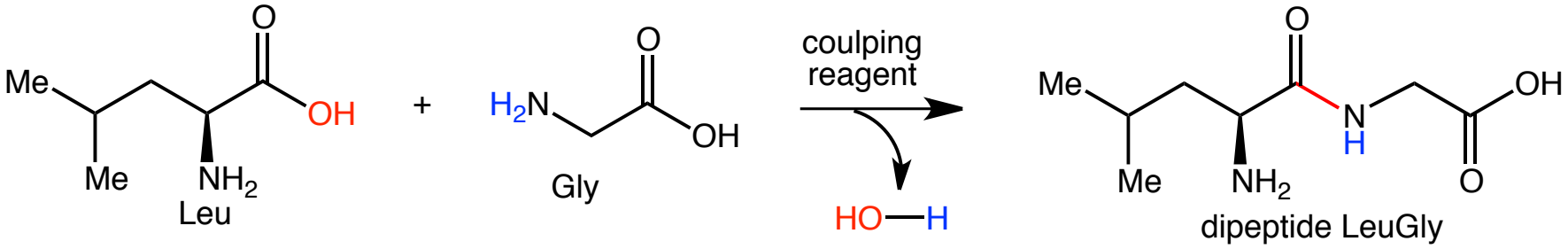
# Medicinal Chemistry: An Overview

## Course Outline

| Lecture | Date | Topic |
|---|---|---|
| 1 | 2015/12/17 | General Aspects of Medicinal Chemistry |
| 2 | 2016/01/07 | General Biochemistry |
| 3 | 2016/01/21 | Principles of Chemical Synthesis |
| 4 | 2016/02/04 | Chemical Synthesis of Small and Complex Molecules |
| 5 | 2016/02/18 | Chemical Synthesis of Peptides |
| 6 | 2016/04/07 | Strategies for Discovering Lead Compounds |
| 7 | 2016/04/14 | Structure Activity Relationship |
| 8 | 2016/04/21 | Spatial Organization, Receptor Mapping and Molecular Modeling |
| 9 | 2016/04/28 | Pharmacokinetic Properties |
| 10 | 2016/05/12 | Legal and Economic Aspects of Drug Development |

# Chemical Synthesis of Peptides

The chemical synthesis of peptides is a reliable and predictable process such that it is usually automated.




A series of coupling reagents have been developed to activate the carboxylic acid for nucleophilic attack. However, the choice of coupling reagent requires careful consideration.

Orthogonal protecting groups have been developed to preclude the formation of undesired products during peptide synthesis.

# Solid-Phase Peptide Synthesis (SPPS)

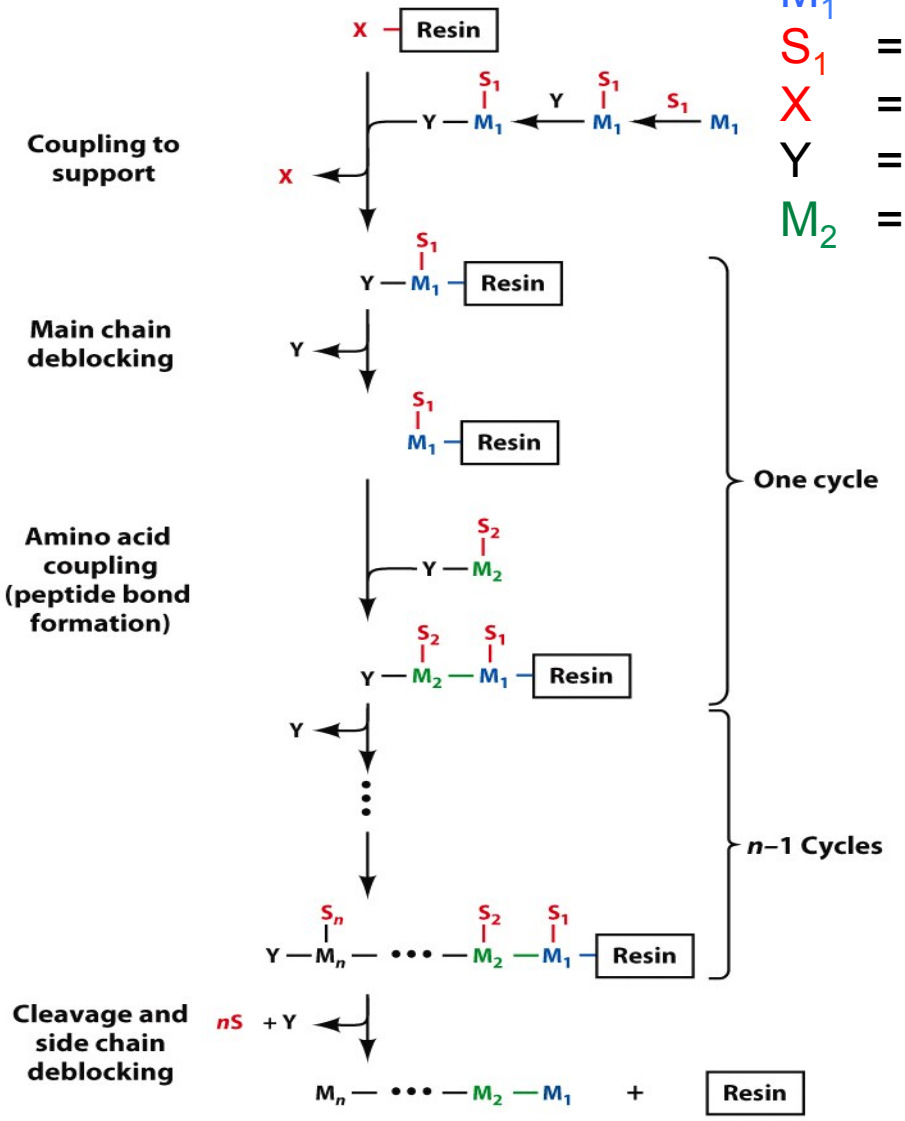



Figure 7-35



$M_1$ = first amino acid from the C-terminus

$S_1$ = protecting group for the side chain of $M_1$

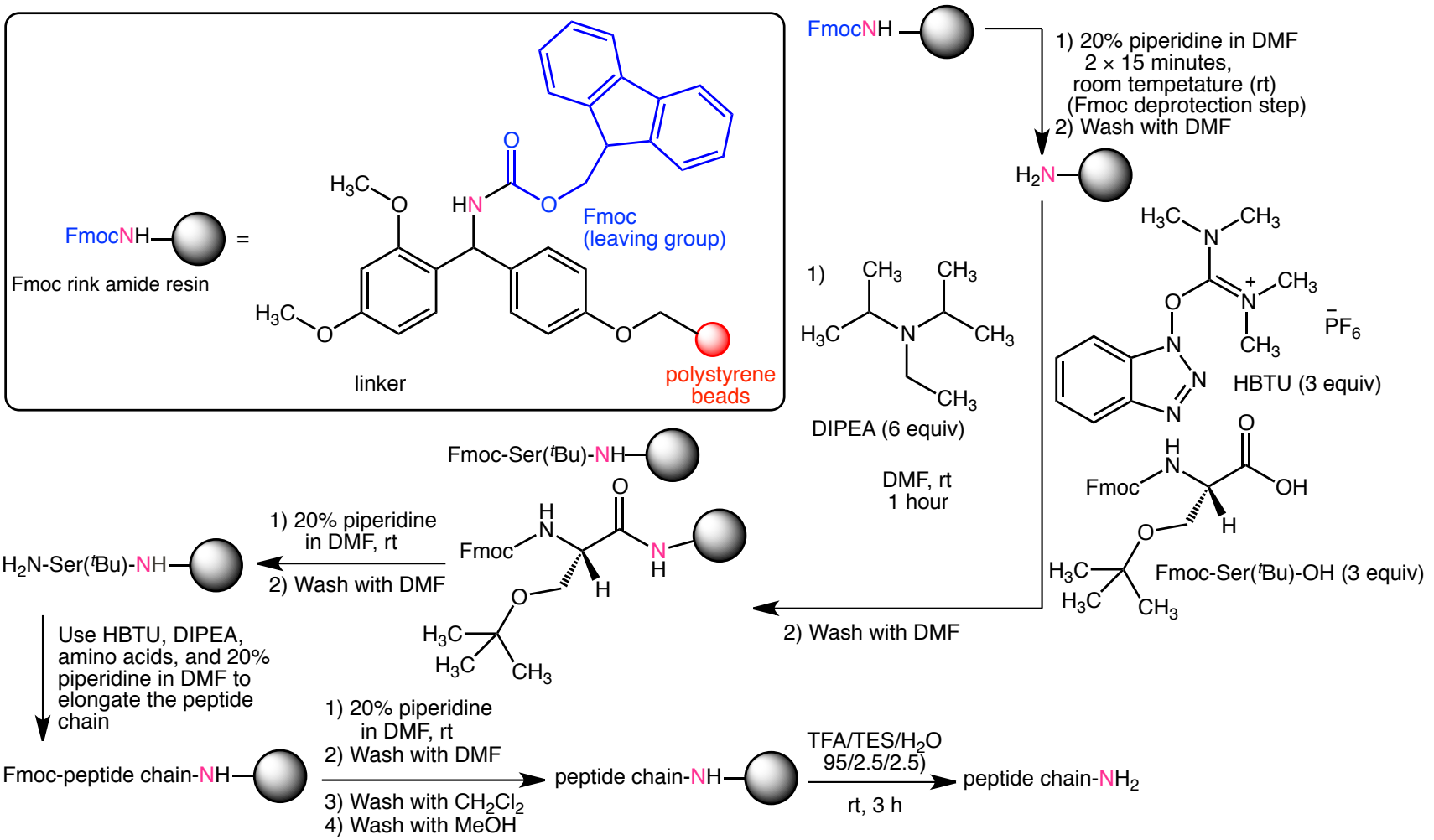
X = leaving group

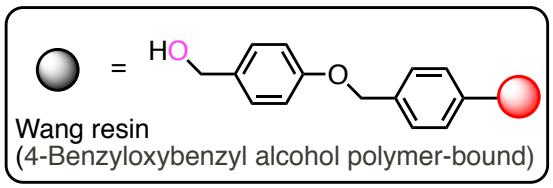
Y = main chain protecting group

$M_2$ = second amino acid from the C-terminus

Liberty Blue SPPS machine from CEM Corporation

# Solid-Phase Peptide Synthesis (SPPS)

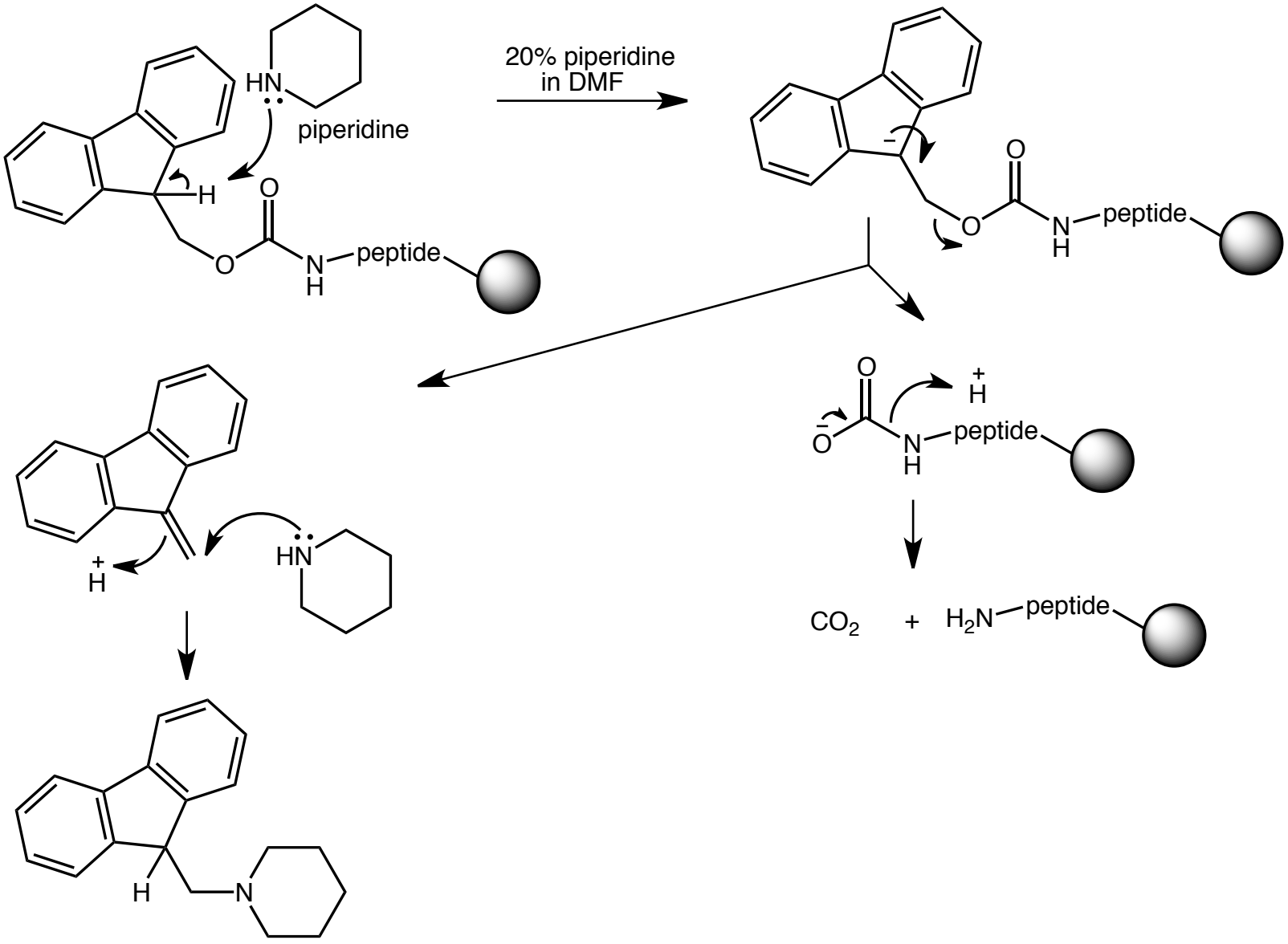


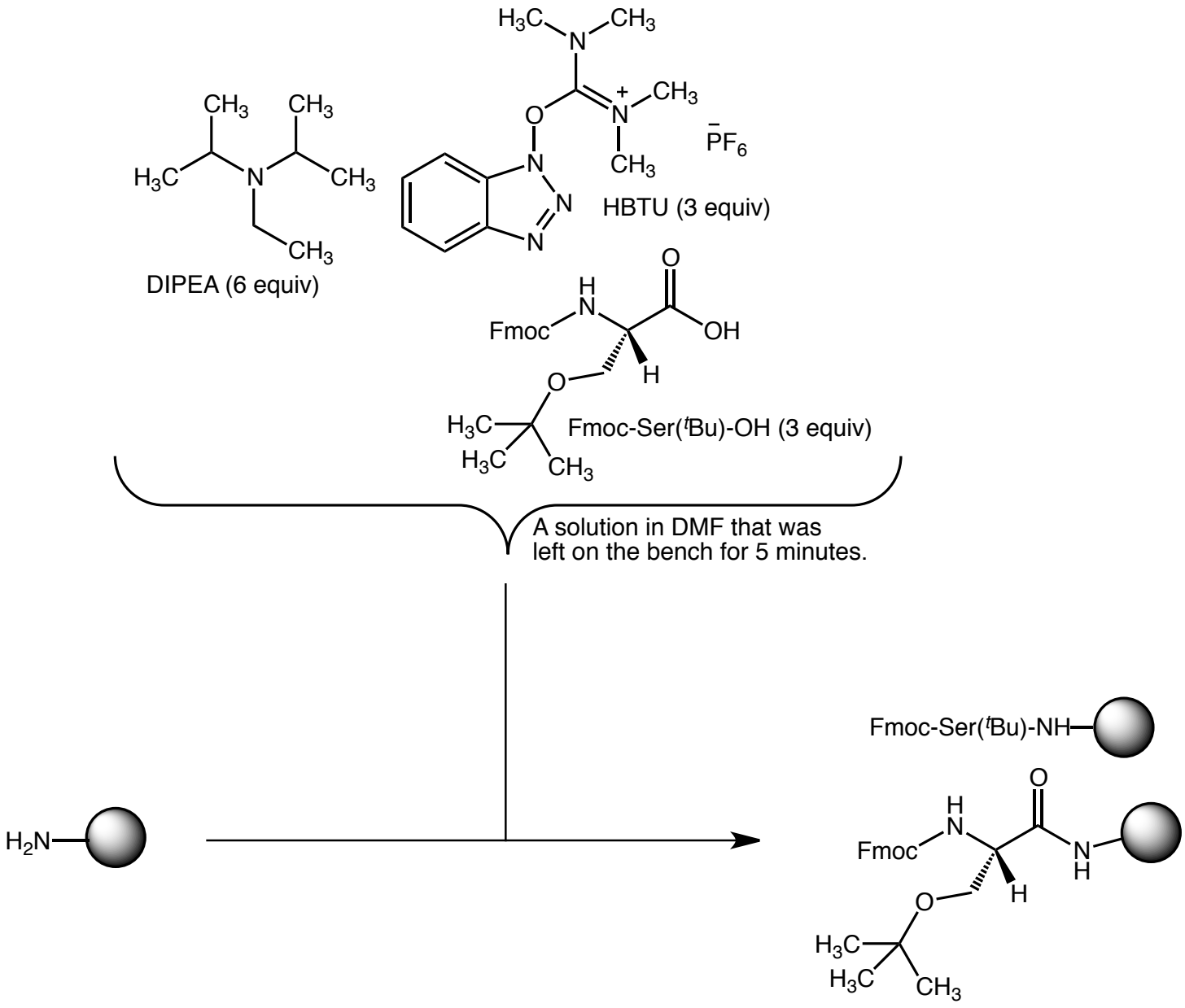

same as above

peptide chain-OH

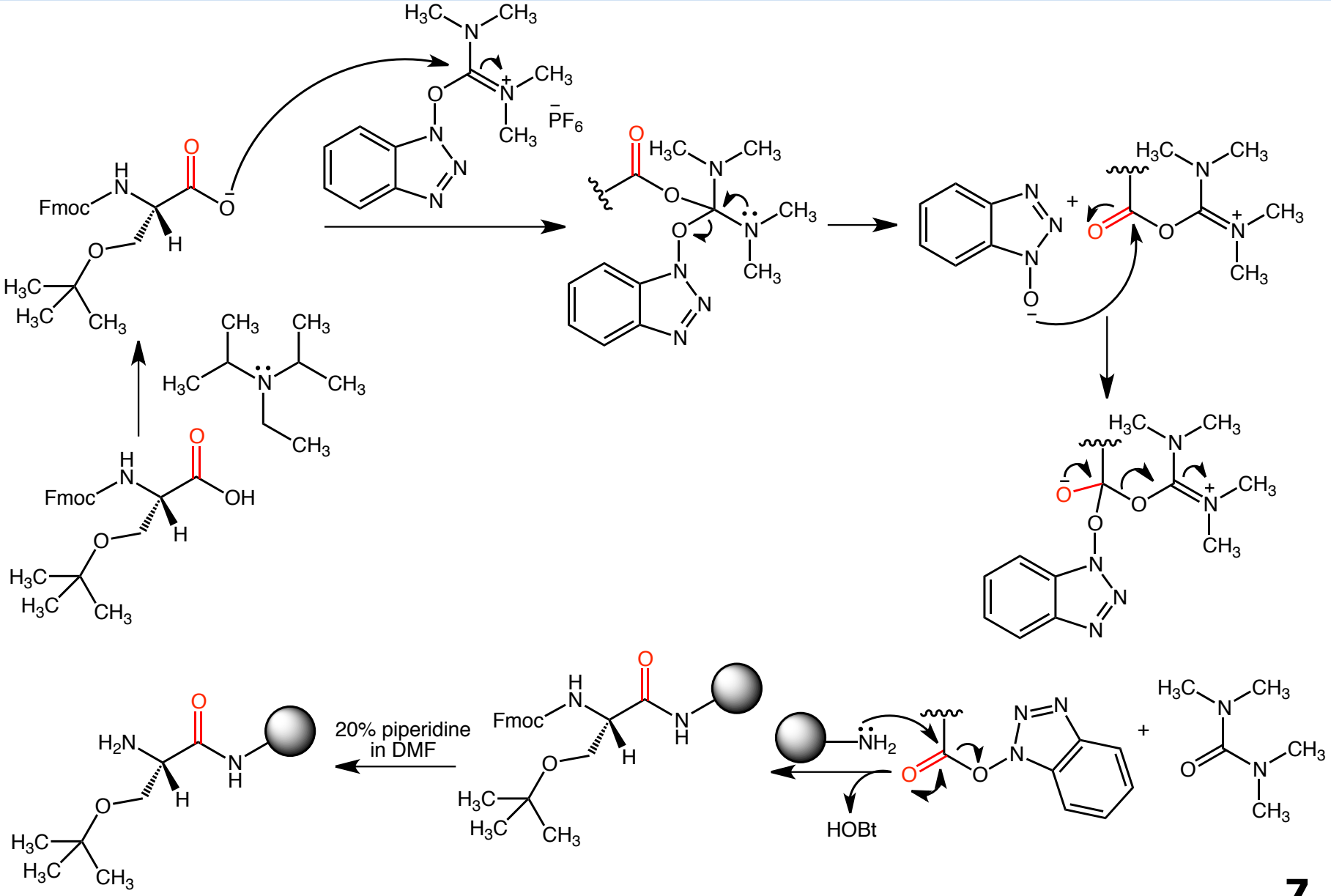
# Fmoc-Deprotection



# Peptide Coupling

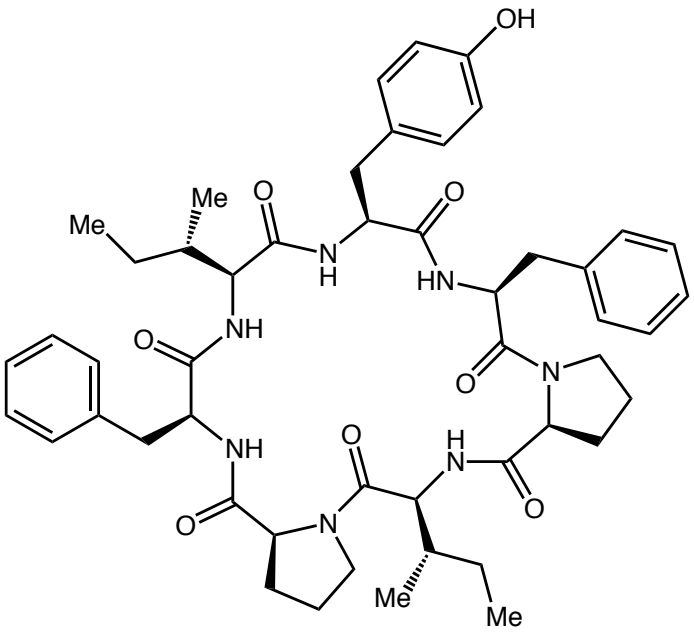


# Mechanism of Peptide Coupling




The resin is ready for the coupling of the second amno acid residue.

# Stylissatin A




**Stylissatin A**

***Stylissa massa*** ©2007 Moorea Biocode

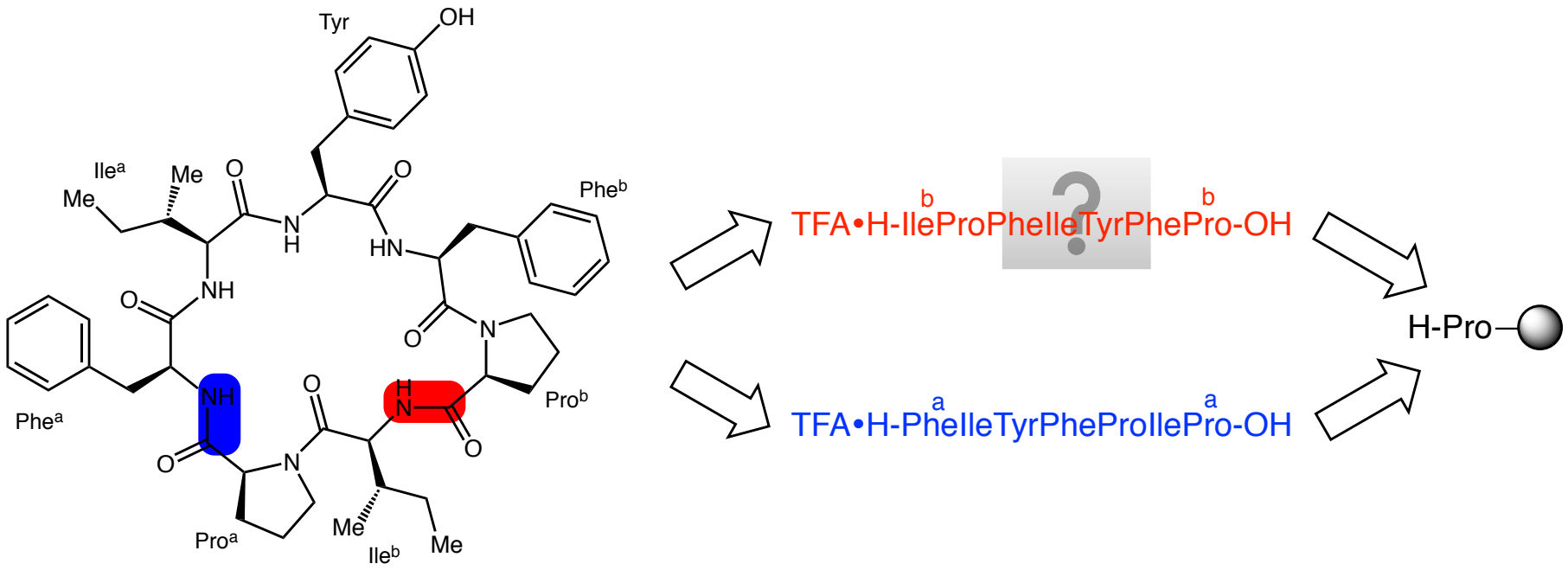
Isolated from *Stylissa massa*, collected from Loloata Island, Papua New Guinea.

Proline-rich cyclic heptapeptide consisting of seven amino acid residues.

Inhibitor of nitric oxide production in lipopolysaccharide-stimulated murine macrophage RAW264.7 cells ($IC_{50}$ = 87 μM).

Kita, M.; Gise, B.; Kawamura, A.; Kigoshi, H. *Tetrahedron Lett.* **2013**, *54*, 6826.

# Retrosynthesis of Stylissatin A




Proline (Pro) is usually positioned at the C-terminus of the linear peptide because it prevents racemization during the cyclization step.

The cyclization site should not be sterically encumbered.


Davies, S. J. *J. Peptide Sci.* **2003**, 9, 471.
Humphrey, J. M.; Chamberlin, A. R. Chem. Rev. **1997,** 97, 2243.
White, C. J.; Yudin, Andrei, K. Y. *Nat. Chem.* **2011**, *3*, 509.

# Solid-Phase Synthesis of Linear Heptapeptides

resin substitution
= (0.71 mmol/g)

H-Pro–

50.5 mg

1) DMF (10 ml/g)
rt, 1.0 h
2) Remove solvent
(swelling of the resin)

H-Pro–

4) Fmoc-Ile-OH (5 equiv)
HBTU (5 equiv)
DIPEA (10 equiv)
HOBt (5 equiv)
DMF (5 ml/g)
rt, 1 h
5) Chloranil test

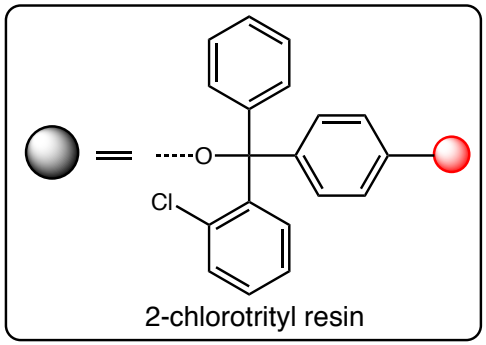
6) DMF wash

Fmoc-IlePro–

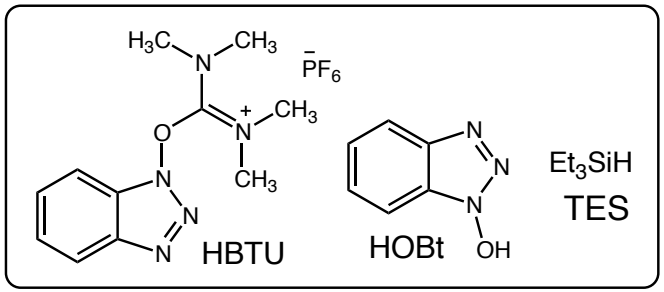
7) 20% piperidine
in DMF (10 ml/g)
rt, (10 min)
(2 times)
8) Kaiser test

H-IlePro–

9) elongation of
the peptide
chain



2-chlorotrityl resin




10) 20% piperidine in DMF
(10 ml/g), rt, (10 min)
(2 times)

11) Kaiser test

H-PheIleTyr(*t*-Bu)PheProIlePro–

Fmoc-PheIleTyr(*t*-Bu)PheProIlePro–

11) DMF wash
12) $CH_2Cl_2$ wash
13) MeOH wash
14) Dried with $N_2$

TFA/TES/$H_2O$
95:2.5:2.5
(1.3 ml)

rt, 3 h

HPLC

TFA•H-PheIleTyrPheProIlePro-OH
(28 mg, 77%)

resin substitution
= (0.71 mmol/g)

H-Pro–

50.5 mg

same conditions
as above

TFA•H-IleProPheIleTyrPhePro-OH
(18 mg, 50%)

# Macrolactamization

TFA•H-Ile$^{b}$ProPheIleTyrPhePro$^{b}$-OH

+

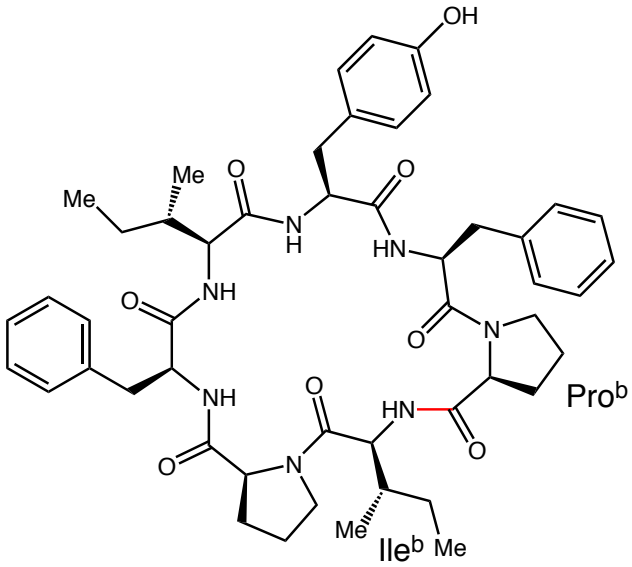
HBTU
(3 equiv)

solution in $CH_2Cl_2$-DMF (5:1)
added at 0.5 ml/h, for 11h
concentration of linear peptide; 1.8 mM

DIPEA
(5 equiv)

$CH_2Cl_2$
rt, 11 h

overall concentration
of the linear peptide
at the end of addition;
0.8 mM




8%

TFA•H-Phe$^{a}$IleTyrPheProIlePro$^{a}$-OH

+

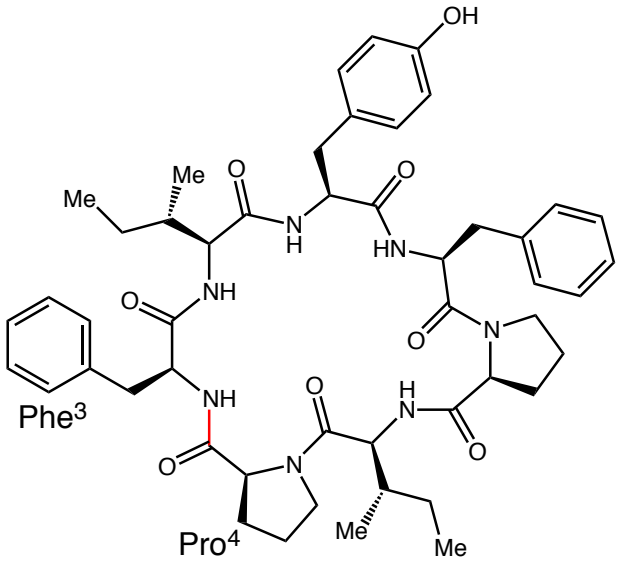
HBTU
(3 equiv)

solution in $CH_2Cl_2$-DMF (5:1)
added at 0.5 ml/h
concentration of linear peptide; 1.8 mM

DIPEA
(5 equiv)

$CH_2Cl_2$
rt, 11 h

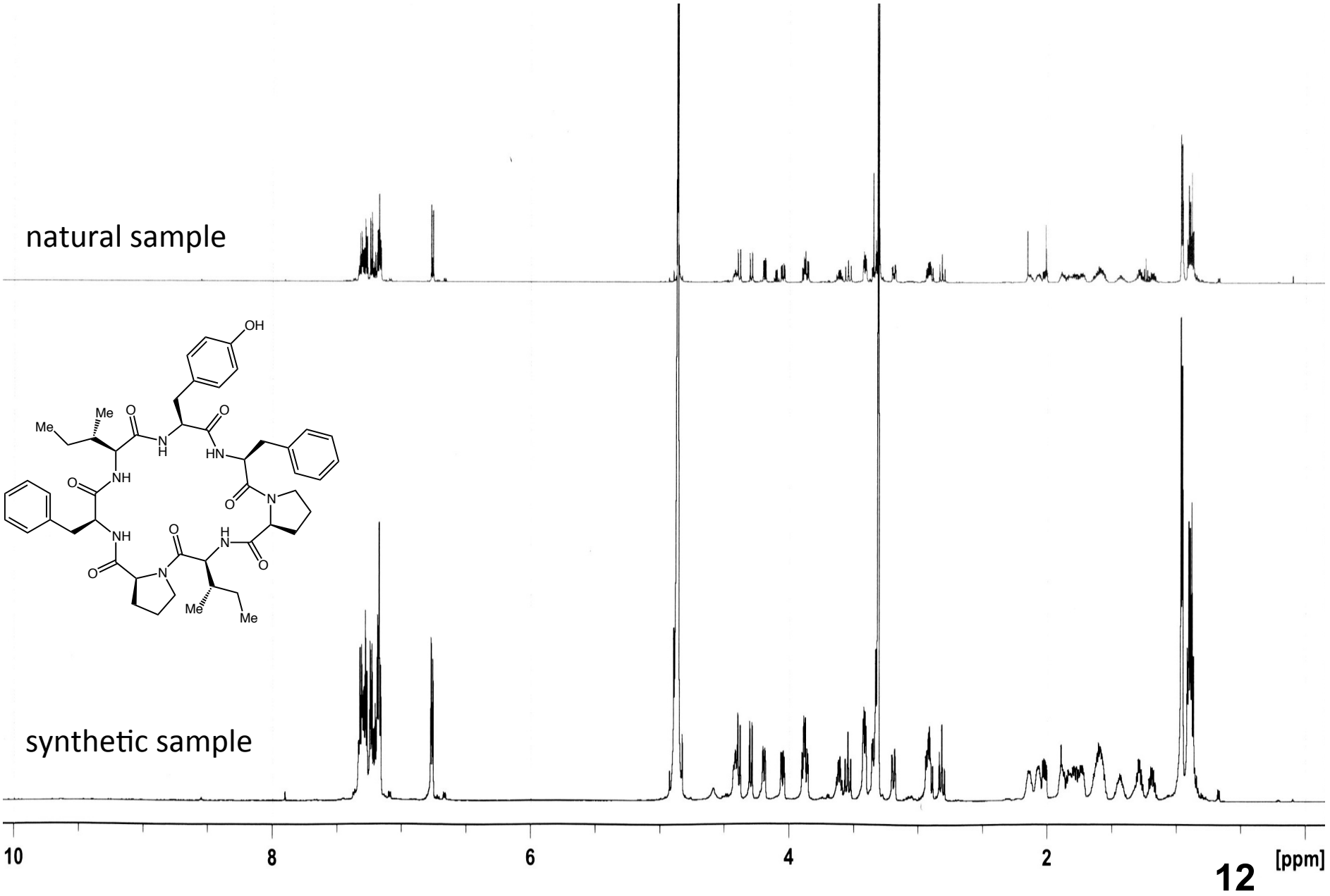
overall concentration
of the linear peptide
at the end of addition;
0.8 mM



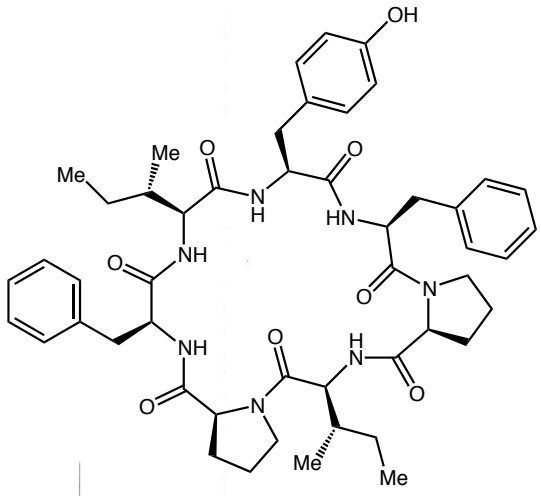

43%

43% (after 72 h)

# $^{1}$H-NMR Overlay Comparisons of Stylissatin A (600 MHz, $CD_3OD$)



# $^{13}$C-NMR Overlay Comparisons of Stylissatin A (600 MHz, $CD_3OD$)

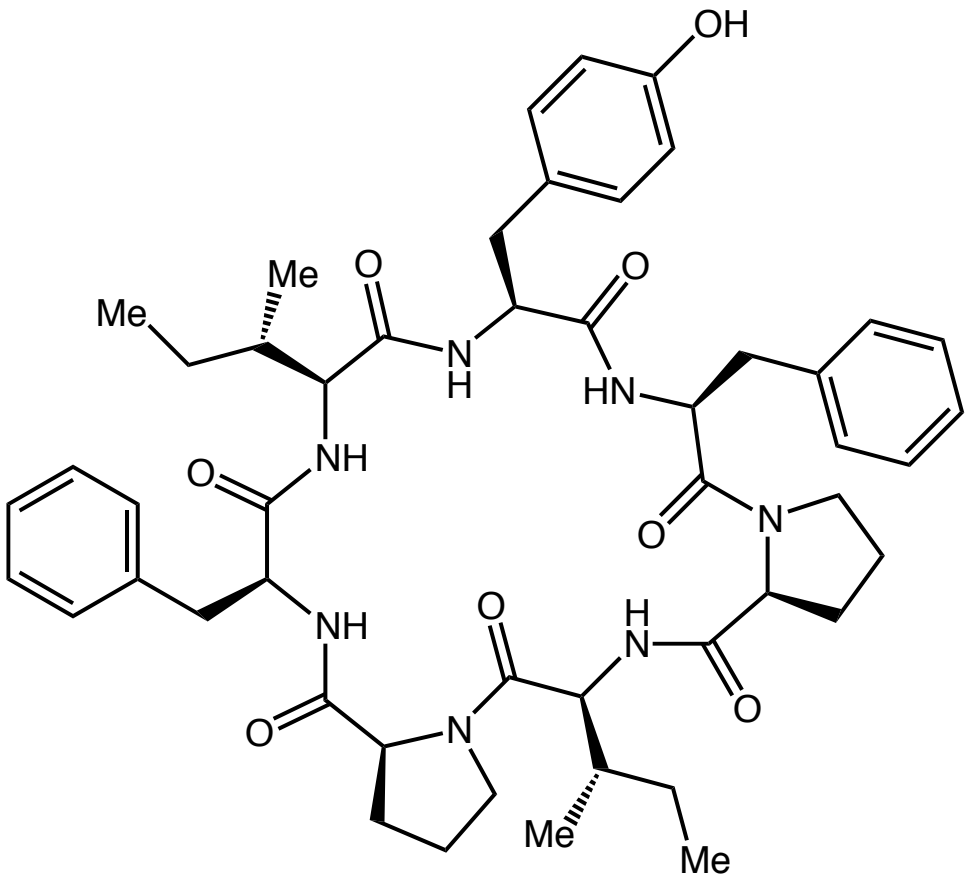



natural sample

synthetic sample

200 150 100 50 13 [ppm]

# Specific Rotation and HRMS of Stylissatin A

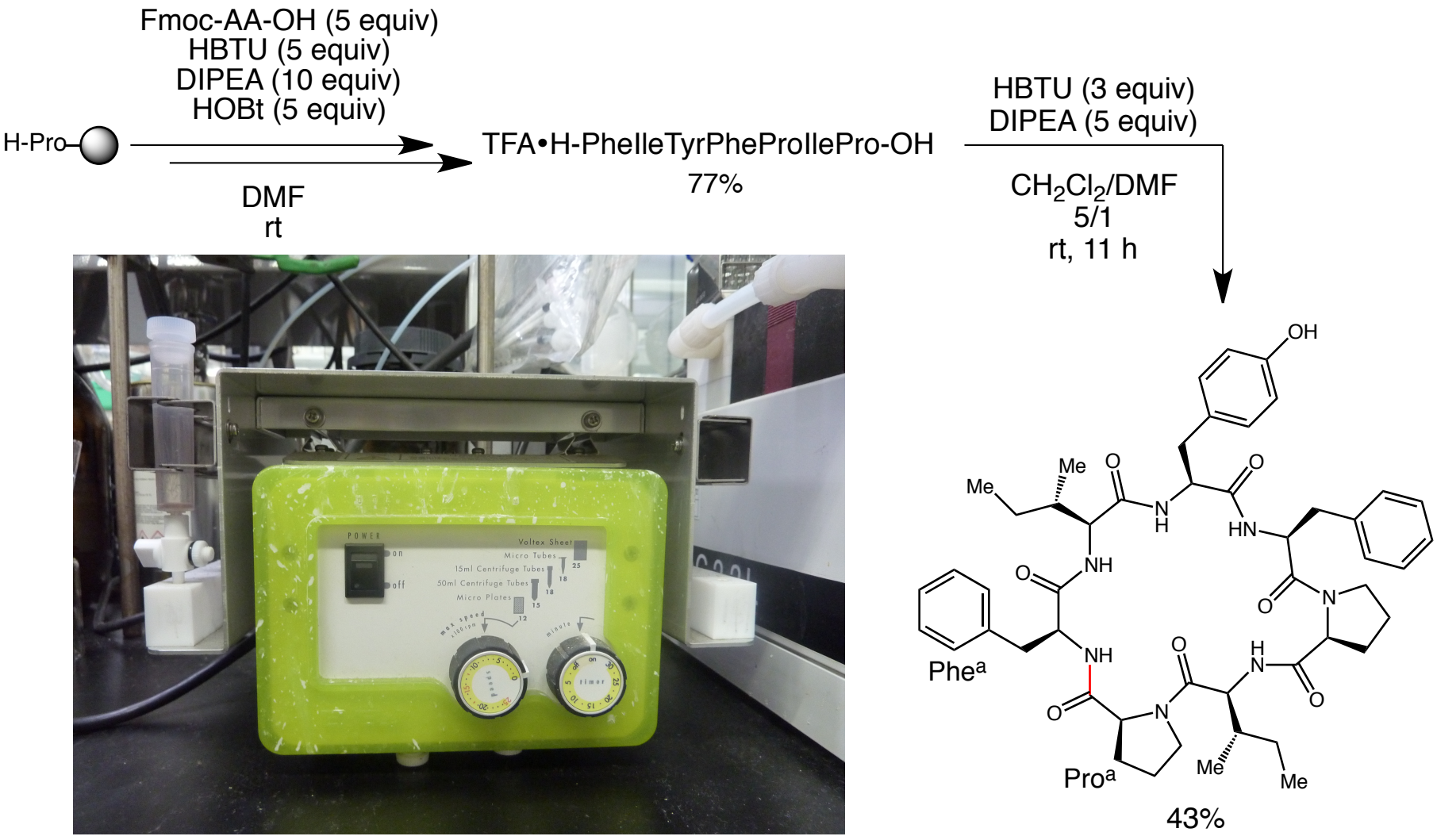



$[\alpha]_D^{25}$ −84 (*c* 0.25, MeOH)
Lit. $[\alpha]_D^{25}$ −27 (*c* 0.11, MeOH)

HRMS (ESI) m/z 900.4614
(calcd for $C_{49}H_{63}N_7NaO_8$ $[M+Na]^+$, Δ −2.2 mmu)

Kita, M.; Gise, B.; Kawamura, A.; Kigoshi, H. *Tetrahedron Lett.* **2013**, *54*, 6826.
Akindele, T.; Gise, B; Sunaba , T; Kita, M.; Kigoshi, H. *Bull. Chem. Soc. Jpn.* **2015**, 600.

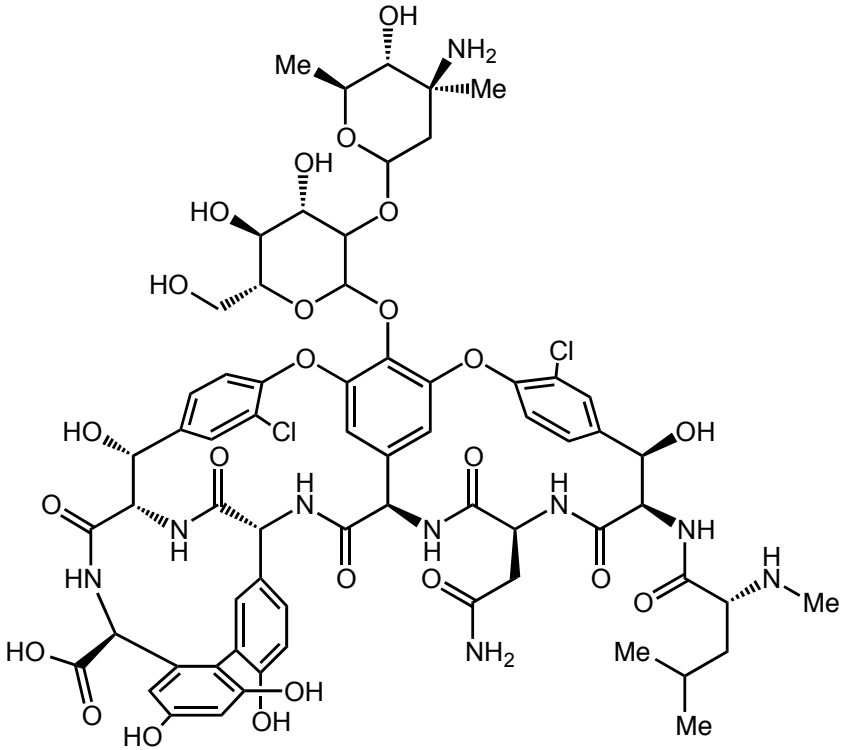
# Summary

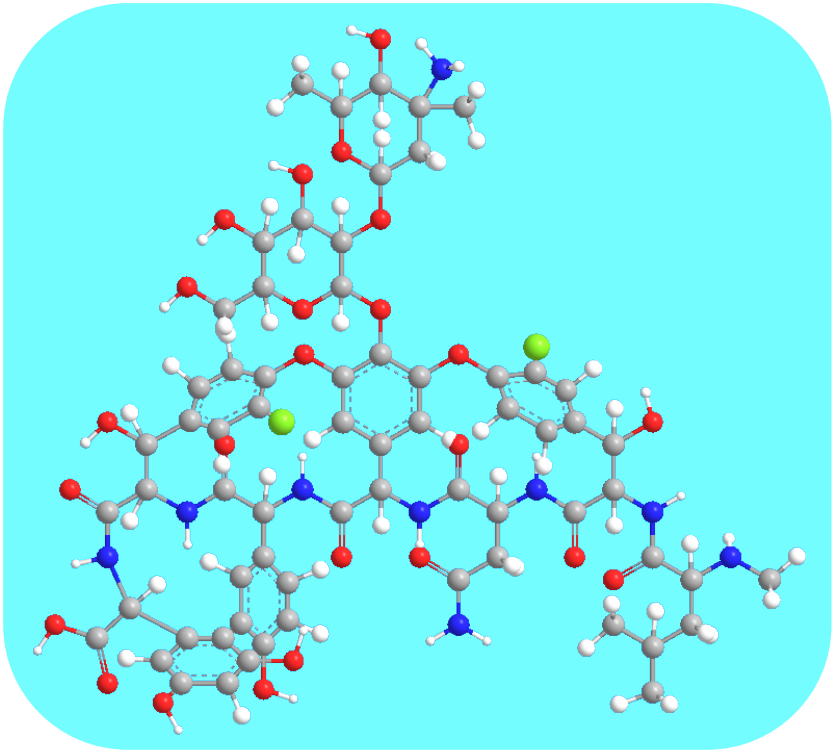





Akindele, T.; Gise, B; Sunaba , T; Kita, M.; Kigoshi, H. *Bull. Chem. Soc. Jpn.* **2015**, 600.

# Vancomycin



Isolated in 1956 by scientists at Eli Lilly from actinomycete *Amycolatopsis orientalis*, a microbe taken from the jungles of Borneo.

A glycopeptide antibacterial agent capable of combating the deadly methicillin resistant strains of *Staphylococcus aureus*.

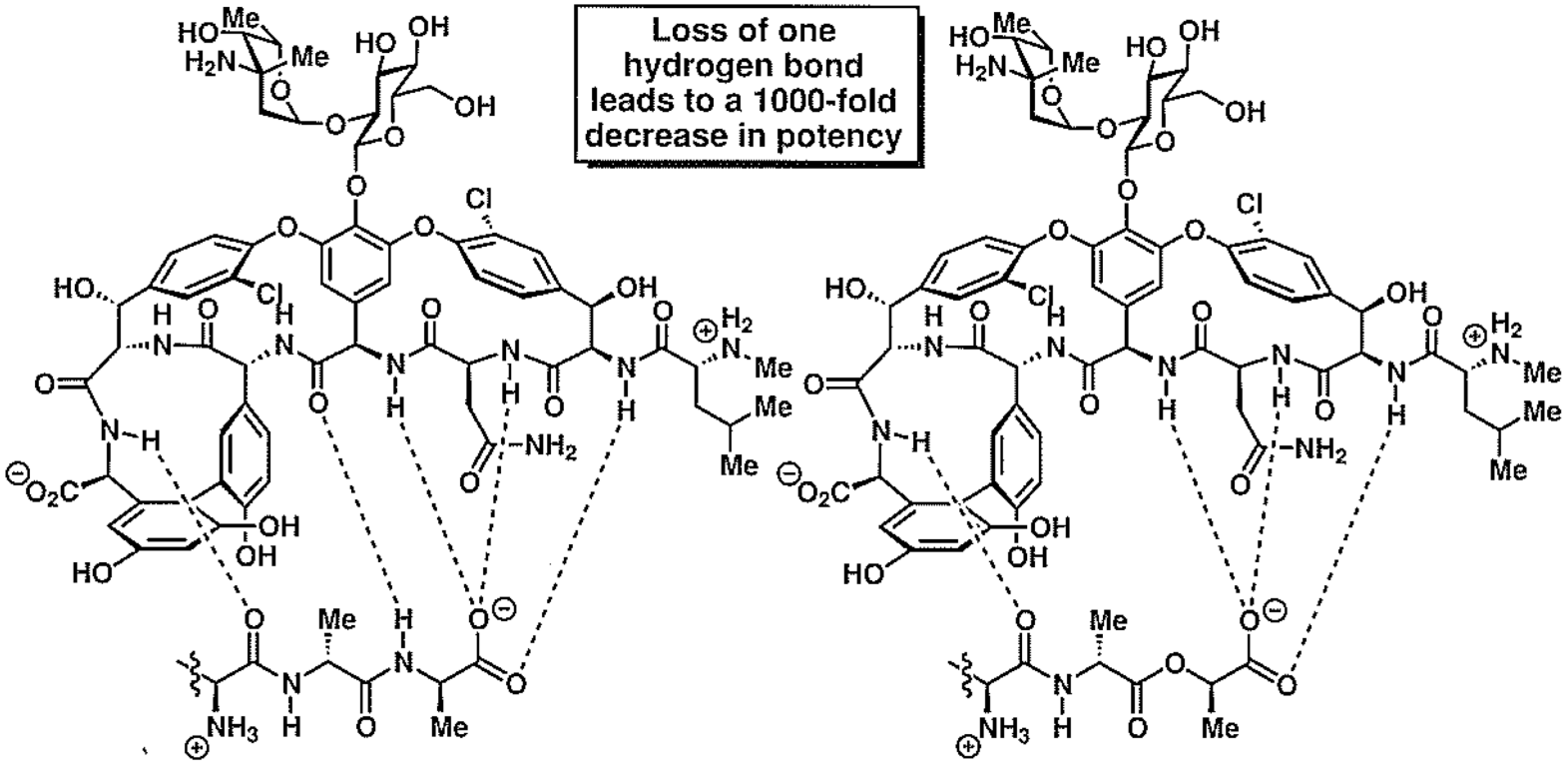
However, vancomycin-resistant strains are emerging.

Nicolaou *et al*. *Angew. Chem. Int. Ed.* **1999**, *38*, 2096.

# Mode of Action of Vancomycin

Vancomycin disrupts bacterial cell wall biosynthesis. It does this by binding to the growing peptidoglycan thus precluding transgylcosidases from polymerizing the sugar unit that is required for forming the cell wall backbone.

Five hydrogen bonds are responsible for the effectiveness of vancomycin. Loss of one of the hydrogen bonds leads to a weaker potency by a factor one thousand.

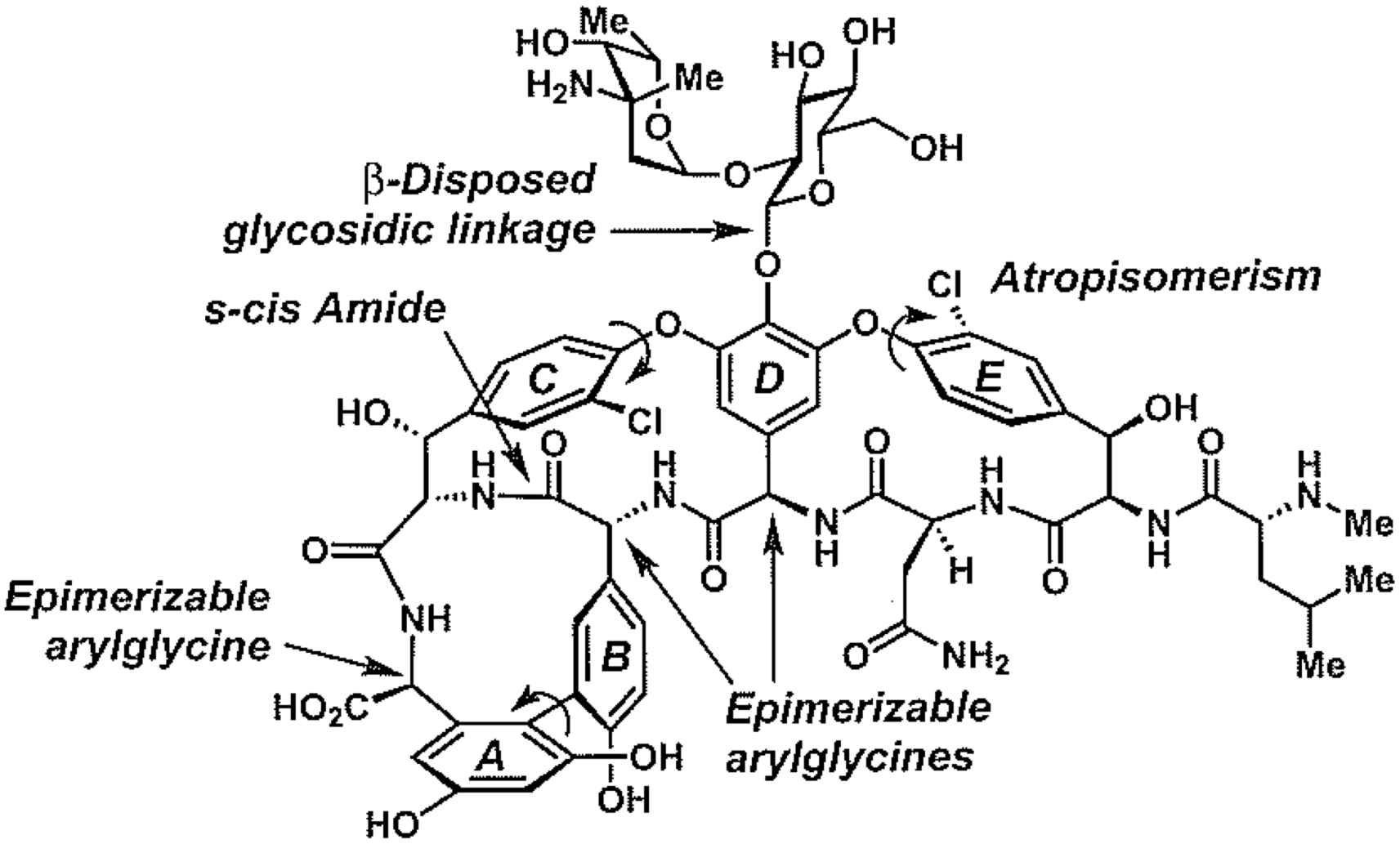




Williams *et al*. *Angew. Chem. Int. Ed.* **1999**, *38*, 1172.

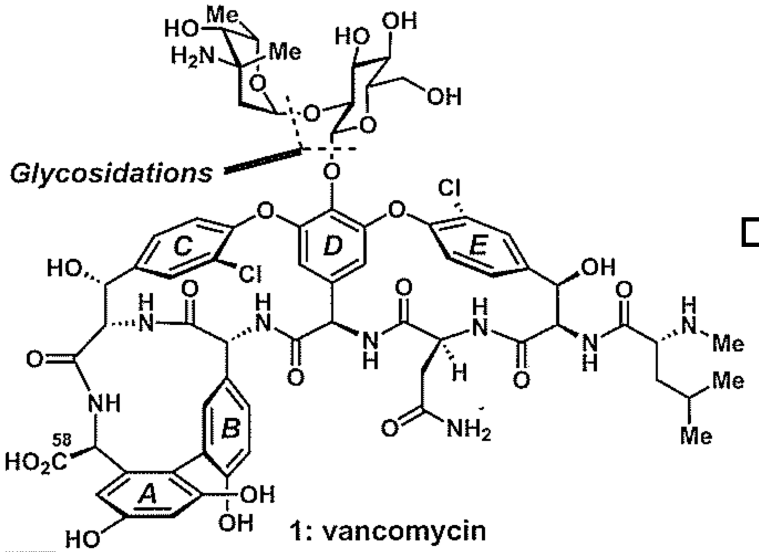
Hubbard, B. K. & Walsh, C. T. *Angew. Chem. Int. Ed.* **2003**, *42*, 730.

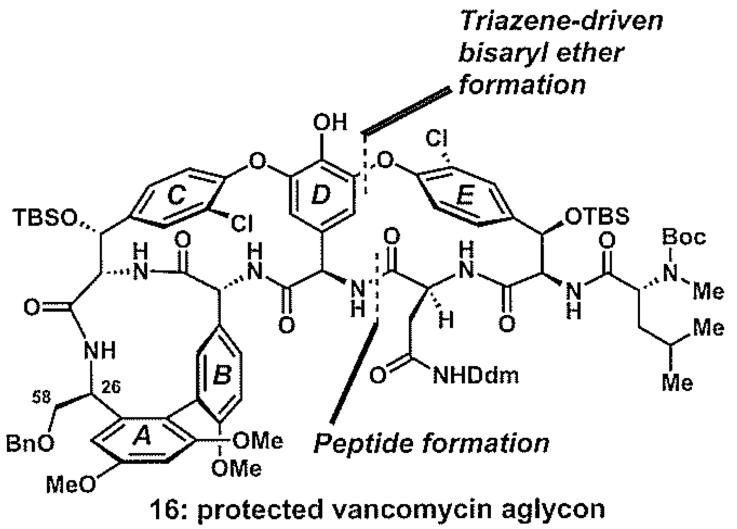
# Synthetic Challenges in Vancomycin



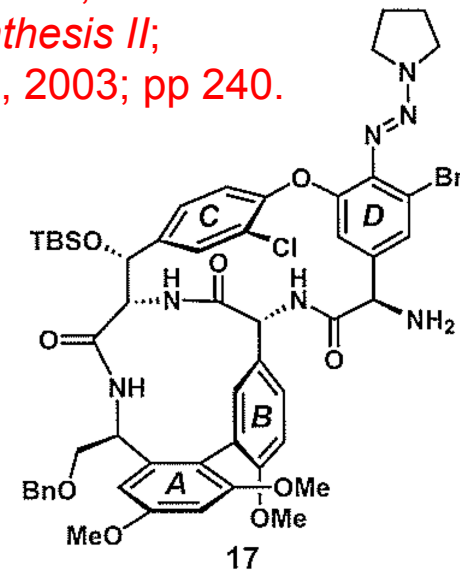

Nicolaou *et al*. *Angew. Chem. Int. Ed.* **1999**, *38*, 240.

# Retrosynthetic Analysis of Vancomycin

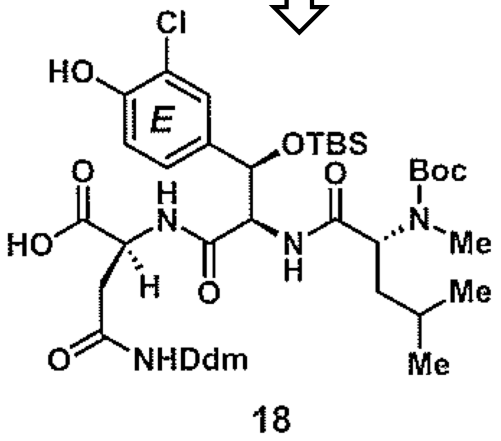


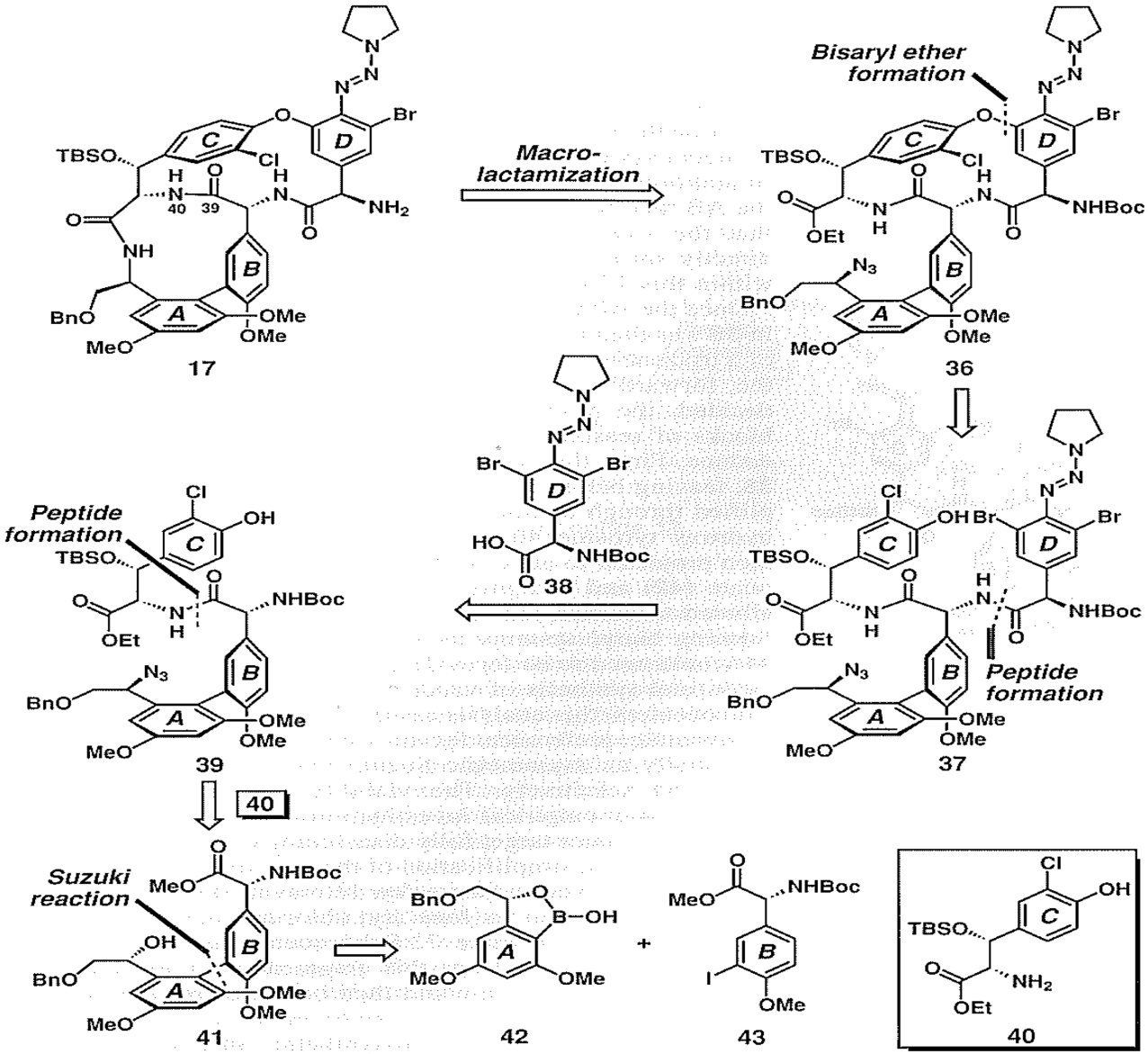

Nicolaou, K. C. & Synder, S. C.
*Classics in Total Synthesis II*;
Wiley-VC: Weinheim, 2003; pp 240.




+

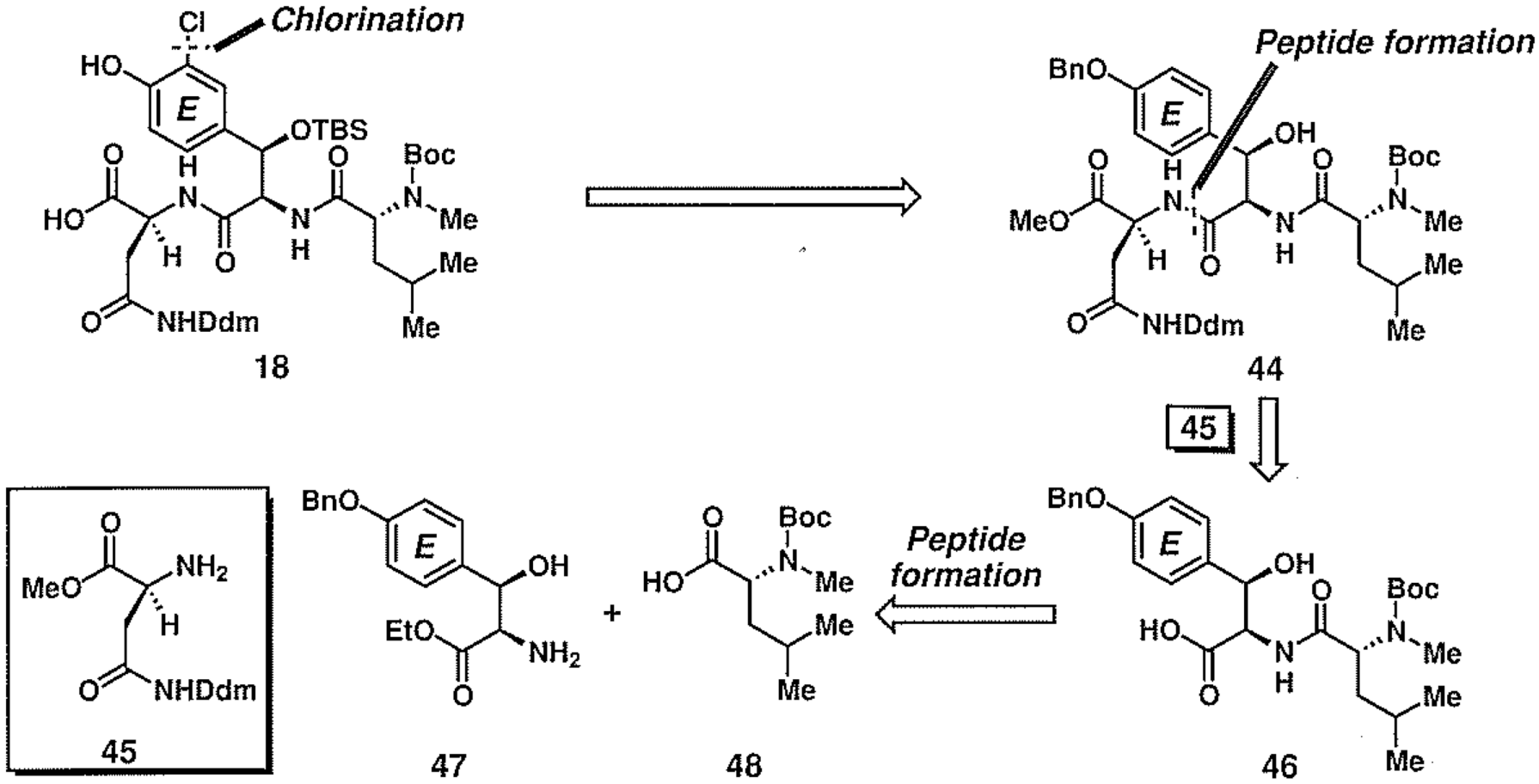


# Retrosynthetic Analysis of Intermediate 17



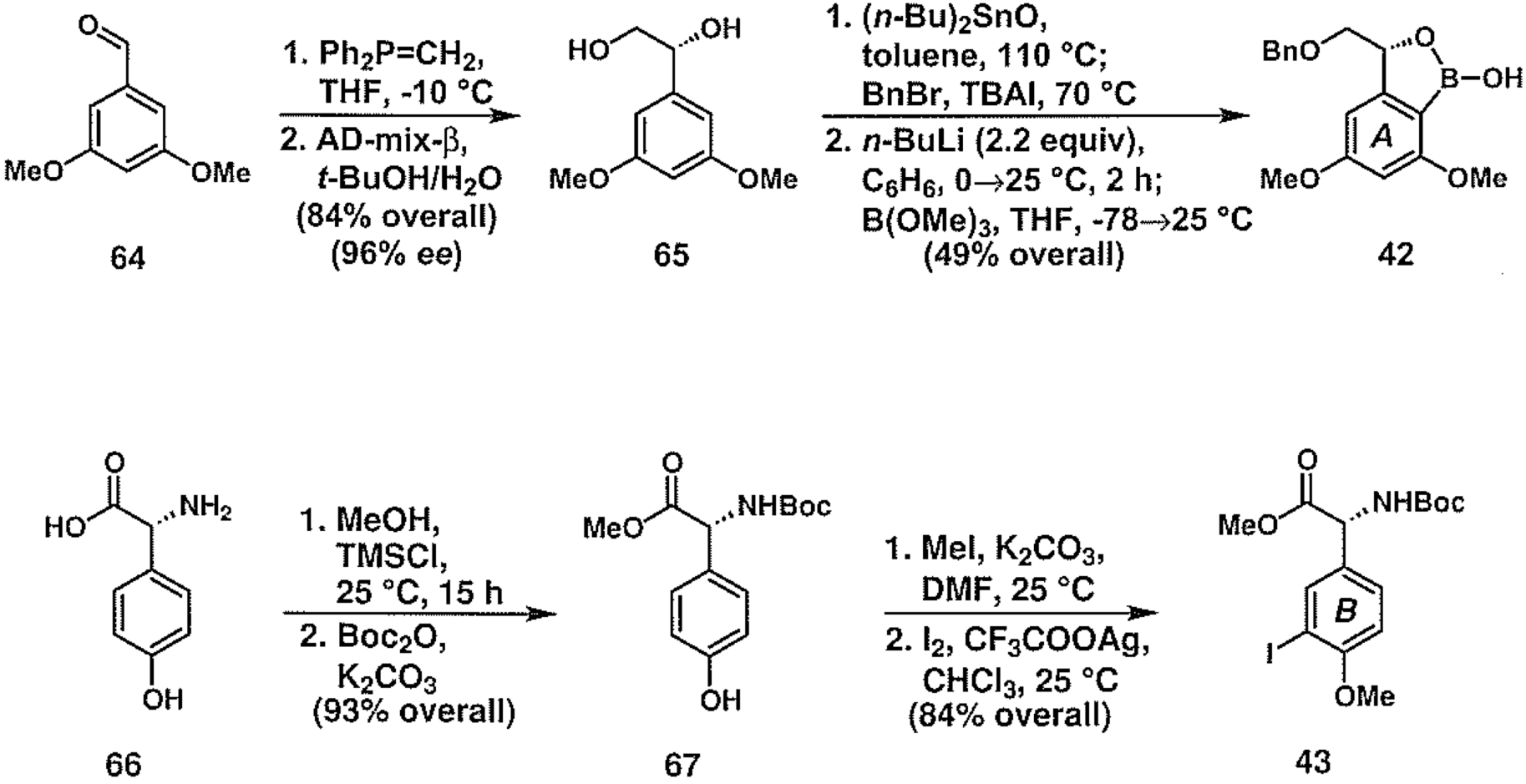

Nicolaou, K. C. & Synder, S. C. *Classics in Total Synthesis II*; Wiley-VC: Weinheim, 2003; pp 240.

# Retrosynthetic Analysis of Intermediate 18



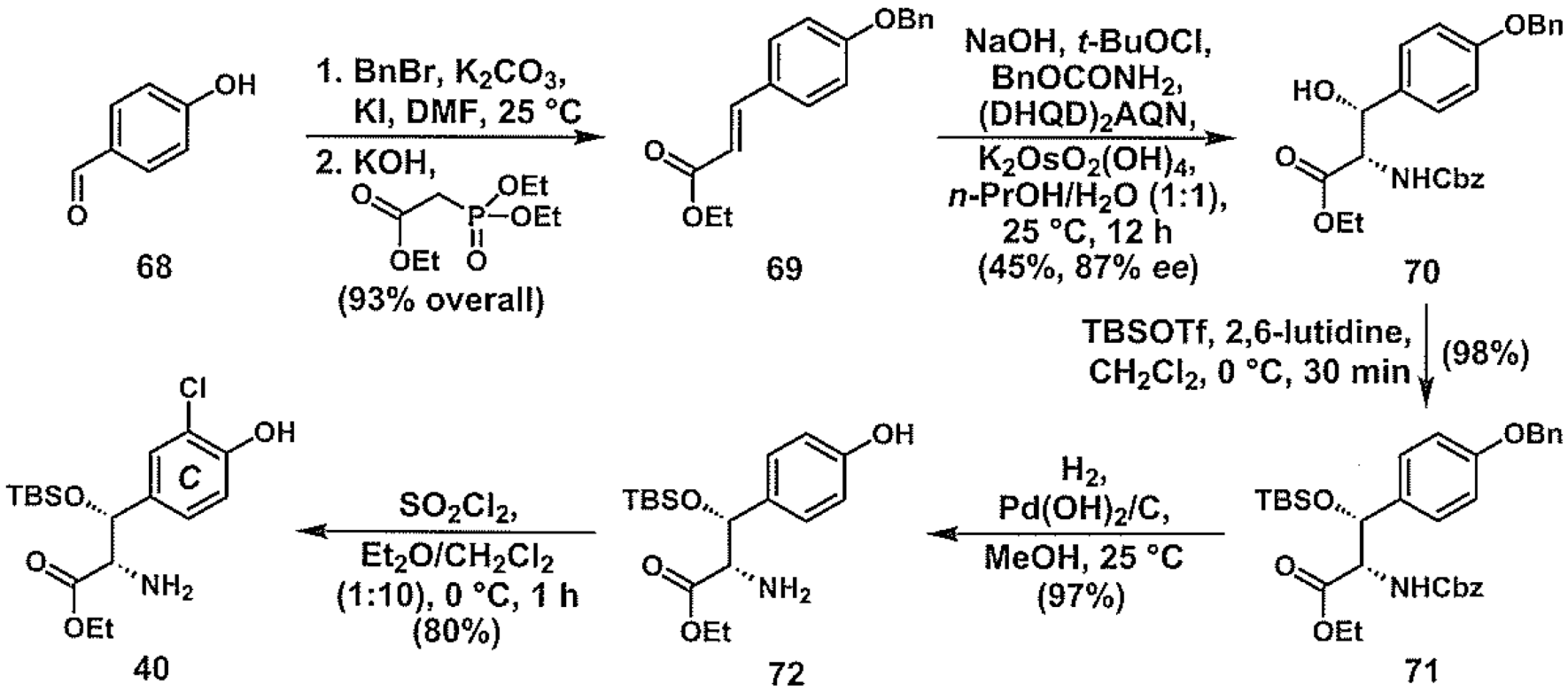

Nicolaou, K. C. & Synder, S. C. *Classics in Total Synthesis II*; Wiley-VC: Weinheim, 2003; pp 240.

# Synthesis of Intermediates 42 & 43



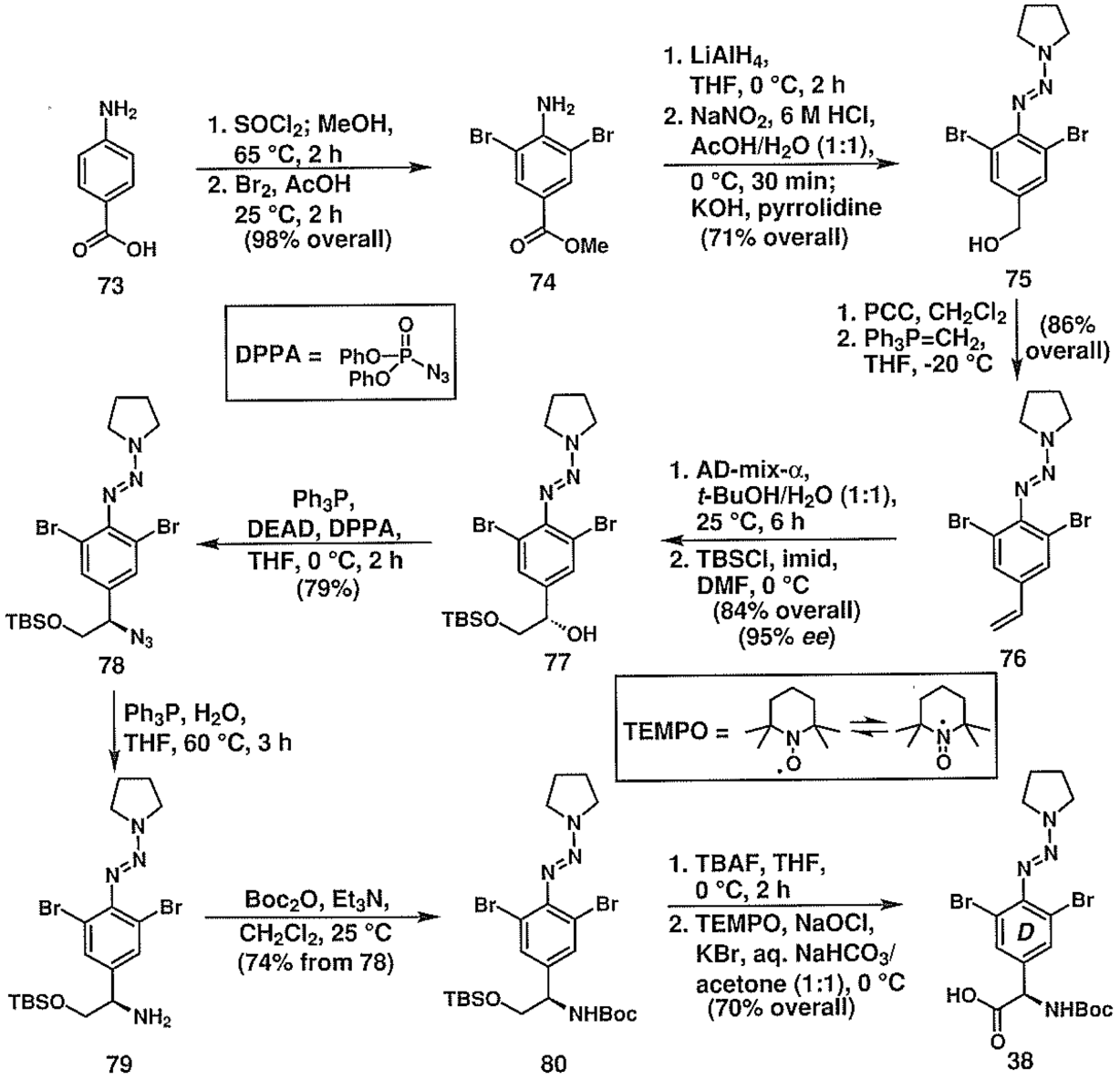

Nicolaou, K. C. & Synder, S. C. *Classics in Total Synthesis II*; Wiley-VC: Weinheim, 2003; pp 240.

# Synthesis of Intermediate 40



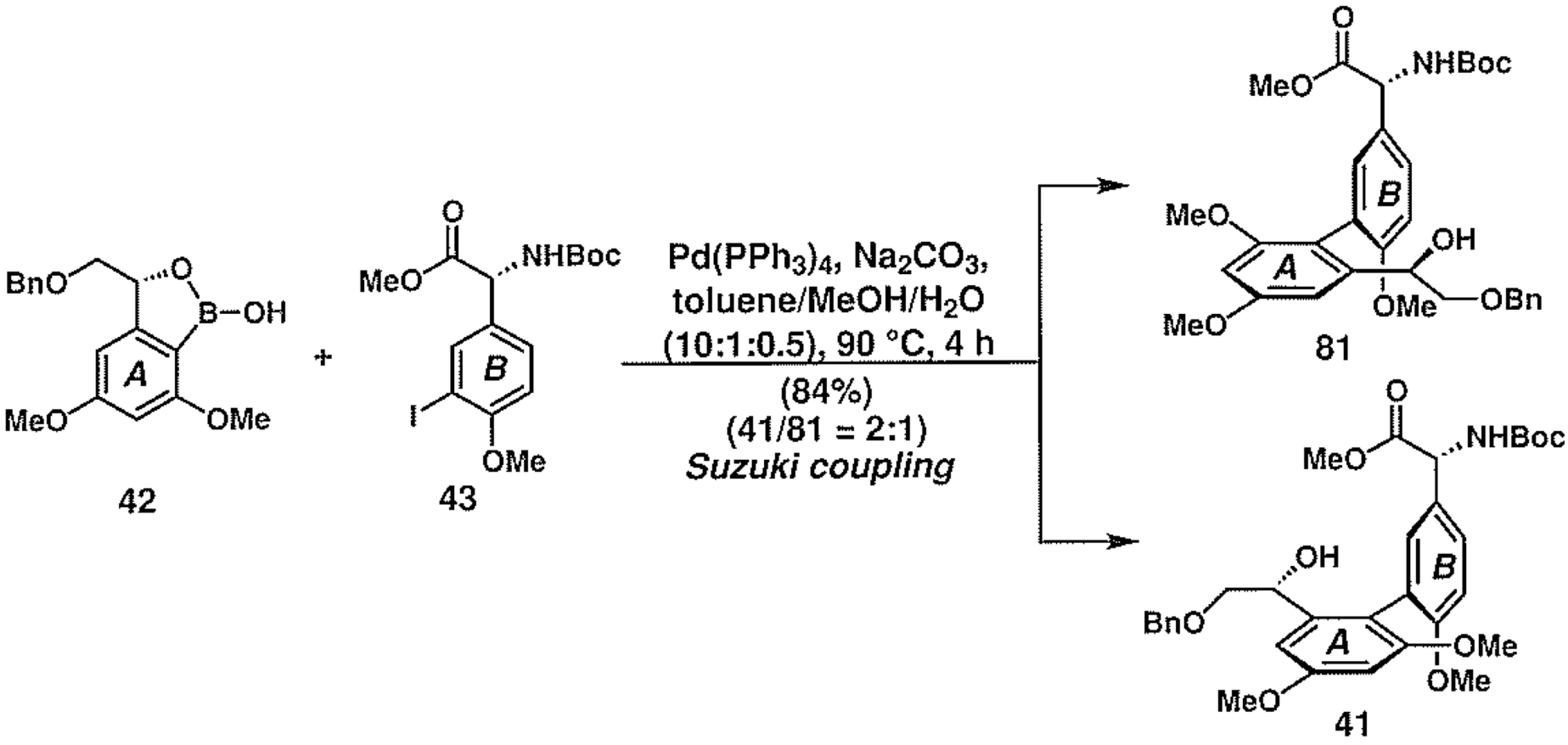

Nicolaou, K. C. & Synder, S. C. *Classics in Total Synthesis II*; Wiley-VC: Weinheim, 2003; pp 240.

# Synthesis of Intermediate 38



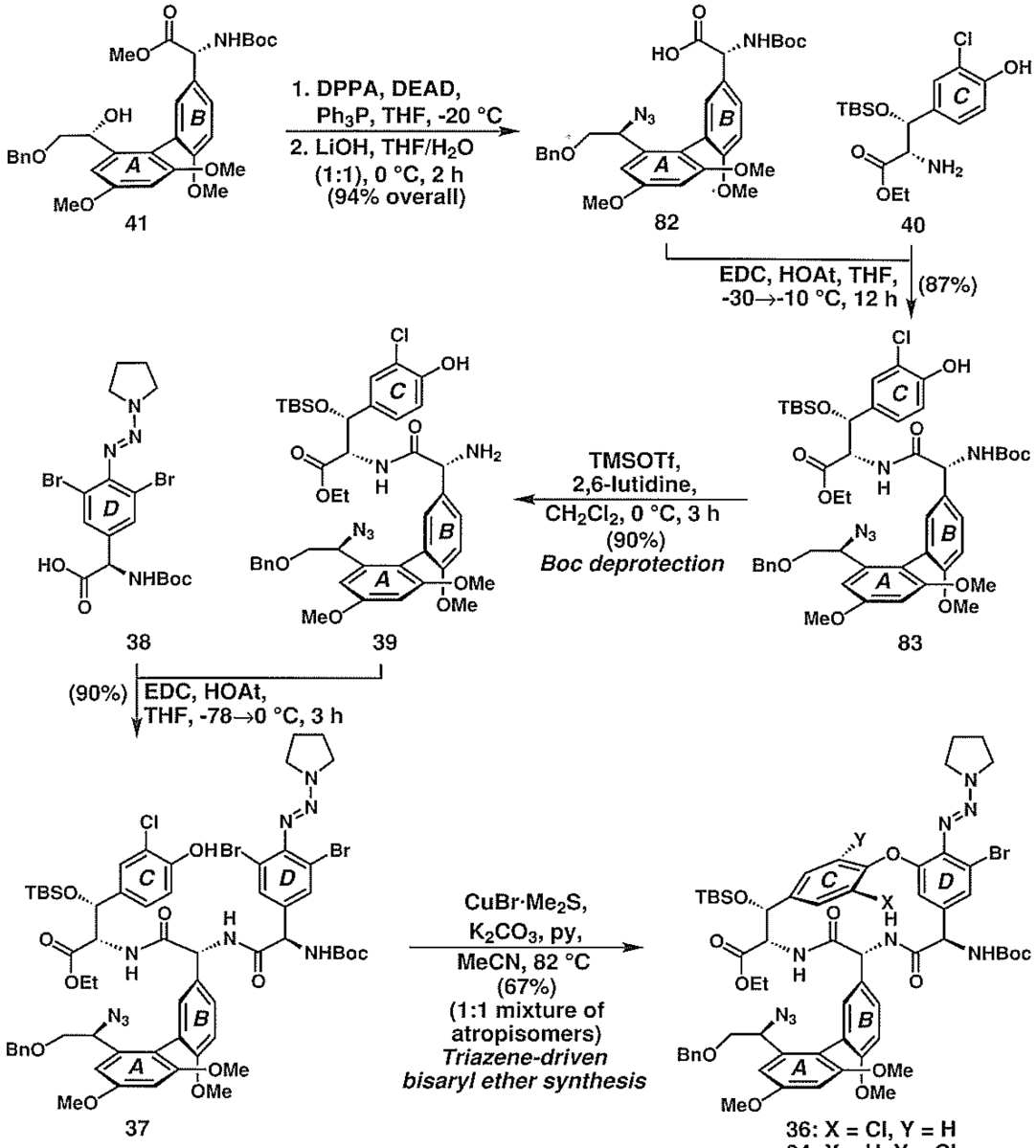

Nicolaou, K. C. & Synder, S. C. *Classics in Total Synthesis II*; Wiley-VC: Weinheim, 2003; pp 240.

# Synthesis of Intermediate 41



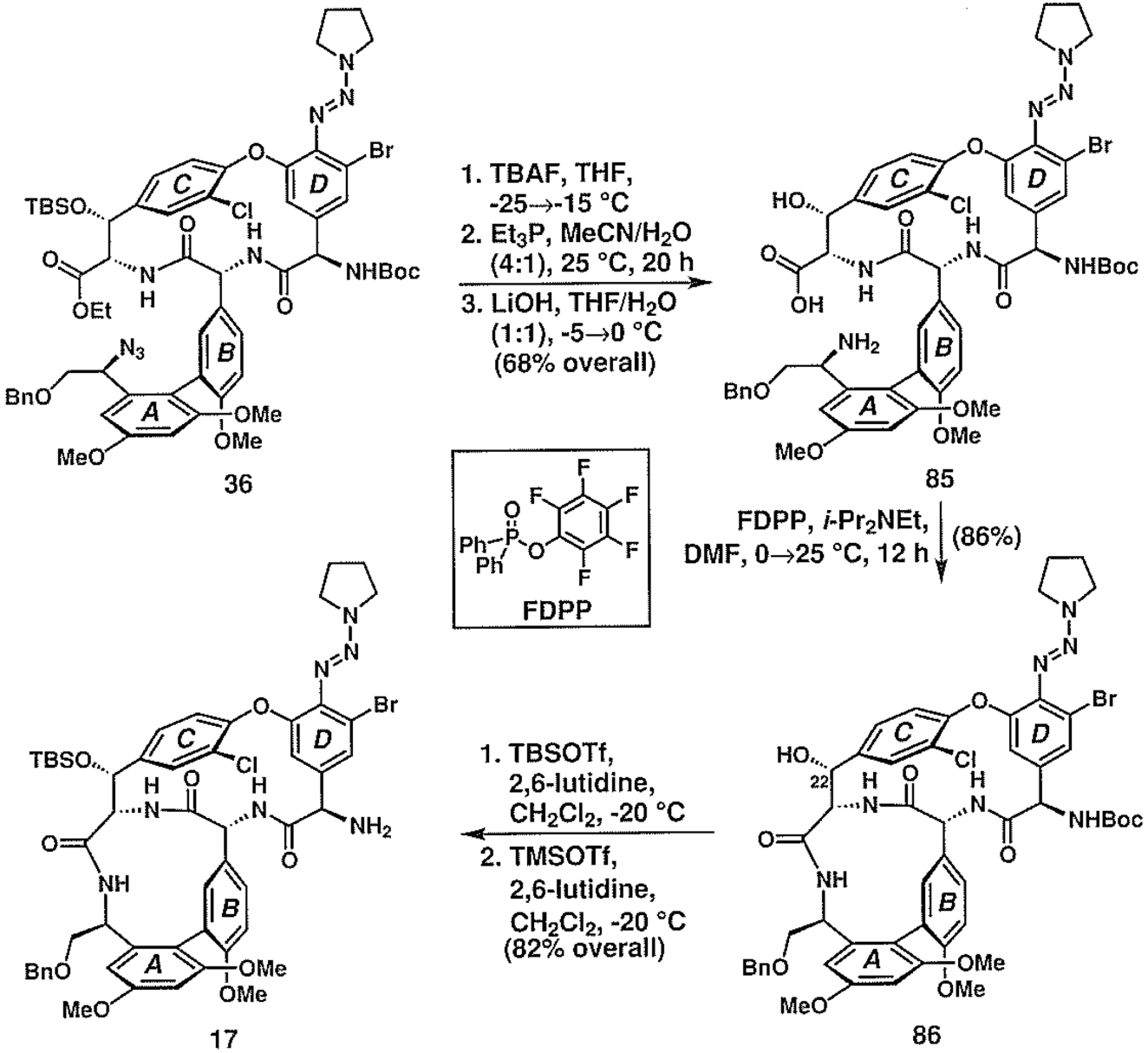

Nicolaou, K. C. & Synder, S. C. *Classics in Total Synthesis II*; Wiley-VC: Weinheim, 2003; pp 240.

# Synthesis of C-O-D Ring System (36)



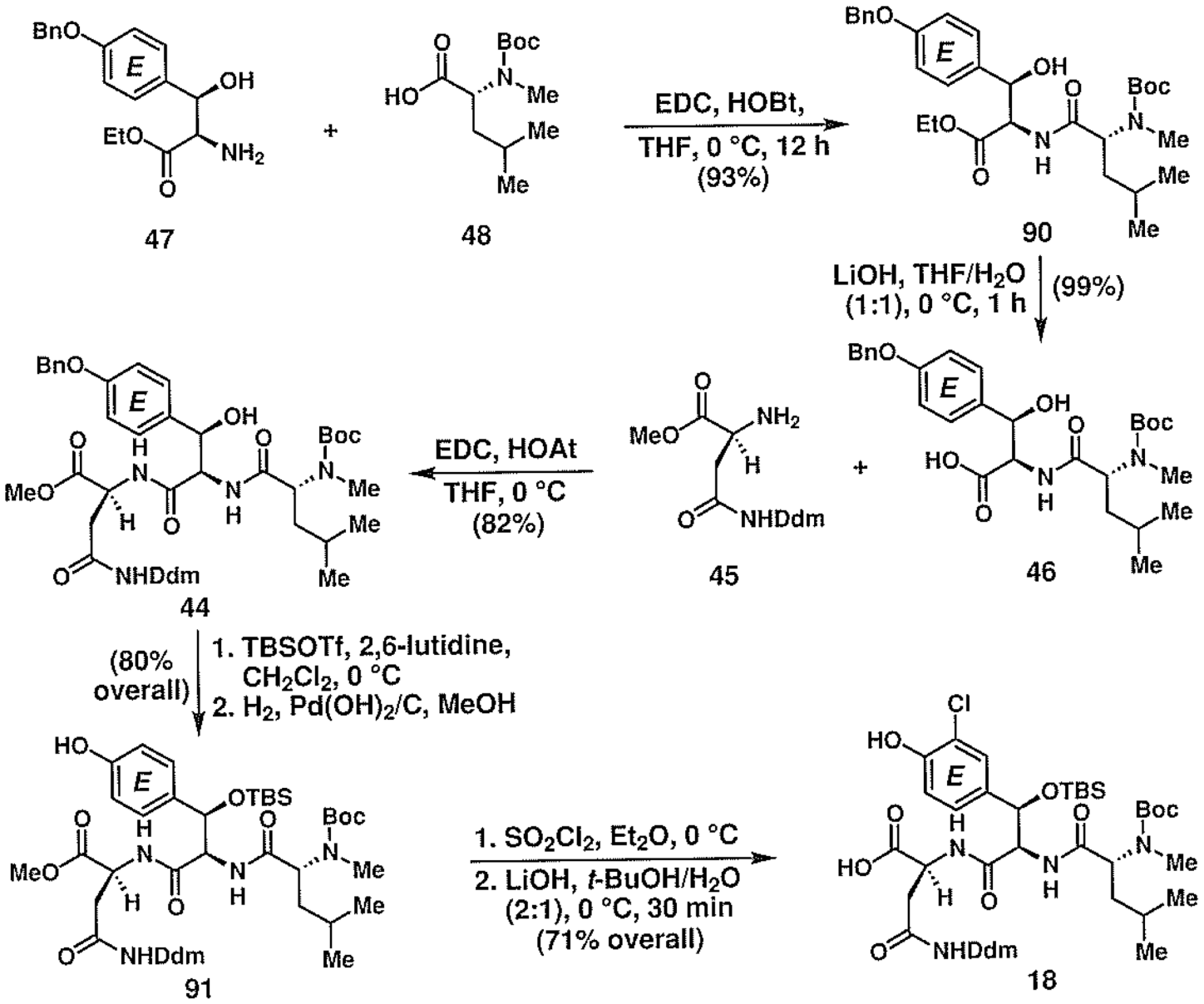

Nicolaou, K. C. & Synder, S. C. *Classics in Total Synthesis II*; Wiley-VC: Weinheim, 2003; pp 240.

# Completion of AB/C-O-D Ring System



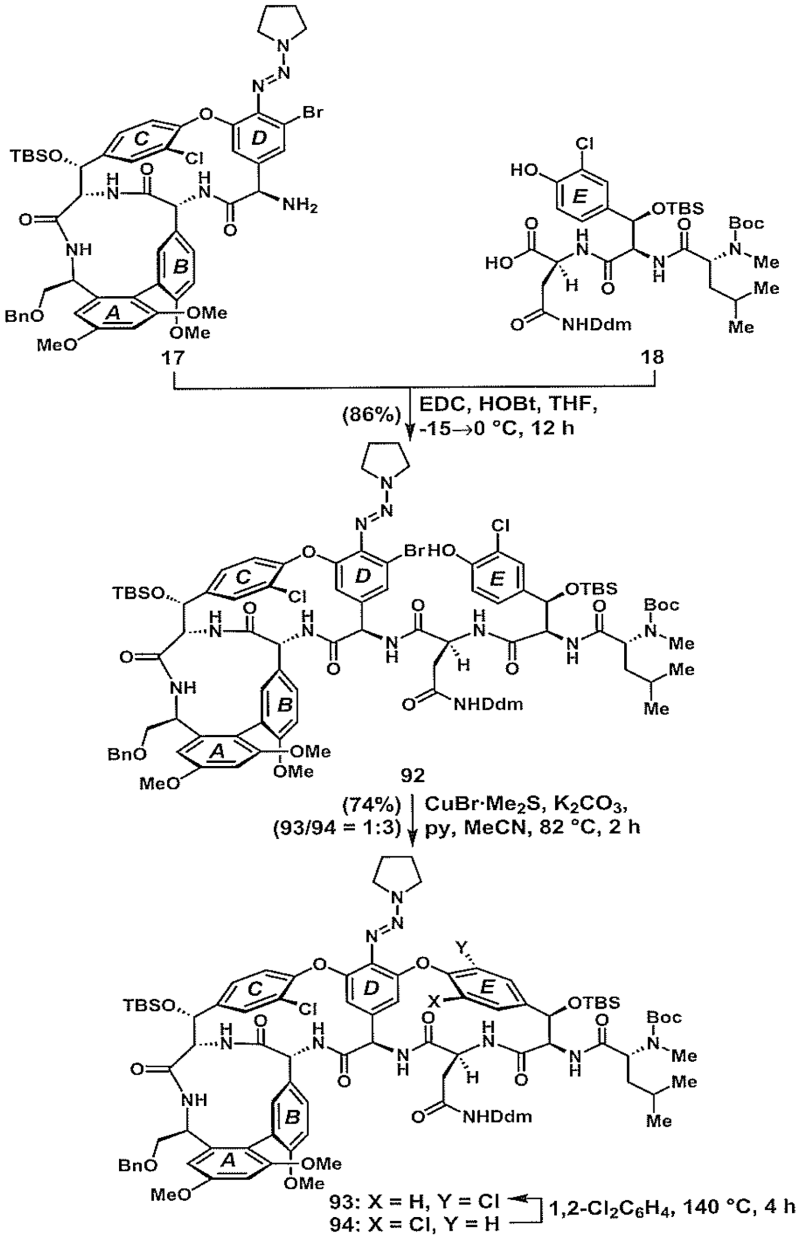

Nicolaou, K. C. & Synder, S. C. *Classics in Total Synthesis II*; Wiley-VC: Weinheim, 2003; pp 240.

# Synthesis of Tripeptide 18

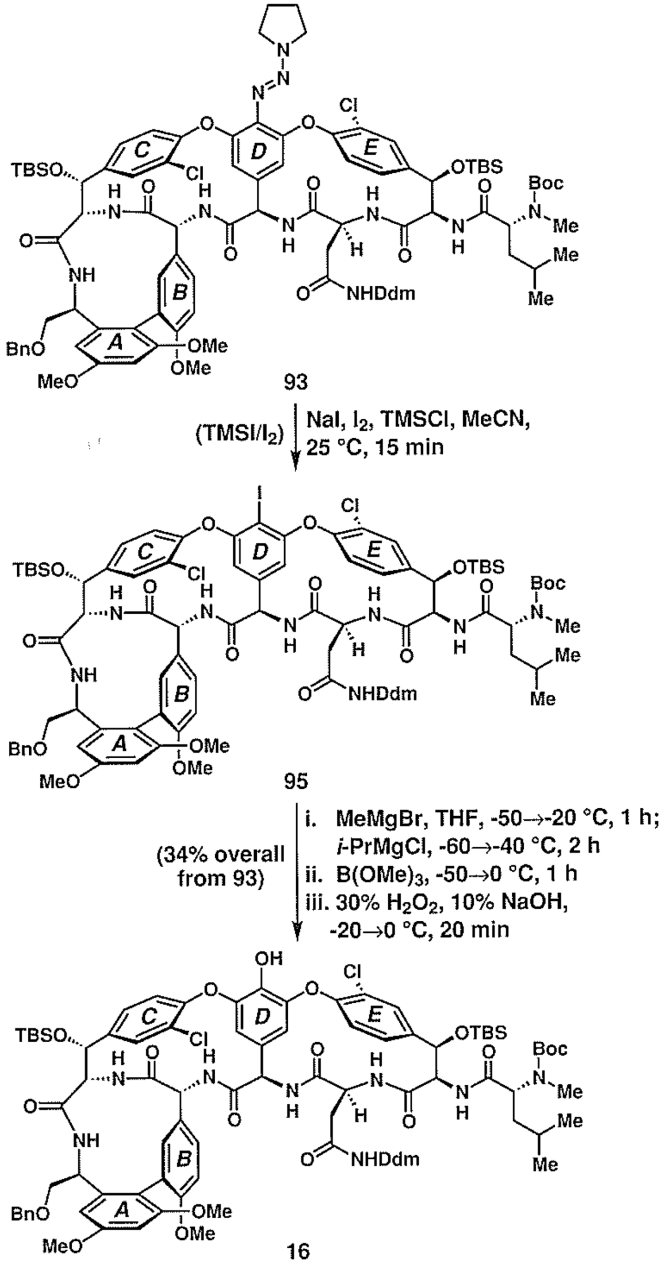



Nicolaou, K. C. & Synder, S. C. *Classics in Total Synthesis II*; Wiley-VC: Weinheim, 2003; pp 240.

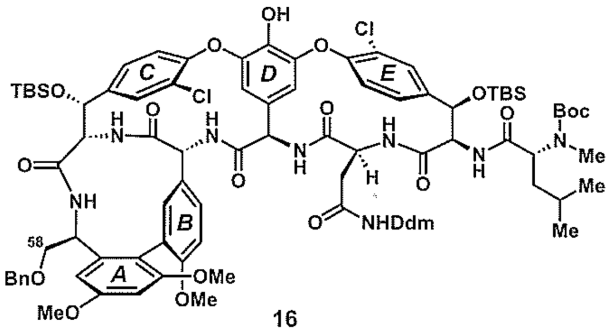
# Construction of the D-O-E Domain




# Removal of the Triazene Moiety



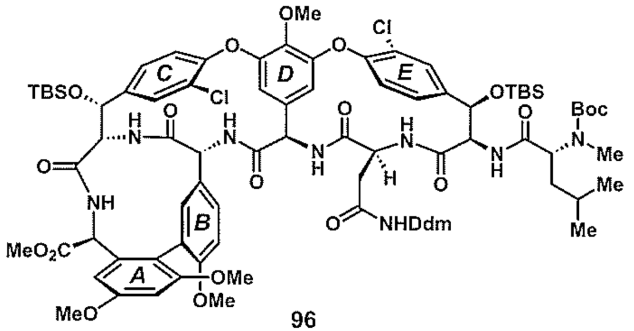
# Synthesis of Aglycon 13



16

(74% overall)

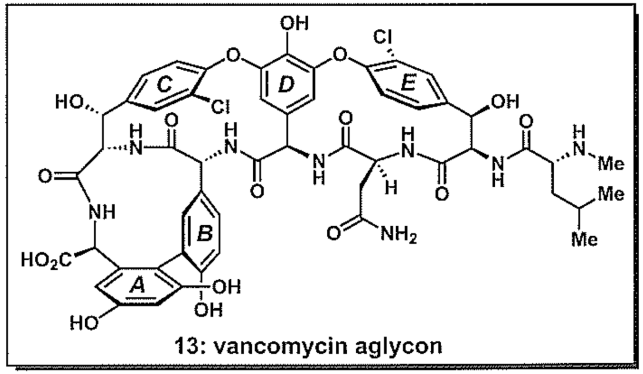
1. $H_2$, Pd/C, MeOH, 25 °C, 1.5 h
2. $Cs_2CO_3$, MeI, DMF, 0 °C, 2 h
3. Dess–Martin [O], $CH_2Cl_2$, 25 °C, 30 min
4. $KMnO_4$, *t*-BuOH/aq. $Na_2HPO_4$ (3.5:1), 30 °C
5. $CH_2N_2$, $Et_2O$, 25 °C, 12 h



96

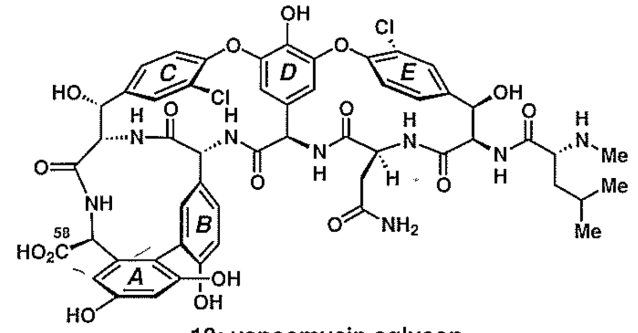
(62% overall)
*Global deprotections*

1. HF·py/py, THF, 0→25 °C, 12 h
2. $AlBr_3$, EtSH/$CH_2Cl_2$ (1:1), 25 °C, 4 h



13: vancomycin aglycon

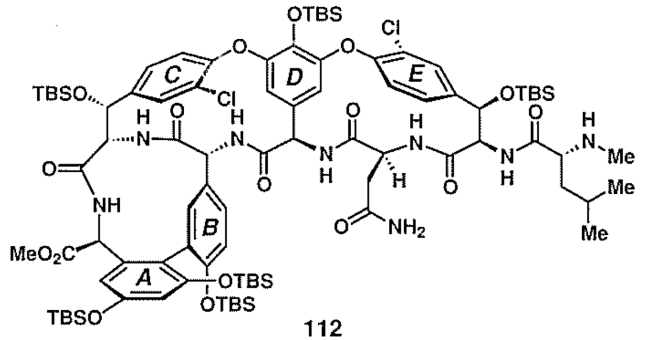
# Protection of Aglycon 13



13: vancomycin aglycon

(66% overall)

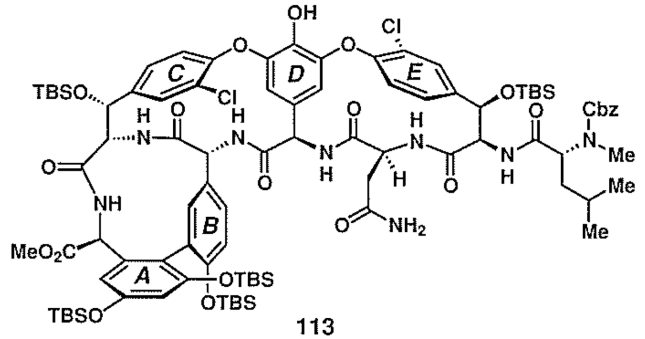
1. TBSOTf (20 equiv), 2,6-lutidine (60 equiv), $CH_2Cl_2$/DMF (10:1), 0→25 °C, 7 h
2. $CH_2N_2$, $Et_2O$, 0 °C, 30 min



112

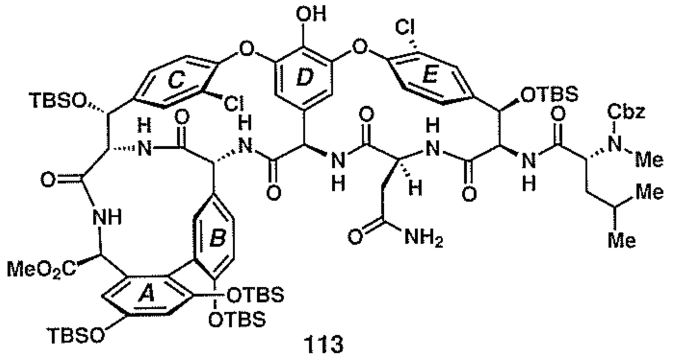
(55% overall)

1. CbzCl, $NaHCO_3$, 1,4-dioxane/$H_2O$ (10:1), 0 °C
2. KF·$Al_2O_3$, MeCN, 0 °C, 2 h



113

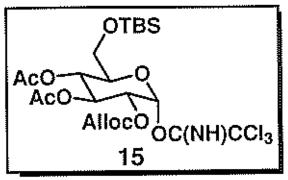
# Completion of the Synthesis



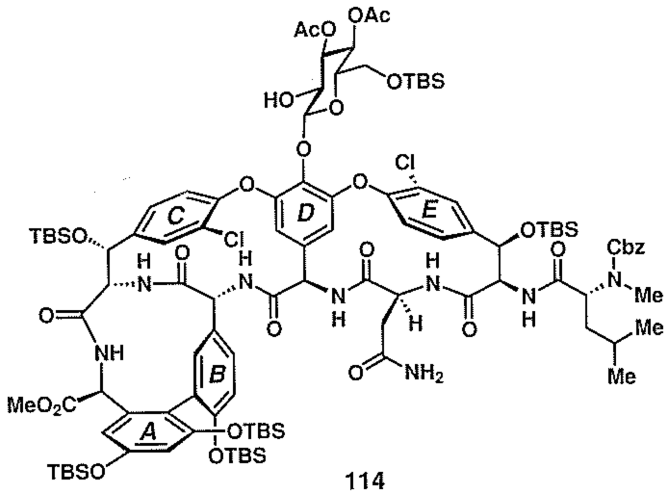
113

(70% overall)

1. 15, $BF_3 \cdot OEt_2$, $CH_2Cl_2$, -78 °C
2. $(n\text{-}Bu)_3SnH$, $Pd(PPh_3)_4$ (cat.), $CH_2Cl_2$, 25 °C



15

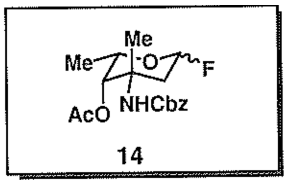


114

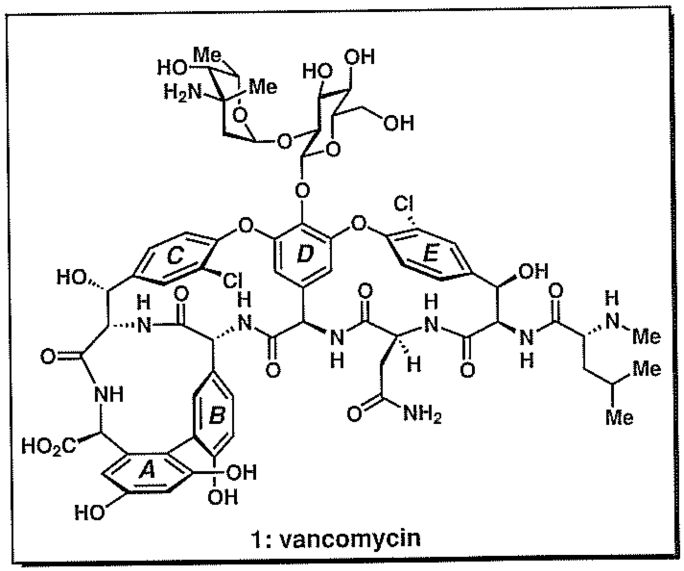
(54% overall)

1. 14, $BF_3 \cdot OEt_2$, $CH_2Cl_2$, -35 °C
2. HF·py/py (1:1), THF, 0→25 °C
3. $K_2CO_3$, MeOH
4. Raney Ni, $n$-PrOH/$H_2O$ (2:1)
5. LiOH, THF/ $H_2O$ (1:1), 0 °C

*Global deprotection*



14



1: vancomycin

# Summary

As is the chemical syntheses of complex molecules, the preparation of complex peptides is demanding. The challenging structures posed by these "*Everests*" and their indispensable medicinal values drive the constant development of novel chemical reactions and synthetic strategies.

*.....although the specific objective in synthetic work is defined with unique precision, the manner of reaching it most emphatically is not. It would be possible to synthesize a molecule....in countless different ways, no one of which would resemble any other except in its outcome. Much of the charm and fascination of this kind of work lies in the free reign which the imagination may be permitted in planning the adventure, as well as in executing it.*

R. B. Woodward, *Harvey Lecture Ser.* **1963–1964**, *59*, 31.

# Next Lecture, 2016/04/07

Strategies for Discovering Lead Compounds