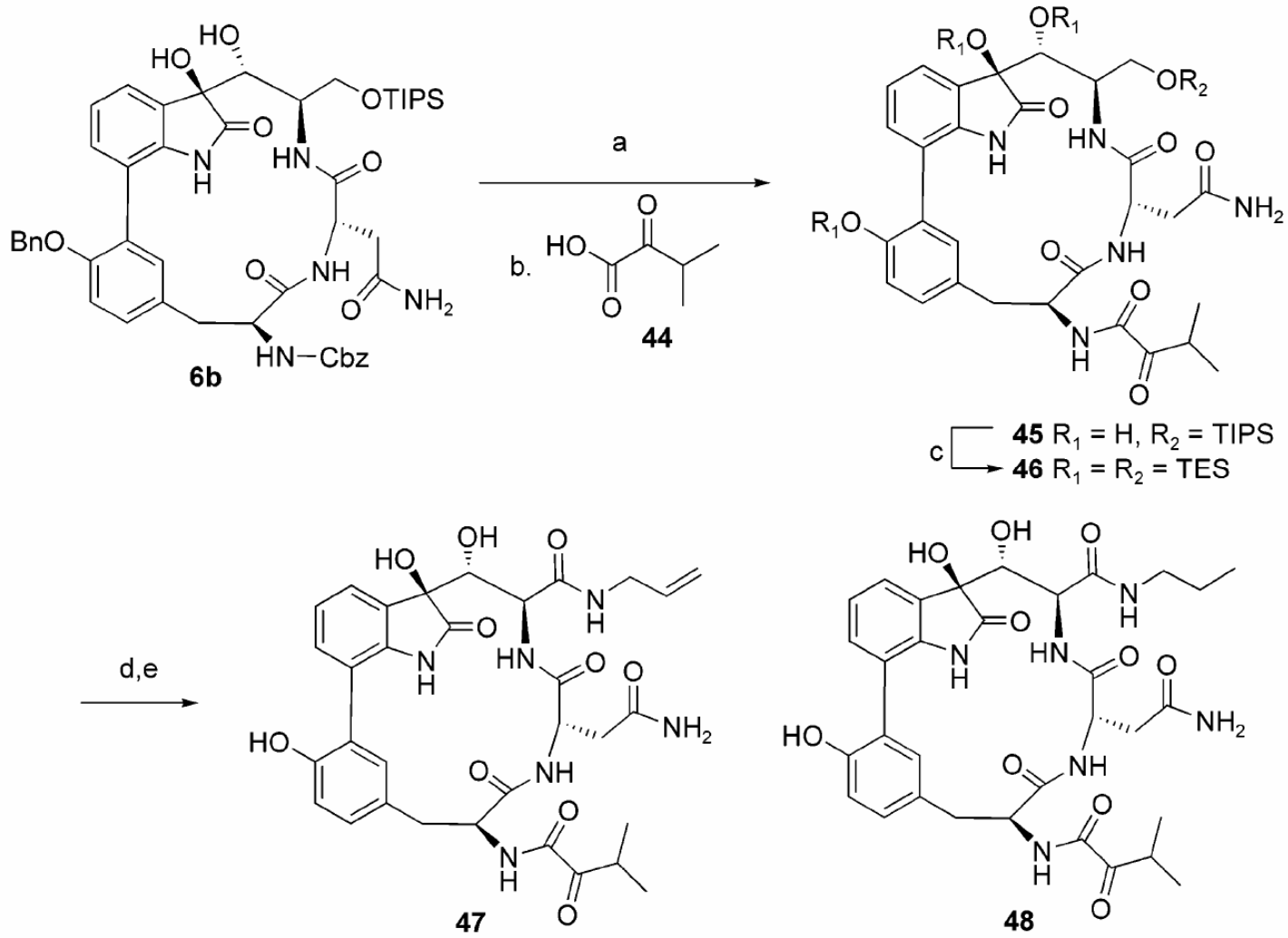
Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

Completion of the Synthesis of TMC-95A/B



(a) (1) Pd/C, H_2, EtOH rt, 19 h, (2) (±)-3-methyl-2-oxopentanoic acid (**5**), EDC/HOAT, CH_2Cl_2/DMF, rt, 2 h, 85% (two steps);
(b) (1) HF/Py, (2) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C to rt, 15 h, (3) $NaHCO_3$, (4) citric acid, EtOAc/H_2O, 73%
(c) (1) Jones reagent, acetone, 0°C, 2 h, (2) **39**, EDC/HOAT, CH_2Cl_2/DMF, rt, 13 h, 45% (two steps);
(d) (1)*o* -xylene, 140°C, 3 d, (2) HF/py, THF/py, then Me_3SiOMe, 49% (two steps).

Synthesis of Analogues



(a) Pd/C, H_2, EtOH rt, 19 h; (b) **44**, EDC/HOAT, CH_2Cl_2/DMF, rt, 2 h, 57% (two steps);
(c) (1) HF/Py, (2) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C to rt, 15 h, (3) $NaHCO_3$, (4) citric acid, EtOAc/H_2O, 56%
(d) (1) Jones reagent, acetone, 0°C, 2 h, (2) allylamine or *n*-propylamine, EDC/HOAT, CH_2Cl_2/DMF, rt, 13 h;
(e) HF/py, THF/py; then Me_3SiOMe, 39% for **47**, 32% for **48** (three steps).

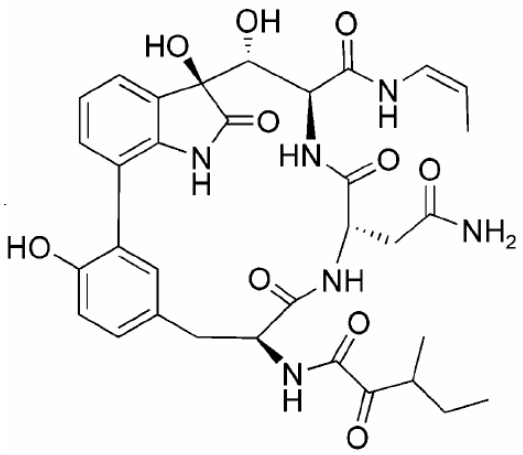
Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

Proteasome Inhibition Studies

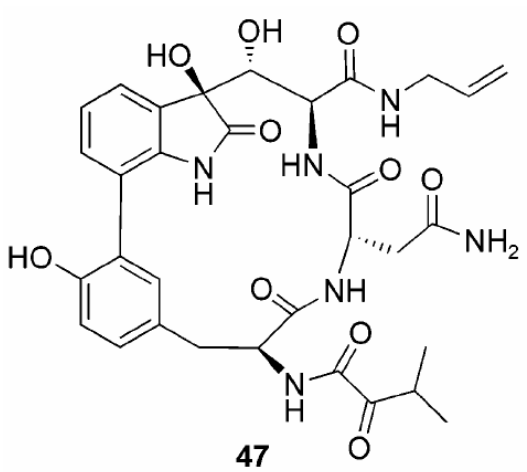
Table 5. Inhibition Constants (K_{iapp}) of Catalytic Activities of the Proteasome by Synthetic Inhibitors[a]

	$K_{iapp} = [I]/(v_0/v_s) - 1]^b$		
	CT-L activity (nM)	PGPH activity (nM)	TL activity (μM)
TMC-95A (**1a**)	1.1	29	0.8
TMC-95B (**1b**)	1.7	23	1.1
47	1.9	23	1.2
48	24	110	13

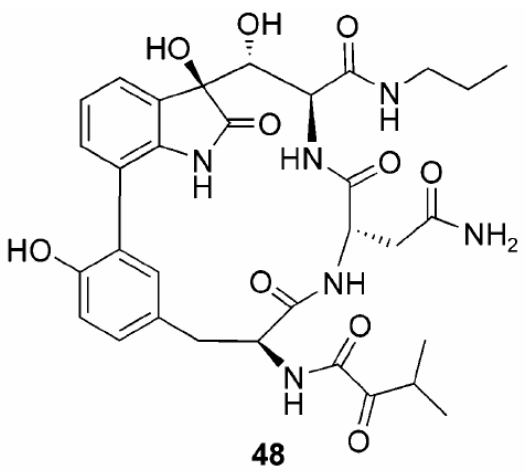
[a] The concentrations required for inhibition of the three proteasome catalytic activities were determined for TMC-95A and -B and their synthetic analogues. [b] The value v_o is the rate of enzyme activity in the absence of inhibitors, and v_s is the steady rate of inhibited enzyme activities.



TMC-95A&B (**1a,b**)



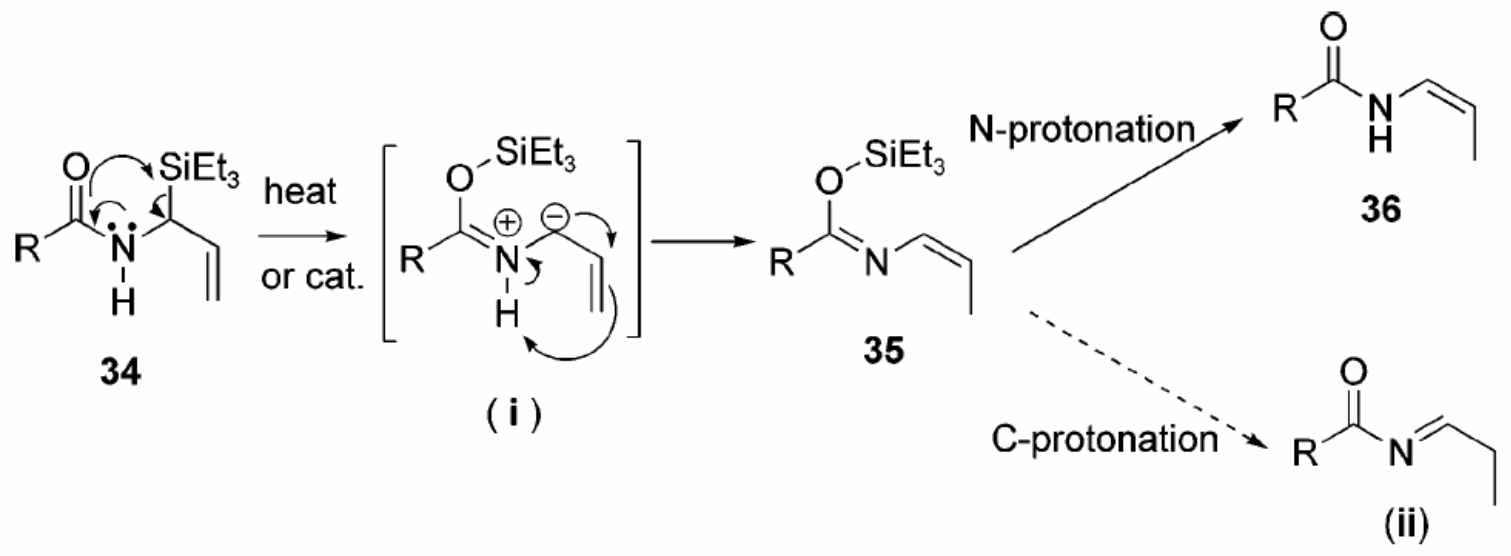
47



48

Danishefsky, S. et al. *J. Am. Chem. Soc*. **2004**, *126*, 6347.

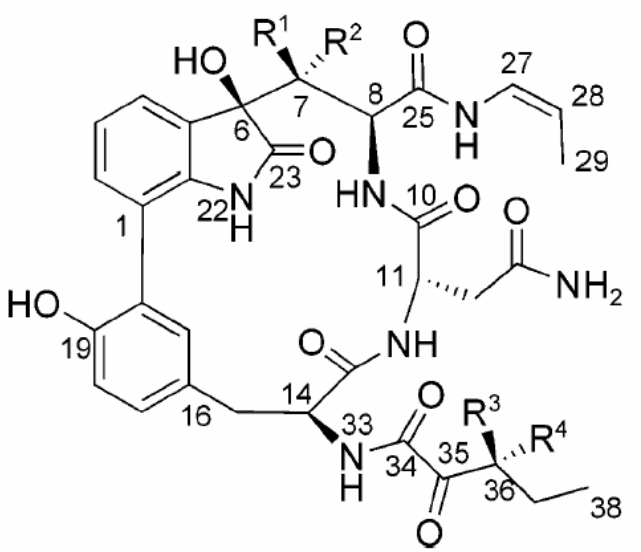
On the Mechanism of *cis*-Enamide Formation



- Silyl imidates **35** was observed by ^{1}H-NMR analysis.
- Density functional calculations of the intermediates and TS suggested a stepwise dyotropic rearrangement mechanism involving sequential 1,4-silyl (fast, reversible) and 1,4-hydrogen shifts (rate determining)
- This mechanism explained well why reactions are much slower when R = alkyl.

Houk, K. N.; Danishefsky, S. et al. *J. Am. Chem. Soc*. **2003**, *125*, 5111.

Summary



TMC-95	R^1	R^2	R^3	R^4
A (1a)	H	OH	Me	H
B (1b)	H	OH	H	Me

A Total Synthesis

A New Methodology

A Simplified Analogue

More Compounds

More Simplified Structure