Five Drugs or Clinical Candidates Derived From Natural Products That Are Produced on Scale by Total Synthesis

Jeff Garber
MacMillan Group Meeting
April 27, 2012
Why Pursue Total Synthesis of Natural Products?
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- Academic and Pegagogical
  - Test New Methodology
  - Develop New Methodology
  - Train Organic Chemists
Why Pursue Total Synthesis of Natural Products?

**Academic and Pedagogical**
- Test New Methodology
- Develop New Methodology
- Train Organic Chemists

**Pragmatic**
- Produce Bioactive Molecules
- Develop Analogues for Testing
- Produce On-Scale for Society
Why Use Total Synthesis?

Why Pursue Total Synthesis of Natural Products?

- Pragmatic
  - Produce Bioactive Molecules
  - Develop Analogs for Testing
  - Produce On-Scale for Society
Why Pursue Total Synthesis of Natural Products?

Why Use Total Synthesis?
- Most Economical
- Only Available Option

Pragmatic
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- Develop Analogs for Testing
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Why Use Total Synthesis?

- Most Economical
- Only Available Option

Needs to be practical
"taxol problem"

Why Pursue Total Synthesis of Natural Products?

Pragmatic

- Produce Bioactive Molecules
- Develop Analogs for Testing
- Produce On-Scale for Society
Natural products are clearly a useful source of new drugs

All 1135 new drugs approved from 1981-2010

- $S^*$ = NP mimic produced by synthesis
- $N$ = NP as isolated
- $ND$ = NP derivative, semi-synthetic
- $S$ = completely synthetic entity

What Makes a Total Synthesis Interesting or Valuable?

**Academic Synthesis**

*Elegant*
concise route  atom efficiency

*Creative*
disconnections  methodology

*Novel Architecture*
complex structure  first synthesis

*Bioactive*
produce for testing  analog synthesis
What Makes a Total Synthesis Interesting or Valuable?

**Commercial Synthesis**

*Proven Bioactivity*
producing for testing or sale

*Practicality of Length*
yield vs. steps reactor time

*Reagent Selection*
safety availability cost

*Purification Methods*
limit chrom. rextl. improv. ee
What Makes a Total Synthesis Interesting or Valuable?

**Academic Synthesis**
- **Elegant**
  - concise route
  - atom efficiency
- **Creative**
  - disconnections
  - methodology
- **Novel Architecture**
  - complex structure
  - first synthesis
- **Bioactive**
  - produce for testing
  - analog synthesis

**Commercial Synthesis**
- **Proven Bioactivity**
  - producing for testing or sale
- **Practicality of Length**
  - yield vs. steps
  - reactor time
- **Reagent Selection**
  - safety
  - availability
  - cost
- **Purification Methods**
  - limit chrom.
  - rextl. improv. ee

*Among many other factors*
Production Considerations: Analogues and Natural Products

- Recrystallization, Resolution
- Utilize Very Robust Chemistry
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Target Considerations: Development of Analogues and Derivatives

- Retain Only Necessary Parts
Production Considerations: Analogues and Natural Products

- Recrystallization, Resolution
- Utilize Very Robust Chemistry

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Target Considerations: Development of Analogues and Derivatives

- Retain Only Necessary Parts
- Improve Activity or Properties
- Shorten Production Route
(-)-galanthamine: Overview

- First studied in USSR in 1950’s
- Inhibits acetylcholine esterase
- USSR used for various CNS disorders
(--)-galanthamine: Overview

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- FDA approved in 2001 for treatment of Alzheimer's
- Used to treat mild to moderate cases
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- First studied in USSR in 1950's
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- USSR used for various CNS disorders

- FDA approved in 2001 for treatment of Alzheimer's
- Used to treat mild to moderate cases

- Natural source (daffodils) not considered economical on scale
- Sanochemia patented (1996) and later improved synthetic route (2008)
(-)-galanthamine: Retrosynthetic Analysis

(-)-galanthamine
(-)-galanthamine: Retrosynthetic Analysis

(-)-galanthamine
**(-)-galanthamine: Retrosynthetic Analysis**

- Uses spontaneous chiral resolution/crystallization
- Rapid synthesis from readily available materials
- Features oxidative phenolic coupling to form key bonds
(−)-galanthamine: Dynamic Resolution

1) MeI, K$_2$CO$_3$<\$10/g

2) Br$_2$, AcOH

3) H$_2$SO$_4$

60-65%, three steps
(-)-galanthamine: Dynamic Resolution

1) MeI, K$_2$CO$_3$  
2) Br$_2$, AcOH  
3) H$_2$SO$_4$  
60-65%, three steps

Then NaBH$_4$  
toluene, reflux  
81%
$(-)$-galanthamine: Dynamic Resolution

1) MeI, $K_2$CO$_3$

2) Br$_2$, AcOH

3) H$_2$SO$_4$

60-65%, three steps

$<$10/g

HCOOEt, HCO$_2$H

DMF, reflux

89%

then NaBH$_4$

toluene, reflux

81%

$<$4/g

$\text{racemic } (-\text{-galanthamine})$
### (-)-galanthamine: Dynamic Resolution

1) MeI, K₂CO₃

2) Br₂, AcOH

3) H₂SO₄

60-65%, three steps

---

K₃[Fe(CN)₆]  
K₂CO₃

---

HCOOEt, HCO₂H  
DMF, reflux

89%

---

<K$10/g>

<4$g>

toluene, reflux

81%

---

racemic 
(−)-galanthamine: Dynamic Resolution
(-)-galanthamine: Dynamic Resolution

1) MeI, K$_2$CO$_3$<br>2) Br$_2$, AcOH<br>3) H$_2$SO$_4$<br>60-65%, three steps

HCOOEt, HCO$_2$H<br>DMF, reflux<br>89%

K$_3$[Fe(CN)$_6$]<br>K$_2$CO$_3$

H$_2$O<br>toluene, reflux<br>then NaBH$_4$

81%

-1 e$^-$
(-)-galanthamine: Dynamic Resolution

1) MeI, K₂CO₃
2) Br₂, AcOH
3) H₂SO₄
60-65%, three steps

HCOOEt, HCO₂H
DMF, reflux
89%

K₃[Fe(CN)₆]
K₂CO₃

HCOOEt, HCO₂H
toluene, reflux
then NaBH₄
81%

racemic

(-)-galanthamine: Dynamic Resolution

\[
\text{H}_2\text{SO}_4, \text{toluene} \quad >99% 
\]
\((-\))\text-galanthamine: Dynamic Resolution

\[\text{H}_2\text{SO}_4, \text{toluene} \quad \text{HCl} \quad >99\% \quad 87\%\]
(-)-galanthamine: Dynamic Resolution

\[
\begin{align*}
\text{H}_2\text{SO}_4, \text{toluene} & \quad \rightarrow & \quad >99\% \\
\text{LiAlH}_4, \text{THF}, \text{reflux} & \quad \rightarrow & \quad 87\%
\end{align*}
\]


\(-\)-galanthamine: Dynamic Resolution

\[
\begin{align*}
\text{Br} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{OH} & \quad \text{OH} \\
\text{O} & \quad \text{Me} \\
\text{Br} & \quad \text{OMe} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{N} \\
\text{O} & \quad \text{C} \\
\text{Br} & \quad \text{OMe} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{N} \\
\text{O} & \quad \text{C} \\
\end{align*}
\]

\(\text{H}_2\text{SO}_4, \text{toluene}\)  
>99%

\[
\begin{align*}
\text{Me} & \quad \text{HO} \quad \text{OH} \\
\text{O} & \quad \text{Me} \\
\text{Br} & \quad \text{OMe} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{N} \\
\text{O} & \quad \text{C} \\
\text{Br} & \quad \text{OMe} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{N} \\
\text{O} & \quad \text{C} \\
\end{align*}
\]

\[\text{LiAlH}_4, \text{THF, reflux}\]
87%

\[\text{then HCl}\]

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\end{align*}
\]

87%

>99% ee

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\end{align*}
\]

9:1 EtOH/Et\text{3N};

reflux

9:1 EtOH/Et\text{3N};

reflux

87%

9:1 EtOH/Et\text{3N};

reflux

>99% ee

\(-\)-narwedine

\[\text{crystalize and seed with (−)-narwedine}\]

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\end{align*}
\]

\[\text{crystalize and seed with (−)-narwedine}\]

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\end{align*}
\]

\[(±)-narwedine\]
(−)-galanthamine: Completion of Synthesis

(−)-narwedine

\[ \text{L-Selektride} \rightarrow \text{then HBr, crystallization} \]

95%

(−)-galanthamine•HBr
(-)-galanthamine: Completion of Synthesis

(-)-narwedine → L-Selektride → then HBr, crystallization 95% → (-)-galanthamine•HBr
(-)-galanthamine: Completion of Synthesis

(-)-narwedine

\[ \xrightarrow{\text{L-Selektride}} \]

then HBr, crystallization

95%

(-)-galanthamine·HBr
(-)-galanthamine: Completion of Synthesis

From isovanillin: 16% overall yield, 9 steps (10 including dynamic resolution)

From commercial bromide: 27% overall yield, 6 or 7 steps

Resolution establishes stereochemistry, no enantioselective reactions
Production Considerations: Analogues and Natural Products

- Recrystallization, Resolution
- Utilize Very Robust Chemistry
Eribuline: Overview

Halichondrin B isolated from sponges in 1986
Activity further demonstrated by Nat. Cancer Inst.
Total synthesis complete by Kishi in 1992

left half found to be unnecessary
**Eribuline: Overview**

Halichondrin B isolated from sponges in 1986

- Activity further demonstrated by Nat. Cancer Inst.

- Total synthesis complete by Kishi in 1992
Eribuline: Overview

Halichondrin B isolated from sponges in 1986
Activity further demonstrated by Nat. Cancer Inst.
Total synthesis complete by Kishi in 1992

Halichondrin B

Left half found to be unnecessary

Highly conserved right hand portion

Eribuline
Eribuline: Overview

Eribuline

- Approved to treat metastatic breast cancer in 2010
- Class has mechanistically unique inhibition pathway
- Marketed by Eisai with global partnerships

Halichondrin B

Left half found to be unnecessary

Highly conserved right hand portion
Eribuline: Retrosynthetic Analysis

Eribuline: Retrosynthetic Analysis

Eribuline: Retrosynthetic Analysis

- Highly convergent
- Late stage coupling
- Utilizes chiral pool

**Eribuline: Eastern Fragment**

1) c-hexanone, pTSA
   PhCH₃, reflux

2) DIBAL-H, -15 °C
   PhCH₃, THF

84%, two steps

L-mannonic acid γ-lactone

$50/g (Aldrich)$
**Eribuline: Eastern Fragment**

1) \( \text{c-hexanone, } p\text{TSA} \)
   \( \text{PhCH}_3, \text{reflux} \)

2) \( \text{DIBAL-H, } -15 \, ^\circ\text{C} \)
   \( \text{PhCH}_3, \text{THF} \)

84%, two steps

L-mannonic acid \( \gamma \)-lactone

\( \$50/g \) (Aldrich)
**Eribuline: Eastern Fragment**

1) c-hexanone, $p$TSA
   PhCH$_3$, reflux

2) DIBAL-H, -15 °C
   PhCH$_3$, THF

84%, two steps

Cl$_3$PCH$_2$OMe

KO$_2$Bu, THF

81%

L-mannonic acid $\gamma$-lactone

$50/g$ (Aldrich)

1) OsO$_4$, NMO
   acetone, H$_2$O

2) Ac$_2$O, AcOH
   ZnCl$_2$, 40 °C

44%, two steps

$\gamma$-lactone
Eribuline: Eastern Fragment

L-mannonic acid γ-lactone
$50/g (Aldrich)

1) c-hexanone, pTSA
   PhCH₃, reflux
   84%, two steps

2) DIBAL-H, -15 °C
   PhCH₃, THF
   81%

1) OsO₄, NMO
   acetone, H₂O
   44%, two steps

2) Ac₂O, AcOH
   ZnCl₂, 40 °C

ClPh₃PCH₂OMe
KOtBu, THF
Eribuline: Eastern Fragment

1) c-hexanone, pTSA
   PhCH$_3$, reflux
   2) DIBAL-H, -15 °C
   PhCH$_3$, THF
   84%, two steps

L-mannonic acid γ-lactone
$50/g$ (Aldrich)

1) OsO$_4$, NMO
   acetone, H$_2$O
   2) Ac$_2$O, AcOH
   ZnCl$_2$, 40 °C
   44%, two steps

BF$_3$•OEt, MeCN

MeO$_2$C-CH$_2$-TMS

ClPh$_3$PCH$_2$OMe
KOtBu, THF
81%

38%, two steps
Eribuline: Completion of Eastern Fragment

![Chemical structures](image)
Eribuline: Completion of Eastern Fragment

\[ \text{MeO}_2C - \text{O} - \text{H} \]

\[ \text{NaIO}_4, \text{EtOAc/H}_2\text{O} \quad 84\%, \text{two steps} \]

\[ \text{NiCl}_2, \text{CrCl}_2, \text{PhCH}_3, \text{reflux} \quad 65\%, \text{two steps} \quad 8.3:1 \text{ dr} \]

\[ \text{MeO}_2C - \text{O} - \text{H} \]

\[ \text{DIBALH} \quad -75^\circ \text{C} \quad 93\% \]

\[ \text{OTBS} \quad \text{NIS, cat. TBSCl} \quad \text{MeCN, PhCH}_3 \quad 90\% \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]

\[ \text{OTBS} \]
Eribuline: Completion of Eastern Fragment

\[
\text{MeO}_2\text{C} - \text{O} - \text{OH} \quad \xrightarrow{\text{NaIO}_4, \text{EtOAc/H}_2\text{O}} \quad \text{MeO}_2\text{C} - \text{O} - \text{OH} \quad \text{84%, two steps}
\]

\[
\text{MeO}_2\text{C} - \text{O} - \text{OH} \quad \xrightarrow{\text{NiCl}_2, \text{CrCl}_2, \text{PhCH}_3, \text{reflux}} \quad \text{PhCH}_3 \quad \text{65%, two steps}
\]

\[
\text{MeO}_2\text{C} - \text{O} - \text{OH} \quad \xrightarrow{1) \text{AcOH, H}_2\text{O}} \quad \text{MeO}_2\text{C} - \text{O} - \text{OH} \quad \text{90 °C; rextl.}
\]

\[
\text{MeO}_2\text{C} - \text{O} - \text{OH} \quad \xrightarrow{2) \text{TBSOTf, 2,6-lut. MTBE}} \quad \text{MeO}_2\text{C} - \text{O} - \text{OH} \quad \text{8.3:1 dr}
\]

\[
\text{MeO}_2\text{C} - \text{O} - \text{OH} \quad \xrightarrow{-75 ° \text{C}} \quad \text{MeO}_2\text{C} - \text{O} - \text{OH} \quad \text{93%}
\]
**Eribuline: Completion of Eastern Fragment**

- **NaIO₄, EtOAc/H₂O:**
  - 84%, two steps

- **NiCl₂, CrCl₂, PhCH₃, reflux:**
  - 65%, two steps
  - 8.3:1 dr

- **AcOH, H₂O (90 °C; refl.):**
  - 90% 53%, two steps

- **TBSOTf, 2,6-lut. MTBE:**
  - 53%, two steps

- **NIS, cat. TBSCl MeCN, PhCH₃:**
  - 90%
**Eribuline: Completion of Eastern Fragment**

- **NaIO₄, EtOAc/H₂O**: 84%, two steps
- **NiCl₂, CrCl₂, PhCH₃, reflux**: 65%, two steps, 8.3:1 dr
- **NIS, cat. TBSCl, MeCN, PhCH₃**: 90%
- **DIBALH**: -75 °C, 93%
- **2.8%, 15 steps**
Eribuline: Northern Fragment Synthesis

1) acetone, H₂SO₄
2) SO₂Cl₂, pyr., MeCN
3) H₂, Pd/C, THF

59%, three steps

<$1/g (TCI)

D-glucorono-6,3 lactone
Eribuline: Northern Fragment Synthesis

1) acetone, H₂SO₄
2) SO₂Cl₂, pyr., MeCN
3) H₂, Pd/C, THF

59%, three steps

1) DIBALH, PhCH₃, -40 °C
2) TMSCH₂MgCl, THF

72%, two steps

D-glucorono-6,3 lactone

<$1/g (TCI)
Eribuline: Northern Fragment Synthesis

1) acetone, \( \text{H}_2\text{SO}_4 \)
2) \( \text{SO}_2\text{Cl}_2 \), pyr., MeCN
3) \( \text{H}_2 \), Pd/C, THF

59%, three steps

1) DIBALH, PhCH\(_3\), -40 °C
2) TMSCH\(_2\)MgCl, THF

72%, two steps

1) KHMDS, THF
2) BnBr, KO\( \text{tBu} \)

89%, two steps

D-glucorono-6,3 lactone

<\$1/g (TCI)
Eribuline: Northern Fragment Synthesis

D-glucorono-6,3 lactone

(DHQ)$_2$AQN
$K_2$OsO$_4$, $K_3$Fe(CN)$_6$

1) acetone, H$_2$SO$_4$
2) SO$_2$Cl$_2$, pyr., MeCN
3) H$_2$, Pd/C, THF

59%, three steps

1) DIBALH, PhCH$_3$, -40 °C
2) TMSCH$_2$MgCl, THF

72%, two steps

<$1/g (TCI)

$K_2$OsO$_4$, $K_3$Fe(CN)$_6$

1) KHMDS, THF
2) BnBr, KOtBu

89%, two steps

$K_2$OsO$_4$, $K_3$Fe(CN)$_6$

1) BzCl, NMM, DMAP
2) AllylTMS, TiCl$_3$

56%, >99.5% de

1) BzCl, NMM, DMAP
2) AllylTMS, TiCl$_3$
3) iPr$_2$O

recrystallize
Eribuline: Northern Fragment Synthesis

<$1/g (TCI)

D-glucoronol-6,3 lactone

(DHQ)$_2$AQN

K$_2$OsO$_4$, K$_3$Fe(CN)$_6$

$<$1/g (TCI)

1) acetone, H$_2$SO$_4$
2) SO$_2$Cl$_2$, pyr., MeCN
3) H$_2$, Pd/C, THF

59%, three steps

1) DIBALH, PhCH$_3$, -40 °C
2) TMSCH$_2$MgCl, THF

72%, two steps

1) KHMDS, THF
2) BnBr, KO$_t$Bu

89%, two steps

1) BzCl, NMM, DMAP
2) AllylTMS, TiCl$_3$OiPr

recrystallize

56%, >99.5% de
**Eribuline: Northern Fragment Synthesis**

1) DMSO, TCAA, Et$_3$N
   PhCH$_3$, -10 °C

2) LHMDS, PHSO$_2$Me

68%, five steps

67%, five steps
**Eribuline: Northern Fragment Synthesis**

1) DMSO, TCAA, Et$_3$N
   PhCH$_3$, -10 °C

2) LHMDS, PHSO$_2$Me

68%, five steps

O

OH

OBz

BnO

OH

OBz

O

MeO

SO$_2$Ph

1) TMSI, 60 °C

2) Bu$_4$NCl, NaBH(OAc)$_3$

3) K$_2$CO$_3$, MeOH

recrystallize

57%, five steps

HO

SO$_2$Ph

CHO

OTBS

OTBS

OH

OH

7.8%, 19 steps
Eribuline: Northern Fragment Synthesis

1) DMSO, TCAA, Et$_3$N, PhCH$_3$, -10 °C
2) LHMDS, PHSO$_2$Me

1) TMSI, 60 °C
2) Bu$_4$NCl, NaBH(OAc)$_3$
3) K$_2$CO$_3$, MeOH

recrystallize

57%, five steps
Eribuline: Northern Fragment Synthesis

1) DMSO, TCAA, Et$_3$N, PhCH$_3$, -10 °C
2) LHMDS, PHSO$_2$Me

68%, five steps

1) TMSI, 60 °C
2) Bu$_4$NCl, NaBH(OAc)$_3$
3) K$_2$CO$_3$, MeOH
recrystallize

57%, five steps

1) 2 M HCl, MeOH
2) TBSCl, imidaz.

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Eribuline: Northern Fragment Synthesis

1) DMSO, TCAA, Et$_3$N
   PhCH$_3$, -10 °C
2) LHMDS, PHSO$_2$Me

1) TMSI, 60 °C
2) Bu$_4$NCl, NaBH(OAc)$_3$
3) K$_2$CO$_3$, MeOH
   recrystallize
   57%, five steps

1) 2 M HCl, MeOH
2) TBSCI, imidaz.

O$_3$, heptane;
then Lindlar’s, H$_2$
recrystallize
68%, five steps

7.8%, 19 steps
Eribuline: Southern Fragment Synthesis

D-quinic acid

$2/g$ (Aldrich)

1) c-hexanone
\[ \text{H}_2\text{SO}_4, 160 \, ^\circ\text{C} \]
2) TMSCl, imidaz.

73%, two steps
Eribuline: Southern Fragment Synthesis

1) c-hexanone
   \[ \text{H}_2\text{SO}_4, 160 \, ^\circ\text{C} \]
2) TMSCl, imidaz.
   73\%, two steps

1) DIBALH, -78 \, ^\circ\text{C}
2) AcOH, \text{H}_2\text{O}
3) Et\(_3\)N, DMAP, Ac\(_2\)O
   recrystallize
   65\%, three steps

D-quinic acid
$2/g$ (Aldrich)
Eribuline: Southern Fragment Synthesis

1) $c$-hexanone
   $\text{H}_2\text{SO}_4$, 160 °C
2) TMSCl, imidaz.
   [73%, two steps]

1) DIBALH, -78 °C
2) AcOH, $\text{H}_2\text{O}$
3) Et$_3$N, DMAP, Ac$_2$O
   recrystallize
   [65%, three steps]
Eribuline: Southern Fragment Synthesis

D-quinic acid

1) c-hexanone
H₂SO₄, 160 °C
2) TMSCl, imidaz.

73%, two steps

1) DIBALH, -78 °C
2) AcOH, H₂O
3) Et₃N, DMAP, Ac₂O

recrystallize
65%, three steps

MeO₂C―CH=CH―AcO

1) NaOMe, MeOH
2) LiAlH₄, THF

62%
**Eribuline: Southern Fragment Synthesis**

**D-quinic acid**

![Chemical Structure]

1) c-hexanone
H$_2$SO$_4$, 160 °C
2) TMSCl, imidaz.

65%, three steps

**$2/g$ (Aldrich)**

1) MsCl, Et$_3$N
2) KCN, EtOH/H$_2$O

recrystallize

65%, three steps

![Chemical Structure]

1) DIBALH, -78 °C
2) AcOH, H$_2$O
3) Et$_3$N, DMAP, Ac$_2$O

62%
Eribuline: Southern Fragment Synthesis

KHMDIS, MeI
PhCH$_3$/THF, -78 °C
recrystallize
65%, five steps
34:1 dr
Eribuline: Southern Fragment Synthesis

Starting material

KHMD, MeI
PhCH₃/THF, -78 °C
recrystallize
65%, five steps
34:1 dr

1) 1M HCl, AcOH
2) MeC(=O)Br

Final product

(Eribuline: Southern Fragment Synthesis)
**Eribuline: Southern Fragment Synthesis**

1. **KHMDs, MeI**
   - PhCH3/THF, -78 °C
   - recrystallize
   - 65%, five steps
   - 34:1 dr

2. **1M HCl, AcOH**
   - 62%, three steps

3. **DBU, 100 °C**
   - 62%, three steps

**Eribuline**
Eribuline: Southern Fragment Synthesis

1) O₃  2) NaBH₄
3) K₂CO₃, H₂O
4) NaIO₄

1M HCl, AcOH, 100 °C, 62%, three steps

DBU, 100 °C, 65%, five steps

recrystallize

34:1 dr

75%, four steps
**Eribuline: Southern Fragment Synthesis**

1. **KHMDH, MeI**
   PhCH$_3$/THF, -78 °C
   recrystallize
   65%, five steps
   34:1 dr

2. 1) 1M HCl, AcOH
   2) 62%, three steps

3. 1) O$_3$ 2) NaBH$_4$
   3) K$_2$CO$_3$, H$_2$O
   4) NaIO$_4$
   75%, four steps

4. (MeO)$_2$POCO$_2$Me
   LiCl, iPr$_2$NEt

DBU, 100 °C
62%, three steps
Eribuline: Southern Fragment Synthesis

1) H₂, PtO₂, MeOH
2) Tf₂O, Et₃N, -78 °C
3) NaI, DMF

75%, four steps
Eribuline: Southern Fragment Synthesis

1) H₂, PtO₂, MeOH
2) Tf₂O, Et₃N, -78 °C
3) NaI, DMF

75%, four steps

1) LiBH₄, THF, PhCH₃
2) Zn, AcOH, MeOH

81%, two steps
**Eribuline: Southern Fragment Synthesis**

1) H₂, PtO₂, MeOH  
2) Tf₂O, Et₃N, -78 °C  
3) NaI, DMF  

75%, four steps

1) HCl, iPrOH  
then PhCH₃, H₂O  
2) TBDPSCl, imidaz.

81%, two steps
**Eribuline: Southern Fragment Synthesis**

1) **H₂, PtO₂, MeOH**
2) **Tf₂O, Et₃N, -78 °C**
3) **NaI, DMF**

- **75%, four steps**

---

1) **HCl, iPrOH**
then **PhCH₃, H₂O**
2) **TBDPSCl, imidaz.**

- **81%, two steps**

---

1) **(OMe)NHMe•HCl**
AlMe₃, DCM
2) **TBSCl, imidaz, DMF**

- **99%, four steps**
Eribuline: Southern Fragment Synthesis

1) H₂, PtO₂, MeOH
2) Tf₂O, Et₃N, -78 °C
3) NaI, DMF

75%, four steps

1) LiBH₄, THF, PhCH₃
2) Zn, AcOH, MeOH

81%, two steps

1) HCl, iPrOH
then PhCH₃, H₂O
2) TBDPSCI, imidaz.

1) (OMe)NHMe•HCl
AlMe₃, DCM
2) TBSCI, imidaz, DMF

99%, four steps
Eribuline: Southern Fragment and Ligand Synthesis

1) HCl, iPrOH, MeOH
2) PivCl, collidine, DMAP
3) MsCl, Et$_3$N, THF

62%, five steps

3.3% overall

33 steps
Eribuline: Southern Fragment and Ligand Synthesis

1) HCl, iPrOH, MeOH
2) PivCl, collidine, DMAP
3) MsCl, Et₃N, THF

62%, five steps

3.3% overall
33 steps

1) [Structural formula]
2) [Structural formula]

97%

N

Me

OH

Me

NH₂

O

Me

NHMe

O

Me

NHMS

Ligand for N-H-K

54% overall

four steps

85%

Eribuline: Southern Fragment and Ligand Synthesis!
Eribuline: Southern Fragment and Ligand Synthesis

1) HCl, iPrOH, MeOH
2) PivCl, collidine, DMAP
3) MsCl, Et₃N, THF
62%, five steps

3.3% overall
33 steps

1) (Cl₃CO)₂CO
2) LiOH, H₂O, 60 °C
97% 65%, two steps

54% overall
four steps
Eribuline: Southern Fragment and Ligand Synthesis

1) HCl, iPrOH, MeOH
2) PivCl, collidine, DMAP
3) MsCl, Et$_3$N, THF

62%, five steps

3.3% overall
33 steps

1) (Cl$_3$CO)$_2$CO

THF

97%

65%, two steps

1) LiOH, H$_2$O, 60 °C

MsCl, pyr., DMAP

85%
**Eribuline: Southern Fragment and Ligand Synthesis**

1. **Eribuline Intermediate**
   - 1) HCl, iPrOH, MeOH
   - 2) PivCl, collidine, DMAP
   - 3) MsCl, Et$_3$N, THF

   ![Intermediate Structure](image)

   - 62%, five steps
   - 3.3% overall
   - 33 steps

2. **Ligand Synthesis**
   - 1) (Cl$_3$CO)$_2$CO
   - 2) LiOH, H$_2$O, 60 °C

   ![Ligand Structure](image)

   - 97%
   - 65%, two steps

3. **Final Mixture**
   - MsCl, pyr., DMAP

   ![Final Mixture](image)

   - 85%

**Ligand for N-H-K**
- 54% overall
- four steps

---

**Notes:**
- TBSO, OTf, OTBDPS, MsO, OPiv, OMe, OMe, THF, NH$_2$, MeOH, (Cl$_3$CO)$_2$CO, LiOH, H$_2$O, 60 °C, MsCl, pyr., DMAP.
**Eribuline: Coupling Western Fragments**

1) KHMDS, THF, -14 °C
2) DIBALH, DCM, 68%, three steps

- 1.1 eq
- 1.0 eq
- 3.55 eq CrCl₂ and NiCl₂, Et₃N, THF
Eribuline: Coupling Western Fragments

1) KHMDS, THF -14 °C chromatography

2) DIBALH, DCM

68%, three steps
(20:1 dr before chrom.)
Eribuline: Completion of Synthesis

1) DMP, DCM
2) SmI₂, -78 °C

nBuLi, THF, 0 °C;
-75 °C then ald.
Eribuline: Completion of Synthesis

1) DMP, DCM
2) SmI₂, -78 °C

64%, three steps
Eribuline: Completion of Synthesis

1) Ts₂O, collidine, pyrid. (cat.)
2) NH₄OH, iPrOH
3) MeSO₃H, NH₂OH, H₂O

84%, three steps

26% for coupling steps

11 final manipulations

PPTS, DCM

72%, two steps
Eribuline: Completion of Synthesis

1) Ts₂O, collidine, pyrid. (cat.)
2) NH₄OH, iPrOH
3) MeSO₃H, NH₄OH, H₂O

72%, two steps
84%, three steps

26% for coupling steps
11 final manipulations
Production Considerations: Analogues and Natural Products

- Recrystallization, Resolution
- Utilize Very Robust Chemistry

Target Considerations: Development of Analogues and Derivatives

- Retain Only Necessary Parts
Production Considerations: Analogues and Natural Products

- Recrystallization, Resolution
- Utilize Very Robust Chemistry

Target Considerations: Development of Analogues and Derivatives

- Retain Only Necessary Parts
- Shorten Production Route
Arterolane: Complete synthesis

Arterolane: Complete synthesis

Artemesinin

- First discovered by Chinese army project, *Project 523*, in 1960's
- Use of source plant, *Artemisia annua*, dates back 2,000 years in China
- Isolated material approved for worldwide treatment of malaria

Arterolane: Complete synthesis

Artemesinin

- First discovered by Chinese army project, *Project 523*, in 1960's
- Use of source plant, *Artemisia annua*, dates back 2,000 years in China
- Isolated material approved for worldwide treatment of malaria

Arterolane

- First synthesized and identified by broad collaboration of chemists in 2001
- Phase III trials began in India in 2009 by Indian company Ranbaxy
- Ozonide bridge retains the active radical reactivity found in artemesin, improved PK

Arterolane: Complete synthesis

<$/g > 98%

Ranbaxy Labs 2011 patent
**Arterolane: Complete synthesis**

1. **Initial Step**:<br>
   
   ![Initial structure](image)
   
   Reagents: Ammonium methylate (NH₂OMe), MeOH, H₂O<br>
   Yield: 98%<br>
   Cost: <$1/g

2. **Subsequent Step**:<br>
   
   ![Subsequent structure](image)
   
   Reagents: O₃, c-hex., DCM, -78 °C<br>
   Yield: 96%

Ranbaxy Labs 2011 patent
Arterolane: Complete synthesis

1) NaOH, H$_2$O
2) 1 M HCl, 0°C

78% overall 4 steps
Ranbaxy Labs 2011 patent
Arterolane: Complete synthesis

1) NaOH, H₂O
2) 1 M HCl, 0 °C

Ranbaxy Labs 2011 patent
Arterolane: Complete synthesis

O
O
ON
2)

NH₂OMe
MeOH, H₂O
98%

O₃, c-hex., DCM, -78 °C

1) NaOH, H₂O
2) 1 M HCl, 0 °C

78%

96%

rxtl'd, 87%

64% overall
4 steps
Production Considerations: Analogues and Natural Products

Recrystallization, Resolution

Target Considerations: Development of Analogues and Derivatives

Retain Only Necessary Parts

Improve Activity or Properties

Shorten Production Route
TP-434 Synthesis: Overview

Produced by Meyers Lab and Tetraphase
TP-434 currently in Phase II trials for treatment of resistant infections
First identified 1945 from soil bacteria
Most recent tetracycline derivative (tigecycline) approved in 2005, 1st in 20 years
All but those produced by Tetraphase are semi-synthetic variants
TP-434 Synthesis: Overview

TP-434

chlorotetracycline
TP-434 Synthesis: Overview

- Produced by Meyers Lab and Tetraphase
- First identified 1945 from soil bacteria
- Broad spectrum antibiotics, though resistance is increasing

TP-434

chlorotetracyclline

First identified 1945 from soil bacteria

- Most recent tetracycline derivative (tigecycline) approved in 2005, 1st in 20 years

- All but those produced by Tetraphase are semi-synthetic variants
**TP-434 Synthesis: Overview**

- Produced by Meyers Lab and Tetraphase
- First identified 1945 from soil bacteria
- Broad spectrum antibiotics, though resistance is increasing
- TP-434 currently in Phase II trials for treatment of resistant infections
- Most recent tetracycline derivative (tigecycline) approved in 2005, 1st in 20 years
**TP-434 Synthesis: Overview**

- Produced by Meyers Lab and Tetraphase
- First identified 1945 from soil bacteria
- Broad spectrum antibiotics, though resistance is increasing
- TP-434 currently in Phase II trials for treatment of resistant infections
- Most recent tetracycline derivative (tigecycline) approved in 2005, 1st in 20 years
- All but those produced by Tetraphase are semi-synthetic variants
TP-434 Synthesis: Retrosynthetic Analysis
TP-434 Synthesis: Retrosynthetic Analysis

TP-434
Multiple generations of dienone synthesis

Highly convergent, easily modified

Similar route used to produce multiple analogs
TP-434 Synthesis: C/D Ring Precursor Synthesis

1) BnBr, Cs
2) NaBH₄, MeOH
83%, two steps

1) MsCl, Et₃N
2) NHMe₂, DMF
98%, two steps

1) n-BuLi, CO(g)
2) H₂SO₄, MeOH
72%

63%, two steps

n-BuLi, SiMe₂PhCl
p-benzoquinone; then CeCl₃, NaBH₄
67%
72%

SiMe₂Ph
meso
TP-434 Synthesis: C/D Ring Precursor Synthesis

1) BnBr, Cs$_2$CO$_3$  
2) NaBH$_4$, MeOH  
83%, two steps

72%
**TP-434 Synthesis: C/D Ring Precursor Synthesis**

1. **First Route**
   - Reaction with DBU in MeOH: 72%

2. **Second Route**
   - Reaction with MsCl and Et₃N in DMF: 98%, two steps

3. **Third Route**
   - Reaction with NaBH₄ in MeOH: 83%, two steps

4. **Fourth Route**
   - Reaction with CeCl₃ and NaBH₄: 67%
TP-434 Synthesis: C/D Ring Precursor Synthesis

- **First Route:**
  1. $\text{BnBr, Cs}_2\text{CO}_3$
  2. $\text{NaBH}_4$, MeOH
  - Result: 83%, two steps

- **Second Route:**
  1. $\text{MsCl, Et}_3\text{N}$
  2. $\text{NHMe}_2$, DMF
  - Result: 98%, two steps

- **Third Route:**
  1. $n\text{-BuLi, CO}_2\ (g)$
  2. $\text{H}_2\text{SO}_4$, MeOH
  - Result: 63%, two steps

**Additional Reaction:**

- **Silicon Functionalization:**
  - $n\text{BuLi}$
  - $\text{SiMe}_2\text{PhCl}$
  - Result: 72%
TP-434 Synthesis: C/D Ring Precursor Synthesis

1) BnBr, Cs\(_2\)CO\(_3\)  
2) NaBH\(_4\), MeOH
83%, two steps

1) MsCl, Et\(_3\)N  
2) NHMe\(_2\), DMF
98%, two steps

n-BuLi, CO\(_2\) (g)  
1) n-BuLi, CO\(_2\) (g)  
2) H\(_2\)SO\(_4\), MeOH
63%, two steps

PhMe\(_2\)Si

nBuLi  
SiMe\(_2\)PhCl
72%

PhMe\(_2\)Si

p-benzoquinone;  
then CeCl\(_3\), NaBH\(_4\)
67%
TP-434 Synthesis: C/D Ring Precursor Synthesis

meso

PhMe₂Si—H

PhMe₂Si—H

H

H

H

H

H

H

H

PhMe₂Si—H

Me—O—C—Me

Amano lipase-PS
NEt₃, 23 °C
95%

PhMe₂Si—H

H

H

OAc

PhMe₂Si—H

H

H

H

H

H

PhMe₂Si—H
TP-434 Synthesis: C/D Ring Precursor Synthesis

\[
\text{meso} \xrightarrow{\text{Amano lipase-PS, NEt}_3, 23 \, ^\circ\text{C}} \quad 95% \quad \xrightarrow{4 \text{ mol } \% \text{ Pd(dpdpf)Cl}_2, \text{HCO}_2\text{NH}_4, \text{DMF}} \quad 82\%
\]
TP-434 Synthesis: C/D Ring Precursor Synthesis

1. Reaction with Amano lipase-PS (95% yield)

2. Reaction with NaHMDS, THF, -50 °C (62%, one step)

3. Reaction with 4 mol % Pd(dppf)Cl₂, HCO₂NH₄, DMF (82% yield)
TP-434 Synthesis: C/D Ring Precursor Synthesis

meso

PhMe₂Si-\(\text{H}^{\text{H}}\text{H}^{\text{OH}}\text{OH}\)

\[\text{Amano lipase-PS}\]
\[\text{NEt}_3, 23 \text{ °C}\]
\[95\%\]

4 mol % Pd(dppf)Cl₂
HCO₂NH₄, DMF

82%

NaHMDS, THF, -50 °C

62%, one step

then

KHMDS, -10 °C

\[\text{PhMe}_2\text{Si-}\text{H}^{\text{H}}\text{H}^{\text{ONa}}\text{MeOOC}\text{OBn}\]

TP-434 Synthesis: C/D Ring Precursor Synthesis
TP-434 Synthesis: C/D Ring Precursor Synthesis

meso

Amano lipase-PS
NEt₃, 23 °C

95%

4 mol % Pd(dppf)Cl₂
HCO₂NH₄, DMF
82%

87%

NaHMDS, THF, -50 °C

62%, one step

then

KHMDS, -10 °C

120 °C
PhCH₃, 10 h
TP-434 Synthesis: A/B Ring Precursor Synthesis

![Chemical structure](attachment:chemical_structure.png)

- Reaction with 20 mol% LiOtBu
- Temperature: -45 to -20 °C

Overall: 13% yield from alkyne, 14 steps including all starting materials.
TP-434 Synthesis: A/B Ring Precursor Synthesis

From Michael-Claisen: 5 steps, 35 %, no chromatographic purification

Overall: 13% yield from alkyne, 14 steps including all starting materials
TP-434 Synthesis: A/B Ring Precursor Synthesis

From Michael-Claisen: 5 steps, 35%, no chromatographic purification

Overall: 13% yield from alkyne, 14 steps including all starting materials
TP-434 Synthesis: A/B Ring Precursor Synthesis

From Michael-Claisen: 5 steps, 35 %, no chromatographic purification

Overall: 13% yield from alkyne, 14 steps including all starting materials
TP-434 Synthesis: C/D Ring Precursor Synthesis

1) sBuLi, TMEDA; then MeI
2) (COCl)$_2$; then PhOH

52%, two steps

1) BBr$_3$, DMF
2) Boc$_2$O, DMAP

94%, two steps
TP-434 Synthesis: Cyclization and Final Steps

LDA, TMEDA, THF

H₂, Pd/C
41%, 2 steps

1) aq. HF 35%

H N Me
Me
O
HO
OH
OH
O
F
H
NH₂
O

H N Me
Me
O
HO
OH
OH
O
OBn
OTBS

1) HNO₃, H₂SO₄
2) H₂, Pd/C
82%, 2 steps

H N Me
Me
O
HO
OH
OH
O
F
H
NH₂
O

H N Me
Me
O
HO
OH
OH
O
OBn
OTBS

LDA, TMEDA, THF
35%

1) pyrrolidine

O
Br
Br

11 additional steps
25 total steps
<1.6% overall

1 dose
≈ 1.4 g alkyne
TP-434 Synthesis: Cyclization and Final Steps

1) aq. HF

2) \( \text{H}_2 \), Pd/C

82%, 2 steps

11 additional steps

25 total steps

<1.6% overall
TP-434 Synthesis: Cyclization and Final Steps

1) HNO₃, H₂SO₄
2) H₂, Pd/C
82%, 2 steps

1) aq. HF
2) H₂, Pd/C
41%, 2 steps

LDA, TMEDA, THF
35 %
TP-434 Synthesis: Cyclization and Final Steps

1) LDA, TMEDA, THF

2) aq. HF, Pd/C

1) HNO₃, H₂SO₄

2) H₂, Pd/C

1 dose ≈ 1.4 g alkyne

11 additional steps

25 total steps

<1.6% overall
TP-434 Synthesis: Cyclization and Final Steps

1) LDA, TMEDA, THF
   \[
   \text{Me-N-Me} \quad \xrightarrow{\text{O}} \quad \text{Me-N-Me}
   \]
   35% 

2) \( \text{H}_2 \text{Pd/C} \)
   \[
   \text{Me-N-Me} \quad \xrightarrow{\text{O}} \quad \text{Me-N-Me}
   \]
   41%, 2 steps

1) aq. HF
   \[
   \text{H}_2 \quad \xrightarrow{\text{O}} \quad \text{H}_2
   \]

2) \( \text{H}_2 \text{Pd/C} \)
   \[
   \text{H}_2 \quad \xrightarrow{\text{O}} \quad \text{H}_2
   \]
   82%, 2 steps

\[
\begin{align*}
\text{F} & \quad \text{Me-N-Me} \\
\text{H} & \quad \text{O} \quad \text{Boc} \\
\text{O} & \quad \text{OTBS}
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{Me-N-Me} \\
\text{H} & \quad \text{O} \quad \text{Boc} \\
\text{O} & \quad \text{OTBS}
\end{align*}
\]

1) \( \text{HNO}_3, \text{H}_2\text{SO}_4 \)
   \[
   \text{F} \quad \text{Me-N-Me} \\
   \text{H} \quad \text{O} \quad \text{Boc} \\
   \text{O} \quad \text{OTBS}
   \]

2) \( \text{H}_2 \text{Pd/C} \)
   \[
   \text{F} \quad \text{Me-N-Me} \\
   \text{H} \quad \text{O} \quad \text{Boc} \\
   \text{O} \quad \text{OTBS}
   \]

11 additional steps
25 total steps
<1.6% overall
1 dose \( \approx 1.4 \) g alkyne
Production Considerations: Analogues and Natural Products

Recrystallization, Resolution

Utilize Very Robust Chemistry

Target Considerations: Development of Analogues and Derivatives

Retain Only Necessary Parts

Improve Activity or Properties

Shorten Production Route
Fingolimod: Introduction

myriocin

\[
\begin{align*}
\text{myriocin} & \quad \text{fingolimod} \\
\end{align*}
\]

fingolimod

Fingolimod: Introduction

- From thermophilic fungi species
- Isolated in 1994, studied for bioactivity

Fingolimod: Introduction

- From thermophilic fungi species
- Isolated in 1994, studied for bioactivity

myriocin

\[
\text{myriocin} \rightarrow \text{fingolimod} \cdot \text{HCl}
\]

Fingolimod: Complete synthesis

1. Reaction with ClCH2Br in the presence of AlCl₃, DCM to yield a 76% yield.
2. Reaction with Na(0), EtOH to yield a 95% yield.
3. Reaction with Et₃SiH, TiCl₄, DCM to yield a 70% yield over two steps.
4. Reaction with LiAlH₄, THF to yield a 38% overall yield over five steps.
5. Reaction with 6 M HCl, EtOH to yield a 76% yield.

Chemical structures and reagents are represented in the diagram.
Production Considerations: Analogues and Natural Products

Recrystallization, Resolution

Utilize Very Robust Chemistry

Target Considerations: Development of Analogues and Derivatives

Retain Only Necessary Parts

Improve Activity or Properties

Shorten Production Route