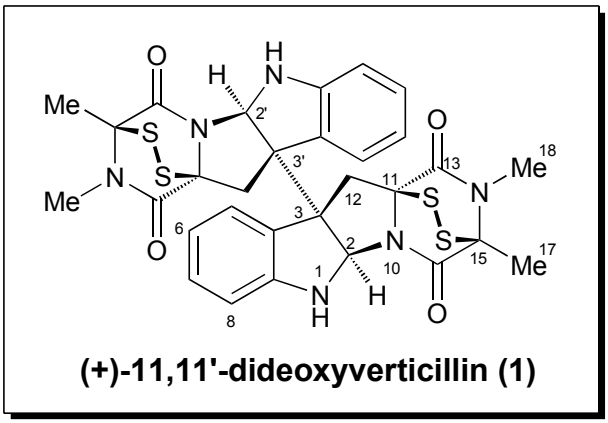
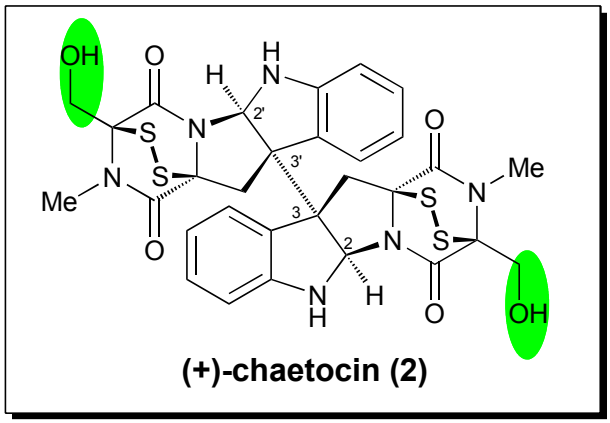
Epidithiodiketopiperazine



(+)-11,11'-dideoxyverticillin (1)

Movassaghi, M. *et al*.
Science **2009**, *324*, 238.



(+)-chaetocin (2)

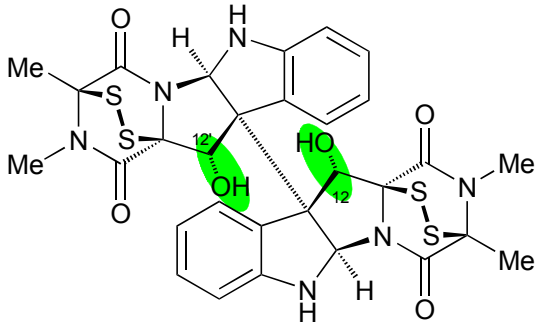
Sodeoka, M. *et al*.
JACS **2010**, *132*, 4078.

Isolation: isolated from a marine *Penicillium* sp. (W. Fenical *et al. Nat. Prod. Res.* **1999**, *13*, 213.)

isolated from *chaetomium minutum* (D. Hause *et al. Helv. Chim. Acta* **1970**, *53*,1061.)

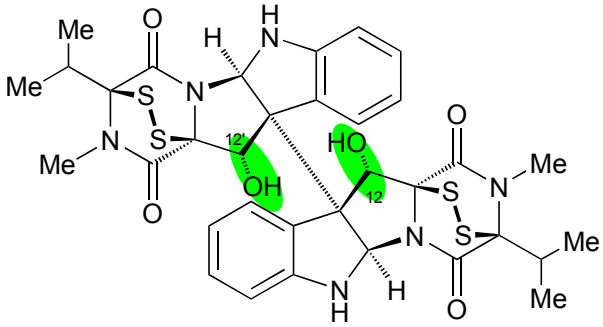
(+)-11,11'-dideoxyverticillin (1): potently inhibits the tyrosine kinase activity of the epidermal growth factor receptor, exhibits antiangiogenic activity, and has efficacy against several cancer cell lines

(+)-chaetocin (2): in addition to its antibacterial and cytostatic activity, **2** is known to be a potent inhibitor of lysine-specific histone methyltransferases (HMTs).



(+)-verticillin A (3)

isolated from a basidiocarp of *Coltricia cinnamomea*
(Katagiri, K. *et al. J. Antibiot.* **1970**, *23*, 420.)

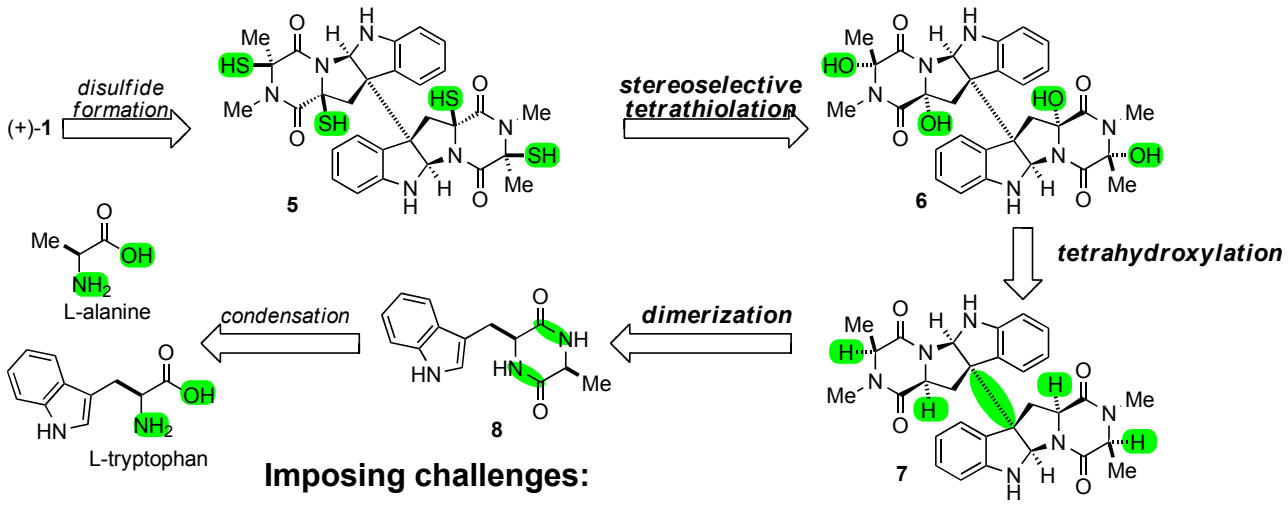


(+)-leptosin K (4)

isolated from a strain of *Leptosphaeia* sp.
(Numata, A. *et al. Tetrahedron*, **1995**, *51*, 3483)

0. Retrosynthetic Analysis
1. Strategies for The Synthesis of Hexahydropyrroloindole Alkaloids
2. Quadruple Cα-Methine Hydroxylation
3. Stereoselective Tetrathiolation and Disulfide Formation
4. Synthesis of Dimerization Precursor (+)-12
5. Over View
6. Sodeoka's Route

0. Retrosynthetic Analysis



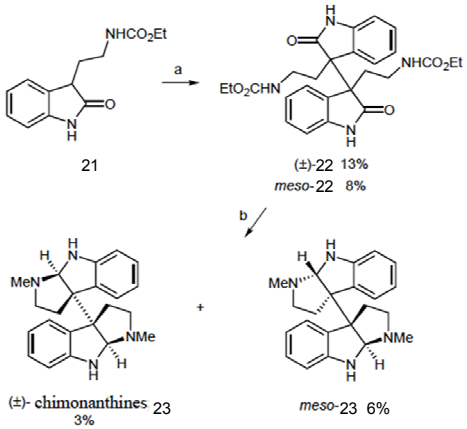
Imposing challenges:

- Absolute and relative stereochemical control of the six tetrasubstituted carbons of (+)-**1** posed noteworthy strategic concerns.
- highly acid-, base-, and redox-sensitive functional groupings
- Quadruple Cα-methine hydroxylation of **7** and the tetrathiolation of intermediate **6.**

1. Strategies for The Synthesis of Hexahydropyrroloindole Alkaloids

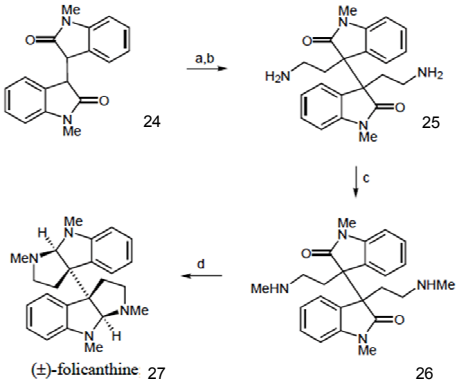
1.1 Background

Hendrickson et al.'s synthesis of chimonanthines
Proc. Chem. Soc., London **1962**, 383.



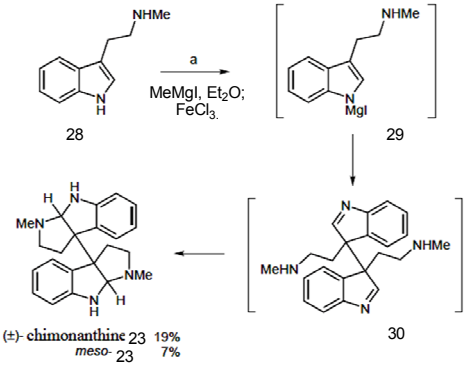
conditions: (a) NaH, THF; I_2, benzene; (b) $LiAlH_4$, THF.

Hino's synthesis of (±)-folicanthine
Chem. Pharm. Bull. **1961**, *9*, 979.

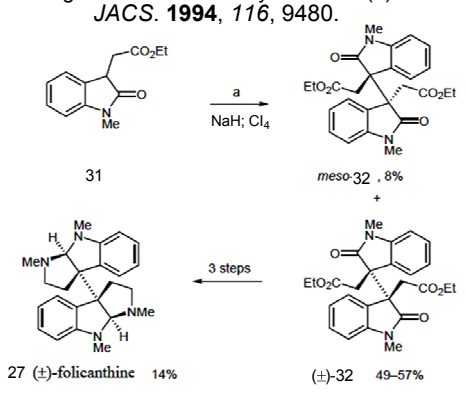


conditions: (a) $ClCH_2CN$, K_2CO_3, NaI; (b) PtO_2, H_2, AcOH, 30% yield (2 steps); (c) imine formation; MeI, 100°C; HCl, H_2O, yields and specific conditions not given; d) $LiAlH_4$, 1,4-dioxane, yield not given.

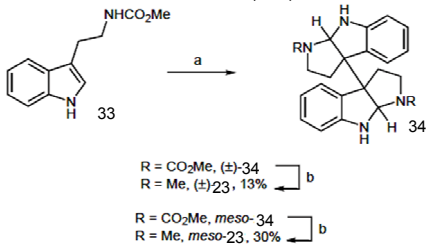
Scott et al's elegant synthesis of chimonanthines
JACS **1964**, *86*, 302.



Rodrigo and co-workers' synthesis of (±)-folicanthine
JACS. **1994**, *116*, 9480.

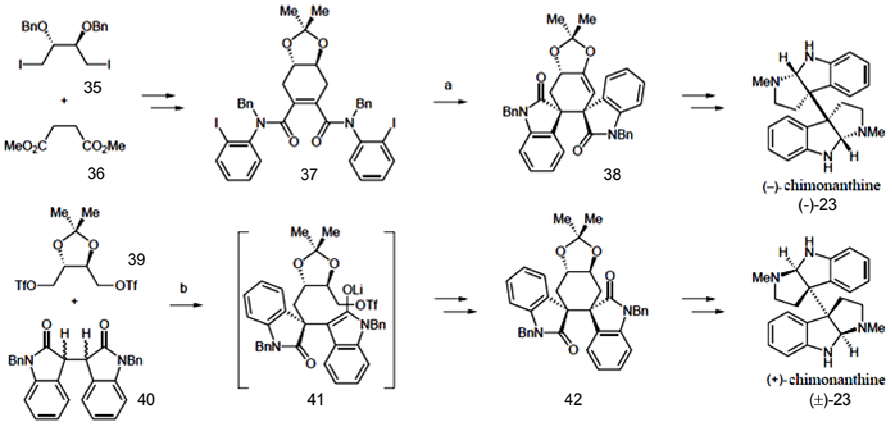


Takayama's synthesis of chimonanthines
Tetrahedron Lett. **2002**, *43*, 5637.



conditions: (a) PIFA, TFE; (b) Red-Al, toluene.

Overman's enantioselective total syntheses of (-)- and (+)-chimonanthine
JACS **1999**, *121*, 7702. ; *ACIE* **2000**, *39*, 213.



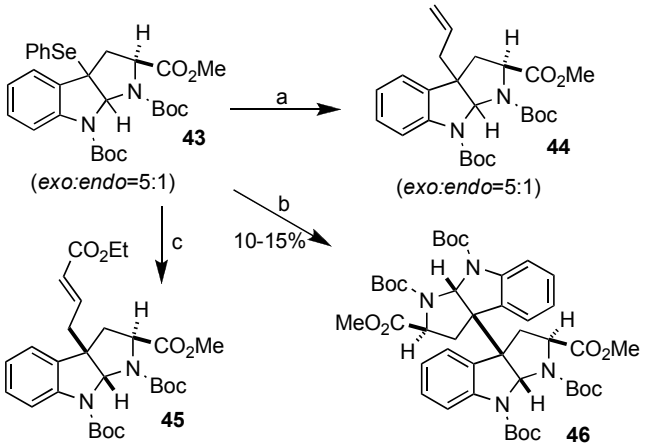
conditions: (a) 10 mol% $Pd(PPh_3)_2Cl_2$, Et_3N, DMA, 100°C, 90% yield; (b) LiHMDS (2.1 equiv), THF, DMPU, -78 °C, 55% yield.

- In the first enantioselective total synthesis of chimonanthinethe key transformation proceeded via two intramolecular Heck cyclizations to sequentially secure the two quaternary stereocenters.
- Second approach relied on two alkylation reactions to sequentially introduce the vicinal quaternary stereocenters

1.2 Cobalt(I)-Promoted Reductive Dimerization Strategy

1.2.1. Related works

Danishefsky, S. J. *et al. JACS.* **1994**, *121*, 11953.



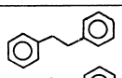
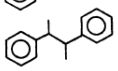
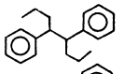
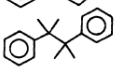
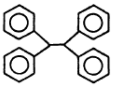
♦observed dimerization products during the radical prenylation.

♦Compound **46** represents a potential solution toward natural products of the dimeric tryptamine and tryptophan class of indole alkaloids.

(a) allyl-Sn(*n*-Bu)$_3$, (n-Bu)$_6$Sn$_2$, toluene, *hv*, 23 °C, 94%;
(b) (*n*-Bu)$_6$Sn$_2$, toluene, *hv*, 23 °C;
(c) (*n*-Bu)$_6$Sn$_2$, ethyl β-tri(n-butyl)stannylacrylate, toluene, *hv*, 23°C, 21%.

Reductive coupling of benzylic halides by $CoCl(PPh_3)_3$

Yamada, Y. *et al. Chem. Lett.* **1981**, 1277.

Benzylic chloride	Reaction condition	Product	Yield(%)[b]
	r.t. 1.5 h		70
	r.t. 1 h		69[c]
	r.t. 2 h		75[d]
	r.t. 2 h		83
	r.t. 17 h		67

[a] Carried out in benzene by the use of 1.2 equiv. of the reagent. [b] Isolated yield. [c] Both meso (mp 124-125°C)[5] and dl (oil)[5] isomers were yielded in a ratio of 1:1 and were separated by silica gel column chromatography. [d] Both meso (mp 96-97°C)[6] and dl (oil) isomers were formed in a ratio of 2:3 and were separated by silica gel column chromatography.

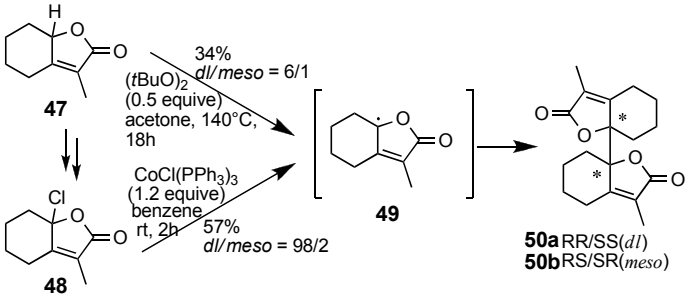
♦$CoCl(PPh_3)_3$ is a rather stalble coplex to manipulate and can be easily prepared.

♦The reaction can be under mild non-basic conditions and can be accomlished in various organic solvents.

♦In the case of benzyl bromide the reaction was completed, within 5 minutes, faster than the reaction of the corresponding chloride under same conditions to give bibenzyl in a similar yield.

Cobalt-Mediated Dimerization of Chloro Lactone

Jack E. Baldwin *et al. JOC.* **2004**, *69*, 9100.



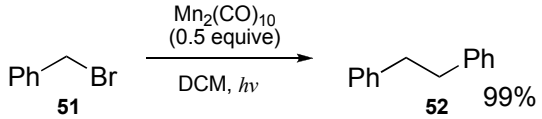
♦Although **48** was a successful dimerization agent for butenolide **47**, the reaction yield could not be further optimized.

TABLE 1. Metal-Mediated Dimerization of Chloro Lactone 47 To Generate Dimer 50

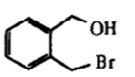
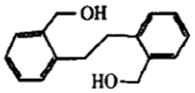
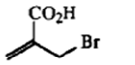
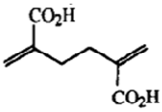
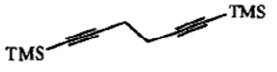
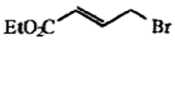
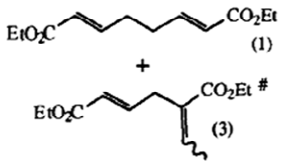
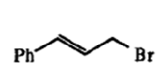
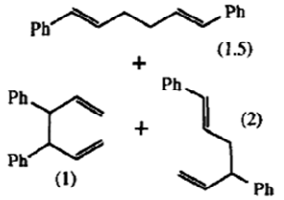
coupling agent	temperature (°C)	reaction time (h)	solvent	yield of 50 (%)
copper	90−100	1	benzene	2
activated copper	90−100	1	benzene	2
zinc	20−25	24	EtOAc	no reaction
$Co(PPh_3)_3Cl$	20−25	2	benzene	57

Radical Coupling of Organobromides Using $Mn_2(CO)_{10}$

B. C. Gilbert *et al. Synth. Commun.* **1999**, *29*, 2711.



♦The photolytic cleavage of the weak Mn-Mn bond in dimanganese decacarbonyl complex [$Mn_2(CO)_{10}$] could lead to bromide abstraction by {$Mn(CO)_5$} under mild reaction conditions.

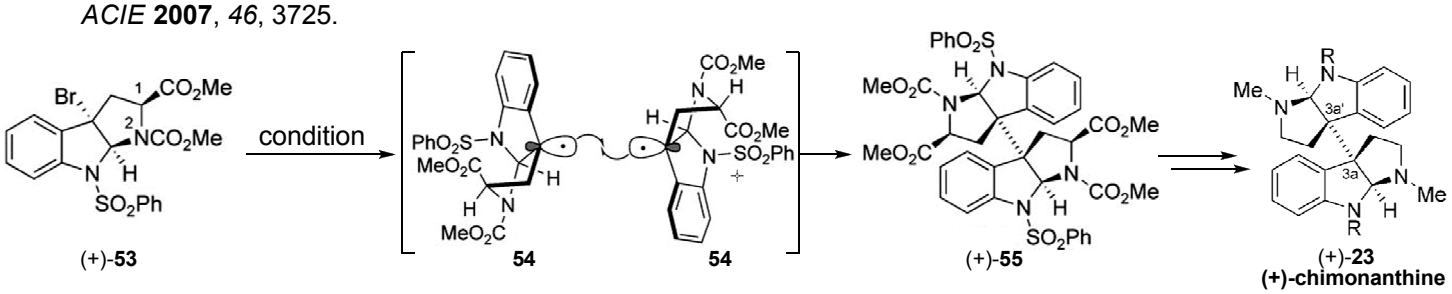
Bromide	Product(s)[1]	Yield (%)
		88
		92
		86
		71[15]
		83

♦This method was found to work well using a variety of substrates containing a number of functional groups.
(included alcohols,esters and acids)

♦Allylic radicals, which could couple in more than one position, reacted predominantly at the least hindered position.

1.2.2. Movassaghi's Total Synthesis of (+)-Chimonanthine.

ACIE **2007**, *46*, 3725.



- A variety of reduction conditions were explored for the generation of the C3 radical center, including the use of magnesium, lithium, samarium(II) iodide, a wide range of reducing copper complexes, iron(III) chloride.magnesiumsystems, and hexabutyldistannane, along with heat or photochemical activation.
- First successful dimerization:

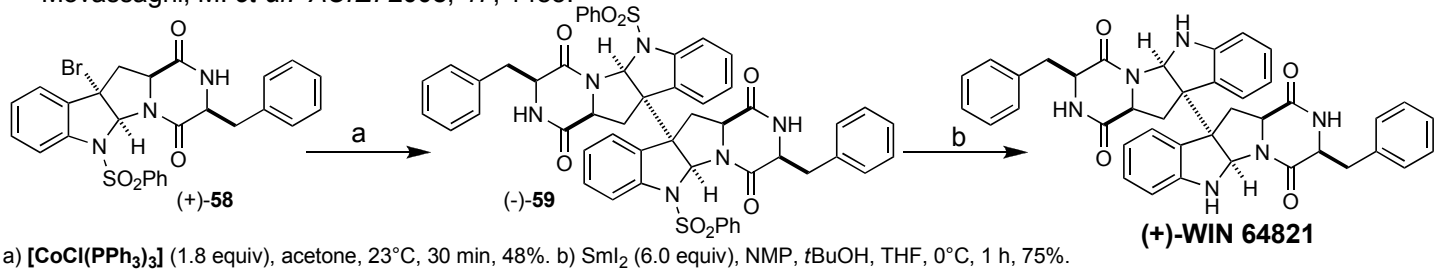
  $[Mn_2(CO)_{10}]$(0.5 equive), DEM, 16h. → 18% yield(single diastereomer), >99% ee.

  $[Mn_2(CO)_{10}]$(1.0 equive) ,, → **33**% yield(single diastereomer), >99% ee.
- No further improvement was observed after an extensive survey of the reaction conditions
- Given the expected second-order dependence of the dimerization rate on the concentration of the activated monomer.
- Cobalt(I) complex **$CoCl(PPh_3)_3$** as a potential solution because of its ability to perform more rapid halogen abstraction from benzylic chlorides in benzene.

  $[CoCl(PPh_3)_3]$(1.2 equive), acetone, 23°C, 15 min → 60% yield(single diastereomer), >99% ee.(3-g scale)

1.2.3. Total Synthesis of (+)-WIN 64821(a nonpeptide neurokinin antagonist).

Movassaghi, M. *et al. ACIE.* **2008**, *47*, 1485.



a) **$[CoCl(PPh_3)_3]$** (1.8 equiv), acetone, 23°C, 30 min, 48%. b) SmI_2 (6.0 equiv), NMP, *t*BuOH, THF, 0°C, 1 h, 75%.

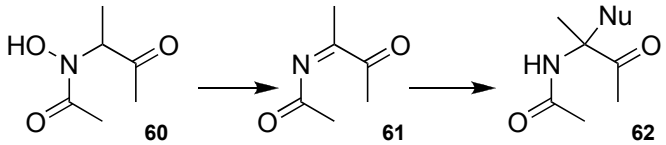
---

2. Quadruple Cα-Methine Hydroxylation

2.1 Methods for Cα-oxidation.

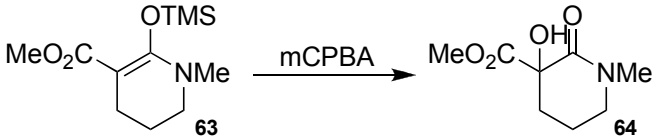
N-hydroxylation-dehydration strategy

H. C. Ottenheijm, *et al. J. Org. Chem.* **1980**, *45*, 1880.



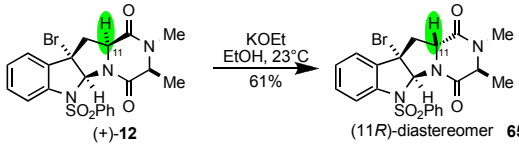
Oxidation of enol tautomers or corresponding enolates

Langlois, Y. *et al. Tetrahedron Lett.* **1985**, *26*, 3563.

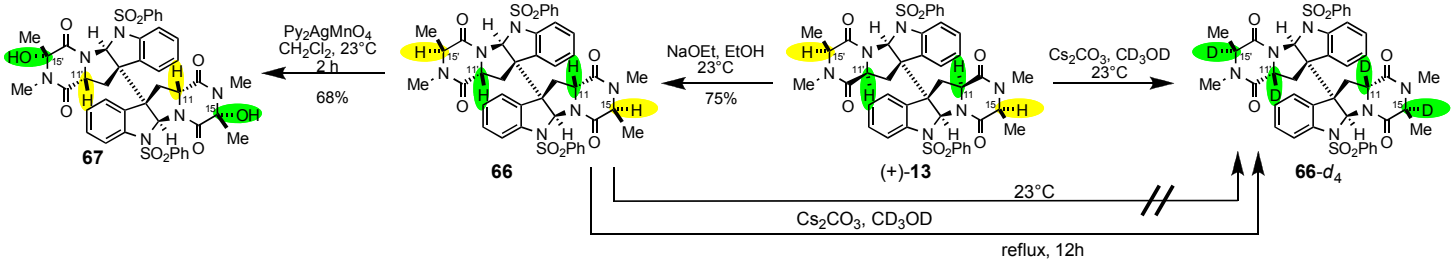


- These strategies including electrophilic amide activation and soft-enolization were failed to provide the necessary Cα-methine oxidation by formation of partially oxidized and diastereomeric products in addition to substantial competing decomposition.

2.2 Sensitivity and epimerization of tetracyclic and dimeric octacyclic diketopiperazines.



- **Octacyclic dimer 66 is less prone to enolization at C11 as compared to (+)-13**
- **Oxidation of 66 using the optimal reaction conditions:**
  The C11 and C11' methines were not hydroxylated, whereas C15 and C15' methines were both hydroxylated.



2.3 Radical-based abstraction of Cα-methine

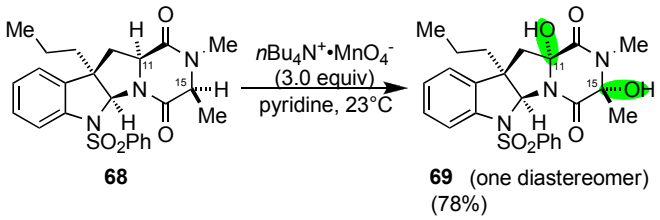
♦The Cα-methine of amino acids has an approximate bond dissociation energies(**BDE**) of 82-96 kcal/mol that varies as a function of the φ,ψ, angles.
Ruchardt, C. *et al. Tetrahedron Lett.* **1997**, *38*, 7721.
Rauk, A. *et al. Biochemistry* **1999**, *38*, 9089.

The **BDE** of all of the amino acid residues, modeled by $HC(O)NHCH(R)C(O)NH_2$ (PH(res)), were determined at the B3LYP/6-31G*//B3LYP/6-31G* level, coupled with isodesmic reactions.

♦Weak Cα-H bonds resulting from stabilization of the ensuing Cα-radicals in diketopiperazines.

⇩

An effective strategy: using mild oxidants typically reserved for hydrogen atom abstraction from formyl groups.



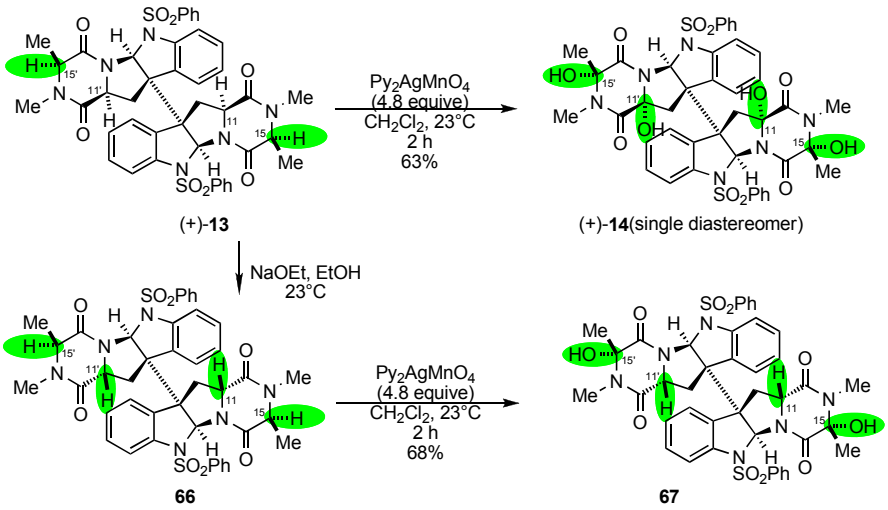
68 → **69** (one diastereomer) (78%)

(+)-**13** → **14'** (diastereomeric mixture) (40%)
(*n*Bu$_4$N$^+$•MnO$_4^-$ (3.0 equiv), pyridine, 23°C)

♦competing epimerization of Cα-methines and incomplete oxidation occured.

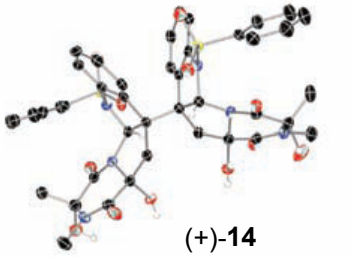
♦A mild and selective oxidant ⟶ bis(pyridine)-silver(I) permanganate (Py_2AgMnO_4)

H. Firouzabadi, *et al. Tetrahedron Lett.* **1982**, *23*, 1847.



(+)-**13** → (+)-**14** (single diastereomer)

66 → **67**



(+)-**14**

♦**Oxidation of 66 using the optimal reaction conditions:**

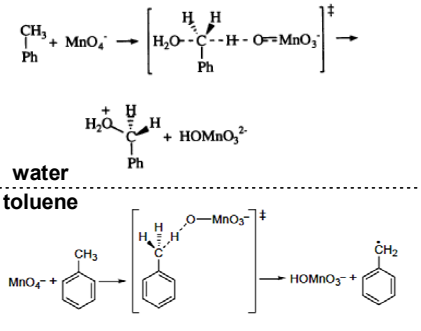
The C11 and C11' methines were not hydroxylated, whereas C15 and C15' methines were both hydroxylated.
(only oxidated at the alanine Cα(L-Ala)-methines, leaved the Cα(D-Trp)-methines unchanged.)

♦This observation, which has important consequences for the choice of natural or unnatural amino acid precursors, is attributed to a nonoptimal conformation of the C-H bond for abstraction and/or the sterically disfavored approach of the oxidant from the concave face of the 5,5-ring system.

2.4 Mechanism of Permanganate Oxidation: *Hydrogen Abstraction and Oxygen Rebound*

(i) *H• Transfer in the Oxidation of Toluene by Permanganate*

J. M. Mayer *et al*. *Science* **1995**, *269*, 1849.



Scheme 5. Calculation of the O–H Bond Strength in $[O_3MnO–H]^-$ [35,41]

MnO_4^- (aq) + e$^-$ ⟶ MnO_4^{2-} (aq)	}	$E° = 0.564$ V
1/2 H_2 (g) ⟶ H^+ (aq) + e$^-$	}	
MnO_4^{2-} (aq) + H^+ (aq) ⟶ $HMnO_4^-$ (aq)		$pK_a = 7.4$
H• (aq) ⟶ 1/2 H_2 (g)		$C = -57 \pm 2$ kcal/mol*
MnO_4^- (aq) + H• (aq) ⟶ $HMnO_4^-$ (aq)		$\Delta H° = -80 \pm 3$ kcal/mol

*$C = \Delta H°\{H•(g) \rightarrow \frac{1}{2}H_2(g)\} - \Delta H°\{H•(g) \rightarrow H•(aq)\} - \frac{1}{2}TS°\{H_2(g)\}$

Table 2. X–H Bond Strengths for Hydrogen Atom Abstracting Agents[30]

X	*D*(X–H) (kcal/mol)	X	*D*(X–H) (kcal/mol)
OH•	119	Br•	87
RO•	105	$[MnO_4^-]$	80
Cl•	103	I•	71
ROO•	89		

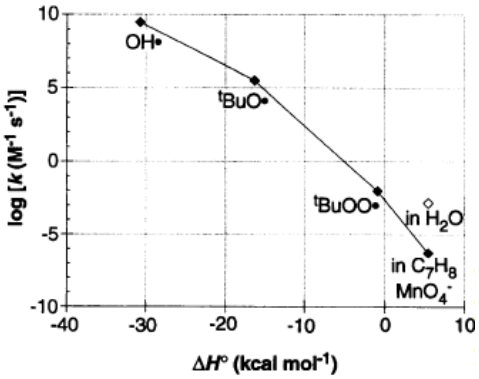


Fig. 2. Plot of the log of the rate constant *k* for hydrogen atom abstraction at 303 K versus $\Delta H°$ for hydrogen atom transfer [BDE($PhCH_2$-H) - BDE(ROH)]. [BDE($PhCH_2$-H) = 88.5 ± 1.5 kcal/mol]

♦In water, the reaction proceeds by hydride (H^-) transfer from toluene to a permanganate oxygen.

♦The oxidation in neat toluene is more than 1000 times slower than the reaction in water.

♦Rate-limiting step of the oxidation in neat toluene is attack of MnO_4^- to cleave the benzylic C-H bond, as in the aqueous reactions. The nature of this bond cleavage is different in the two solvents.

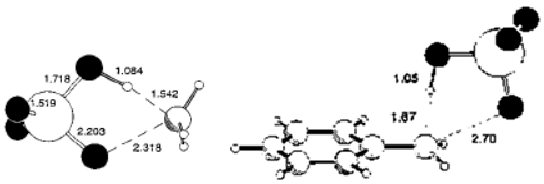
♦Oxidation in neat toluene most likely occurs by H• transfer from toluene to MnO_4^-.

♦MnO_4^- can make a strong bond to a hydrogen atom, and reactivity correlates with bond strengths and $\Delta H°$ for H-atom transfer.

♦Permanganate abstracts H• at essentially the rates expected for an oxygen radical that would make an 80 kcal/mol O-H bond. This occurs even though permanganate is not a radical.

(ii) *Hydrogen Abstraction and Oxygen Rebound*

K. N. Houk *et al*. *JACS,* **2000**, *122*, 7821



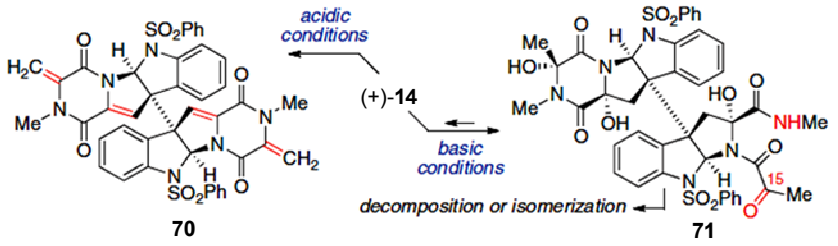
(a) CH_4/MnO_4^- (b) toluene/MnO_4^-

Figure 3. UB3LYP/6-311+G** transition state for the hydrogen abstraction from CH_4 and toluene.

- The preferred mechanism is a hydrogen atom abstraction followed by immediate collapse (oxygen rebound) of the radical pair to alkyl manganate ester.
- The manganese(V) product of $Mn(OH)(OMe)O_2^-$ is 20.7 kcal/mol more stable than the reactants.
- In both permanganate transition states, two oxygens of the permanganate are involved significantly in the transfer of the hydrogen. The hydrogen is clearly transferred to one, but a second oxygen is in the vicinity of the forming radical.
- The interaction between the permanganate O and the CH_2 group stabilizes the transition state. The activation energy of the reaction is calculated to be 21.8 kcal/mol.

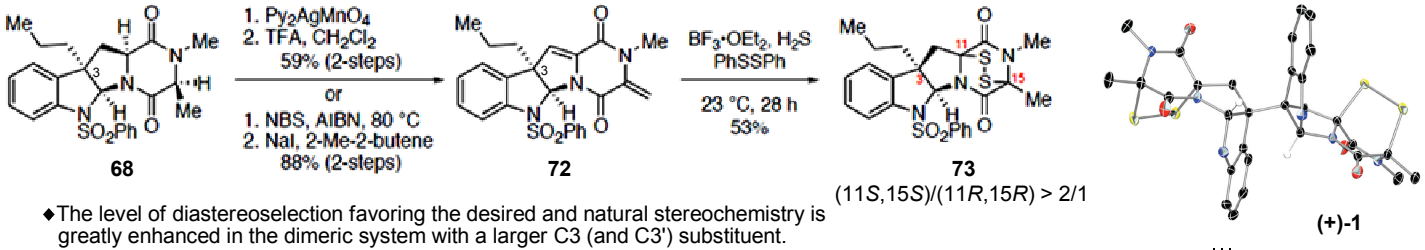
---

3. Stereoselective Tetrathiolation and Disulfide Formation

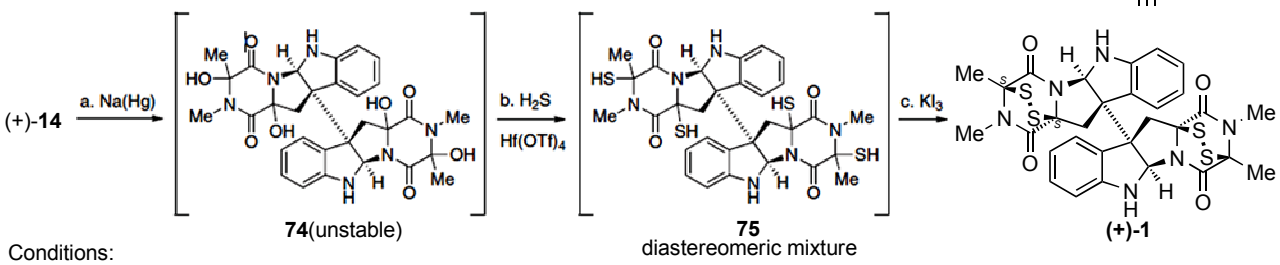


- The dimeric octacyclic tetraol (+)-**14** proved highly acid- and base-sensitive.
- Even dissolution of (+)-**14** in methanol at ambient temperature led to slow decomposition.

Synthesis of the pentacyclic epidithiodiketopiperazine ***73.****(tetracyclic model system)*



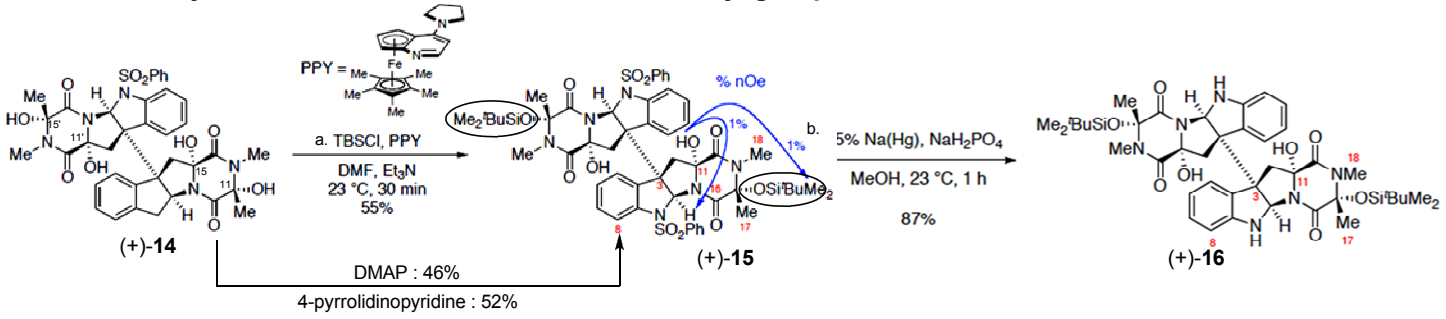
- The level of diastereoselection favoring the desired and natural stereochemistry is greatly enhanced in the dimeric system with a larger C3 (and C3') substituent.



Conditions:
(a) 5% Na(Hg), Na_2HPO_4, MeOH, 23°C. (b) H_2S, CH_2Cl_2, $[Hf(OTf)_4]$, -78→23°C, 14 hours.
(c) KI_3, pyridine, CH_2Cl_2, 23°C, 2-15% for three steps.

- Low overall yields may be due in part to competing reduction of the tautomeric α-ketoamide **71** or the corresponding derivative from the highly sensitive diaminotetraol **74.**

3.1 Selective silylation and Removal of the benzenesulfonyl groups

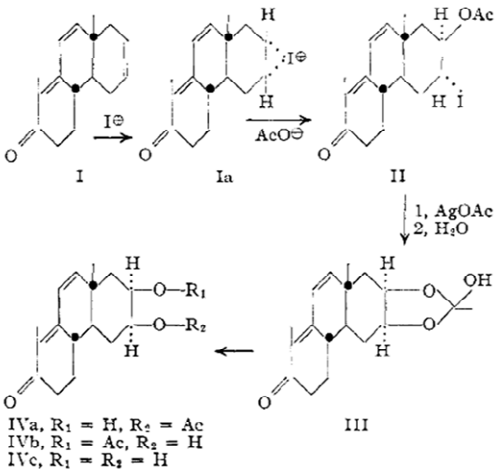


Conditions: (a)TBSCl(5.0 equive), PPY(5 mole %), Et_3N(6.0 equive), DMF, 23°C, 30 min.
(b) 5% Na(Hg), NaH_2PO_4(40.0 equive), MeOH, 23°C.

- A simple tactical conversion of the tetraol (+)-**14** to the diol (+)-**15** imparted considerable stability to this structure. (prevent from undesired diketopiperazine ring opening)
- Only one t-butyldimethylsilyl group per diketopiperazine substructure is allowed, and the attenuation of the C15 alcohol reactivity is critical.
- Fu's (R)-(+)-4-pyrrolidinopyridinyl(pentamethylcyclopentadienyl)-iron (**PPY**) catalyst (5 mole %) was optimal for the selective derivatization of both alaninederived hemiaminals of (+)-**14.**
- Comparison of the base stability of octacyclic tetraol (+)-**14** with octacyclic diol (+)-**15**.

3.2 Woodward-Prevost *cis*-dihydroxylation

R. B. Woodward, F. V. Brutcher, *JACS.* **1958**, *80*, 209.

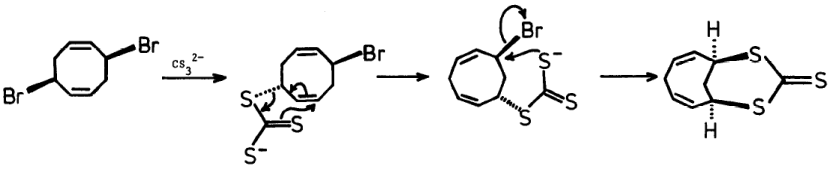


♦It is important to note that simple exposure of the penultimate intermediate **5** to air leads to direct and rapid formation of (+)-**1**, suggesting the *cis*-dithiodiketopiperazine stereochemistry of **5** as illustrated.(page 2)

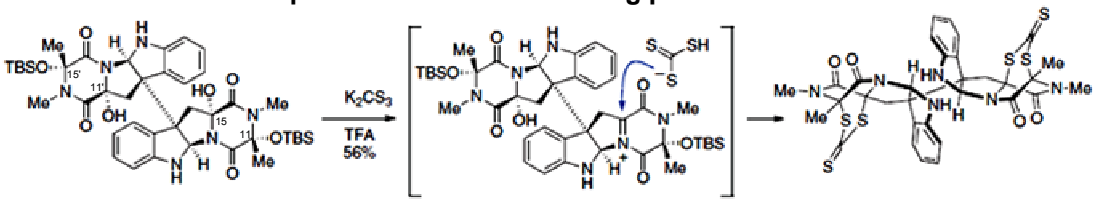
♦A series of studies for the nucleophilic introduction of the carbon-sulfur bonds at C11 and C15, all point to a high preference for nucleophilic thiol addition at C11 favoring the (11*S*)-stereochemistry.

cis-three-atom bridge formation using trithiocarbonate

D. D. MacNicol *et al. Tetrahedron Lett.* **1975**, *16*, 1345.



3.3 Intramolecular dithiepanethione formation using potassium trithiocarbonate.



(+)-**16** (+)-**17** (+)-(11S,11'S,15S,15'S)-**18** + (11R,11'S,15R,15'S)-**18a** (11R,11'R,15R,15'R)-**18b**

18:18a:18b = 25:7:1

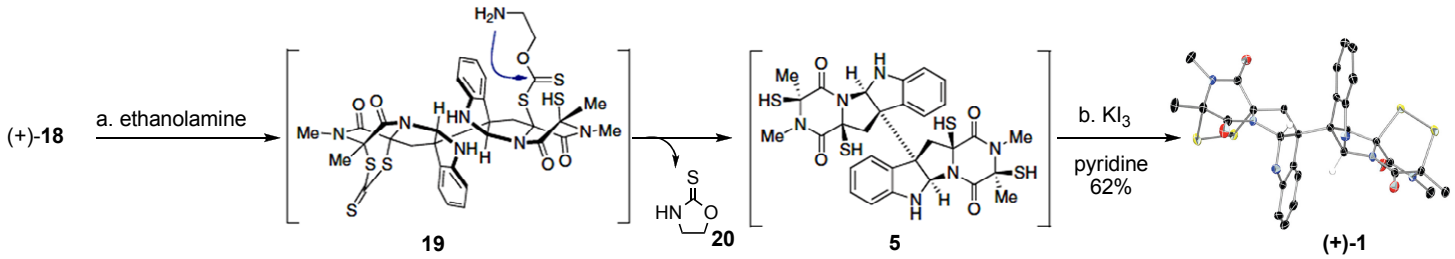
Conditions: K_2CS_3(10.0 equive), TFA, CH_2Cl_2, 23°C, 28 min.

♦four carbon-oxygen bonds are exchanged for four carbon-sulfur bonds, the stereochemistry at all four tertiary thiols is secured

♦the targeted *cis*-dithiodiketopiperazine substructure of **5** is attained.

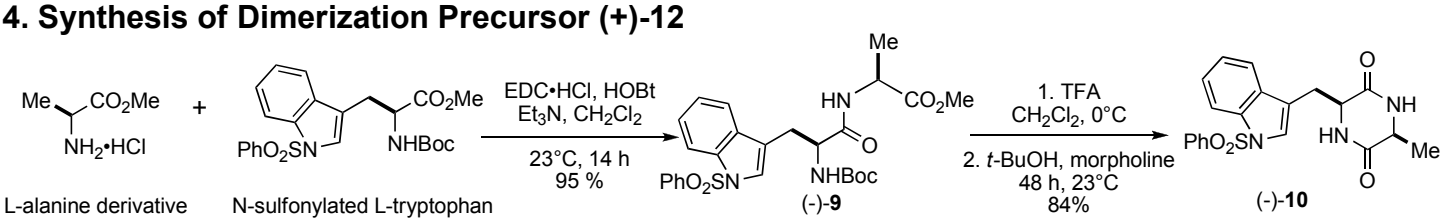
♦conversion of (+)-**16** to (+)-**18** enabled tetrathiolation with concomitant inversion of all four Cα-stereocenters, allowing rapid epidithiodiketopiperazine formation.

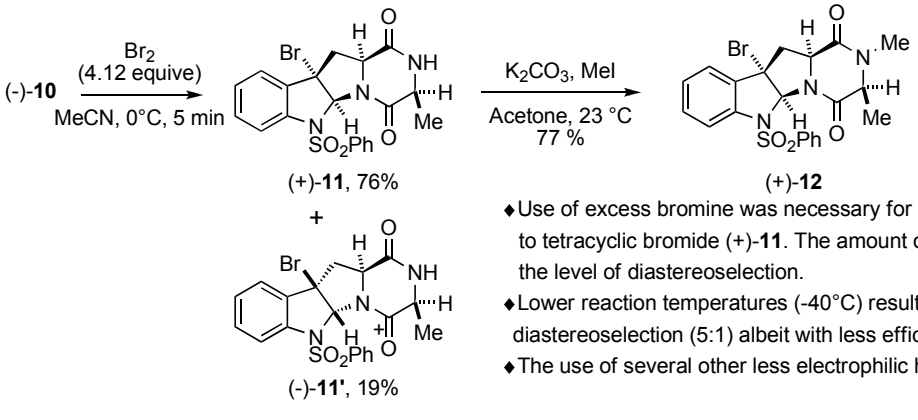
3.4 Diaminotetrathiol formation and triiodide oxidation



Conditions: (a) ethanolamine, acetone, 23°C; (b) KI_3, pyridine, CH_2Cl_2, 23°C.

4. Synthesis of Dimerization Precursor (+)-12



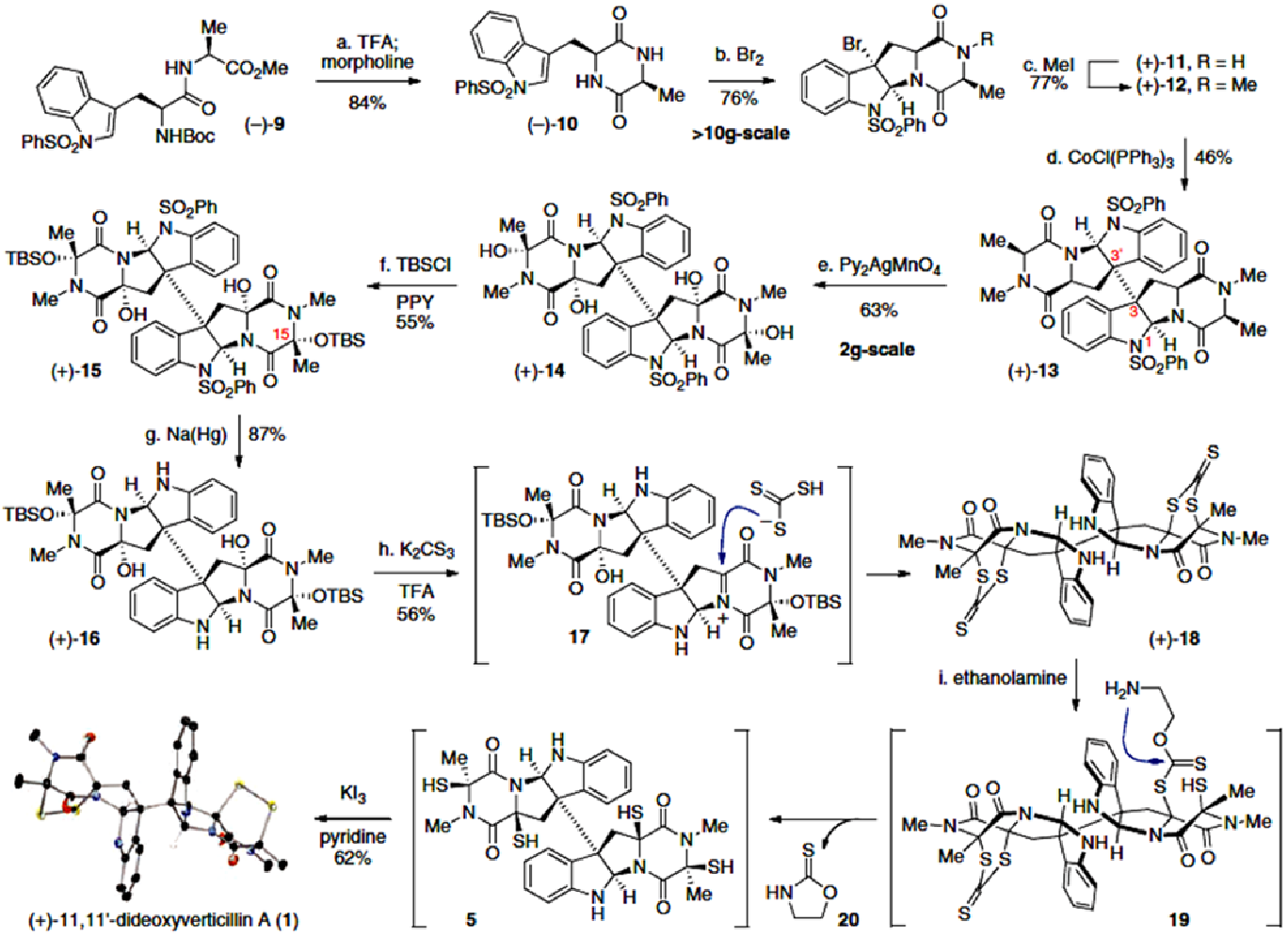


♦Use of excess bromine was necessary for complete conversion of (-)-**10** to tetracyclic bromide (+)-**11**. The amount of bromine used did not affect the level of diastereoselection.

♦Lower reaction temperatures (-40°C) resulted in a slightly higher level of diastereoselection (5:1) albeit with less efficient conversion.

♦The use of several other less electrophilic halogenating agents was less effective.

5. Over View Movassaghi, M. *et al*. *Science* **2009**, *324*, 238.



Concise enantioselective total synthesis of (+)-11,11'-dideoxyverticillin A (1). Isolated yields are given for each step. Reaction conditions are as follows: (a) trifluoroacetic acid (TFA), dichloromethane (CH_2Cl_2), 23°C, 4 hours; tert-butanol (tBuOH), morpholine, 23°C, 48 hours. (b) Br_2, acetonitrile (MeCN), 0°C, 5 min. (c) methyl iodide (MeI), K_2CO_3, acetone, 23°C, 5 days. (d) tris(triphenylphosphine)cobalt(I) chloride [$CoCl(PPh_3)_3$], acetone, 23°C, 30 min. (e) bis(pyridine)silver(I) permanganate (Py_2AgMnO_4), CH_2Cl_2, 23°C, 2 hours. (f) tert-butyl(chloro) -dimethylsilane(TBSCl), PPY 5 mole %, triethylamine (Et_3N), N,N-dimethyl formamide (DMF), 23°C, 30 min. (g) 5% Na(Hg), NaH_2PO_4, methanol (MeOH),23°C. (h)K_2CS_3, TFA, CH_2Cl_2, 23°C, 28 min. (i) ethanolamine, acetone, 23°C; KI_3, pyridine, CH_2Cl_2, 23°C. The thermal ellipsoid representation of synthetic (+)-1 from x-ray crystallographic analysis is shown with most hydrogens omitted for clarity.

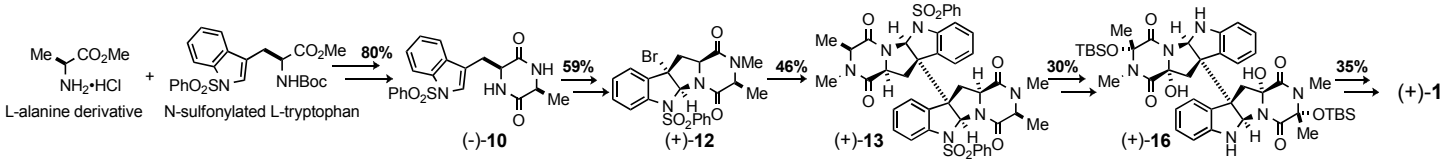
- **Cobalt(I)-Promoted Reductive Dimerization**
- **Highly stereo- and chemoselective advanced-stage tetrahydroxylation and tetrathiolation reactions**
- **A mild strategy for the introduction of the epidithiodiketopiperazine core in the final step**

---

6. Sodeoka's Route

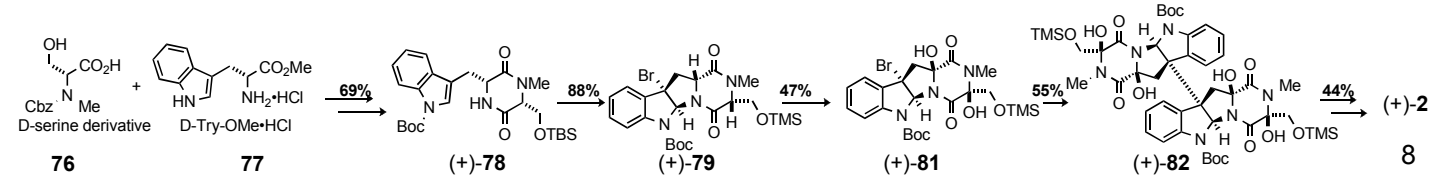
Movassaghi's strategy

natural amino acid ⟹ Dimerization ⟹ α-Hydroxylation of monomer ⟹ tetrathiolation(with inversion) and S-S bond formation

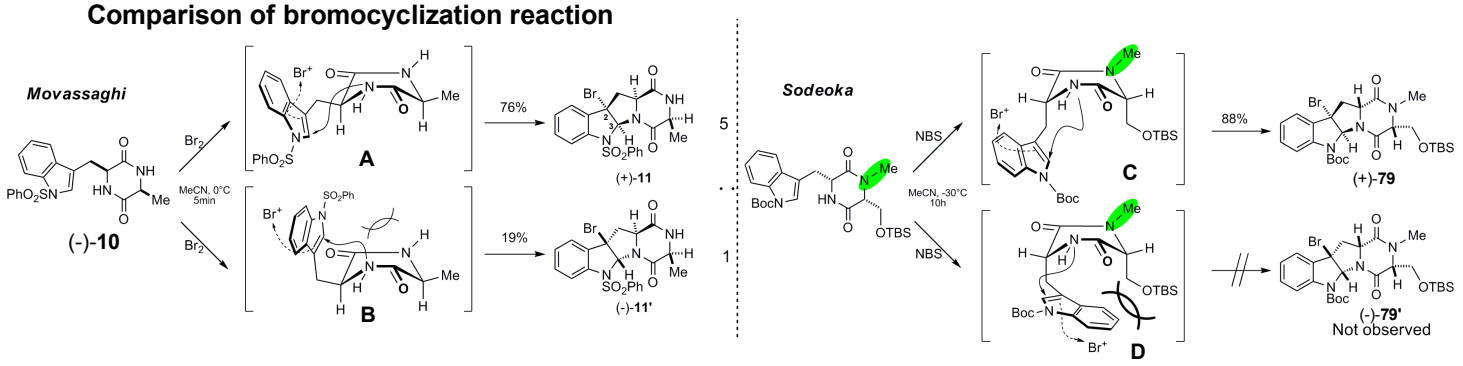


Sodeoka's strategy

unnatural amino acid ⟹ α-Hydroxylation of monomer ⟹ Dimerization ⟹ tetrathiolation and S-S bond formation

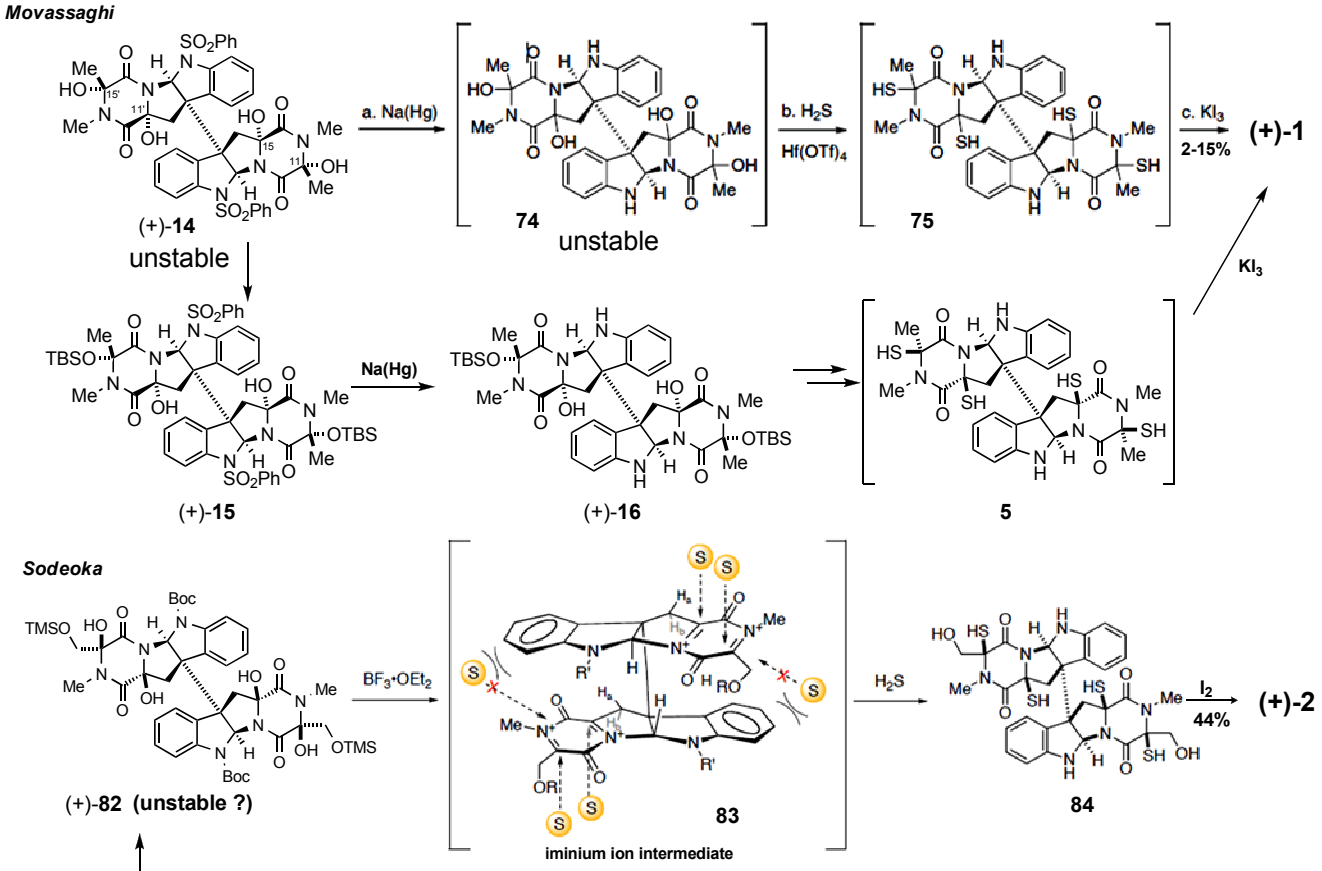


Comparison of bromocyclization reaction



- **The difference in stereoselectivity depends upon whether or not an *N*-methyl group is present.**
- The diketopiperazine ring being co-planar, the *N*-Me group is considered to be on the same plane.
- TBS-oxymethyl group is located at the pseudo-axial position.
  (In order to avoid steric interaction with the N-Me group)

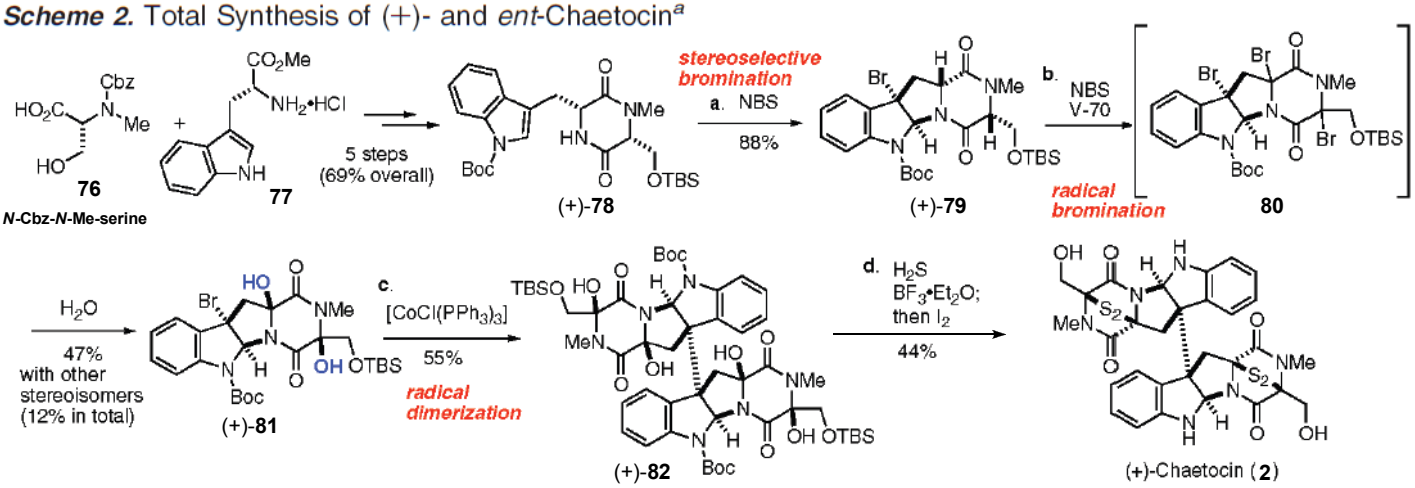
Comparison of final-stage



- The diol (+)-**81** was relatively unstable in $CDCl_3$.
- However,the hemiaminal was not sensitive to a reductive coupling reaction using a Co(I) complex.
- The unprotected diol (+)-**81** could be directly used to furnish the desired octacyclic tetraol (+)-**82** as a single isomer in 55% yield
- The stereochemistry at the α-position would be cancelled by formation of the iminium ion.
- Hydrogen sulfide mainly attacked from the outer surface of the double-decker core structure, affording the tetrathiol precursor stereoselectively.

Sodeoka, M. *et al*. *JACS* **2010**, *132*, 4078.

Scheme 2. Total Synthesis of (+)- and *ent*-Chaetocin[a]



[a] Conditions: (a) NBS, MeCN, -30°C, 10 h; (b) NBS, V70, CCl_4, rt, 5 h; then pH_7 phosphate buffer/MeCN) $1/_1$, rt, 3 h; (c) $CoCl(PPh_3)_3$, acetone, rt, 1.5 h; (d) H_2S, $BF_3.Et_2O$, CH_2Cl_2, -78°C to rt, sealed tube, 1.5 h; then I_2.

$[\alpha]_D^{26}$ +537 (c = 0.2, $CHCl_3$) (synthetic)
$[\alpha]_D^{24}$ +520 (c = 0.04, $CHCl_3$) (natural)

- In the final step, no less than ten bond-forming and cleaving events.
  - ◊four substitution reactions (OH→SH)
  - ◊deprotection of four Lewis acid-sensitive protecting groups (TBS and Boc groups)
  - ◊two S-S bond formations
- The first total synthesis of (+)-chaetocin has been accomplished in only nine steps starting from the known *N*-Cbz-*N*-Me-serine.