Comparative Syntheses of Vancomycin

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Dave Evans, Harvard
1996

K.C. Nicolaou, Scripps
1998, 1999

Dale Boger, Scripps
1999
Structural Features of Vancomycin Type Glycopeptide Antibiotics

- Generally characterized by an aryl-rich polypeptide backbone with varying crosslinking and glycosidation patterns

\[ \text{X} = \text{Y} = \text{Cl}; \text{Vancomycin} \]
\[ \text{X} = \text{H}, \text{Y} = \text{Cl}; \text{Eremomycin} \]
\[ \text{X} = \text{Y} = \text{H}; \text{Orientin C} \]

Useful references


Proposed Biosynthesis of Vancomycin-Type Glycopeptides

- Remarkably, genes and proteins responsible for the biosynthesis of these molecules have been characterized.
- Biosynthesis can be reduced to peptide elongation and post-translational modification.
- The challenge to the synthetic chemist is immense: biosynthesis entails 35 total steps.
**Biological Activity (Gram-Positive Bacteria)**

- Vancomycin inhibits cell wall cross-linking through tight binding, eventually leading to cell lysis.

![Alanine dimer - normally linked to glycan outer wall of cell](image)

- Disruption of just one of the five hydrogen bonds leads to a 1000-fold loss in activity.
The Evans Design

- Chiral auxiliary technology will be used to create most amino acid stereocenters

- This strategy relies on atropdiastereoselective macrocyclizations
**Oxazolidinone-Based Amino Acid Synthesis**

- Chiral auxiliary approach creates labile arylglycine stereocenters in controlled fashion

![Chemical Reaction Diagram]

- This strategy is applied to all arylglycines in the Evans synthesis

Evans, *JACS*, 4011, 1990
The auxiliary approach proves unsuccessful for the central resorcinol-type arylglycine.
Oxazolidinone methodology is employed to stereoselectively access a protected amino alcohol.

\[
\text{Sn(OTf)}_2, \text{NMP} \quad \text{THF, } -78 \, ^\circ\text{C}
\]

72% yield

1. \text{Boc}_2\text{O}; \text{HCO}_2\text{H}, \text{H}_2\text{O}_2
2. \text{LiOOH}

46% from benzaldehyde
Synthesis of the Left Macrocycle

- Functional group adjustment and amino acid coupling

![Chemical structures](image_url)
Synthesis of the Left Macrocycle

Oxidative coupling provides undesired atropisomer

Vanadium serves as oxidant, BF₃ as trap for oxygen nucleophiles, silver as trap for chloride ion impurities, TFA as part of solvent mixture, NaBH(OAc)₃ as reductive quench

see: Evans, JACS, 6426 1993
Synthesis of the Left Macrocycle

- Oxidative coupling proceeds via radical cation

\[
\text{Oxidative coupling proceeds via radical cation.}
\]

![Chemical structure](image-url)
**Synthesis of the Left Macrocycle**

Careful coupling introduces the central aryl fragment.

![Chemical structures](image)
Synthesis of the Left Macrocycle

- Macrocyclization occurs with good selectivity

![Chemical Structures]

1) HF•pyridine
2) Na$_2$CO$_3$, DMSO; PhNTf$_2$
3) Zn$^0$, AcOH
4) NaNO$_2$, H$_3$PO$_2$, cat. Cu$_2$O

62% yield
5:1 dr

(10:1 dr w/o Cl)
Synthesis of the Left Macrocycle

Thermal equilibration provides the desired atropisomer

1) Pd(dppf)Cl₂, HCHO, DMF, 75 °C
2) Piv Cl
3) TFA, DMS; TFAA
4) AlBr₃, EtSH
5) MeOH, 55 °C

44% yield
19:1 dr

see: Evans, JACS, 6426 1993
**Synthesis of the Left Macrocycle**

Thermal equilibration provides the desired atropisomer.

1) BnBr, Cs$_2$CO$_3$
2) LiSEt, THF, 0 °C
3) allyl-Br, Cs$_2$CO$_3$
4) LDA, -78 °C
5) LiOH, THF/MeOH

65% yield
Synthesis of the Right Macrocycle

- Fragment coupling completes the peptide chain

For synthesis of tripeptide, see Nicolaou *Classics II*, p. 290
Synthesis of the Right Macrocycle

Closure of the second macrocycle proceeds with the desired atropdiastereoselectivity.

1) CsF, DMSO
2) Zn⁰, AcOH
3) HBF₄, tBuONO, MeCN; CuCl/CuCl₂

60% yield
5:1 dr
Synthesis of the Right Macrocycle

- Closure of the second macrocycle proceeds with the desired atropdiastereoselectivity

Mechanism for Sandmeyer reaction not fully known, but may be as follows:

\[
\begin{align*}
\text{ArN}_2^+X^- + \text{CuX} & \rightarrow \text{Ar}^- + \text{N}_2 + \text{CuX}_2 \\
\text{Ar}^- + \text{CuX}_2 & \rightarrow \text{ArX} + \text{CuX}
\end{align*}
\]

60% yield
5:1 dr
Completion of Vancomycin

- An unusual mild deprotection reveals a carboxylic acid

- Nitrosation in the presence of seven amide functionalities

68% yield
Completion of Vancomycin

- Final deprotection proves uneventful

- Completion of vancomycin aglycon in 40 linear steps

Evans, Wood, Trotter, Richardson, Barrow, Katz *ACIEE*, 1998, 2700
The Nicolaou Design

- Sharpless asymmetric catalysis will be used to create most amino acid stereocenters

- Atropdiastereoselectivity left unaddressed in the design
Dihydroxylation/Aminohydroxylation Based Approach

- Sharpless methodology used to create aryl amino acid stereocenters

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{MeO} & \quad \text{MeO} \\
& \quad 1) \text{Ph}_2\text{P=CH}_2 \\
& \quad 2) \text{AD-mix-\(\beta\)} \\
\end{align*}
\]

84% yield, 96% ee

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{MeO} & \quad \text{MeO} \\
& \quad 1) (\text{n-Bu})_2\text{SnO}, \\
& \quad \text{BnBr, TBAI, 70 °C} \\
& \quad 2) \text{n-BuLi; B(OMe)}_3 \\
\end{align*}
\]

49% yield

\[
\begin{align*}
\text{O} & \quad \text{Bn} \\
& \quad \text{O} \\
& \quad 1) \text{TBSOTf,} \\
& \quad \text{lutidene} \\
& \quad 2) \text{H}_2, \text{Pd/C} \\
& \quad 3) \text{SO}_2\text{Cl}_2 \\
\end{align*}
\]

78% yield

- Enantioenrichment attained through amino acid coupling
Dihydroxylation/Aminohydroxylation Based Approach

As in the Evans synthesis, creating the central fragment is challenging.

1) SOCl₂, MeOH
   2) Br₂, AcOH

1) LAH, THF, 0 °C
   2) NaN₃, 6 M HCl,
      AcOH/H₂O, 0 °C;
      KOH, pyrrolidine

71% yield

1) PCC, CH₂Cl₂
   2) Ph₃P=CH₂, THF
   3) AD-mix-α,
      tBuOH/H₂O
   4) TBSCl, imidazole

DPPA

1) Boc₂O, TEA
   2) TBAF, THF
   3) TEMPO, NaOCl,
      KBr, NaHCO₃

70% yield

1) PPh₃, DEAD,
   DPPA, 0 °C
   2) PPh₃, H₂O, 60 °C

68% yield

72% yield

95% ee
Nicolaou's Triazene-Driven Ether Synthesis

Triazene serves to activate aryl ring for $S_\text{NAr}$ and acts as functional handle for phenol

Nicolaou, *JACS*, 119, **1997**, 3421
**Approach to the Left Macrocycle**

- A Suzuki coupling builds the biaryl bond

![Chemical structures and reactions](image-url)

1. **Suzuki coupling**
   - Reaction conditions: Toluene/H$_2$O, 90 °C
   - Products: 87% yield, 2:1 dr

2. **Second Suzuki coupling**
   - Conditions: 1) DPPA, DEAD, Ph$_3$P, THF, -20 °C
   - 2) LiOH, THF/H$_2$O
   - Yields: 80% for the first coupling, 94% for the second coupling
Approach to the Left Macrocycle

Peptide coupling sets up biaryl ether synthesis

90% yield
Closure of the Left Macrocycle

- Ether formation proceeds without atropdiastereoselectivity

1) CuBr, K$_2$CO$_3$
MeCN, 82 °C

2) TBAF, -15 °C
3) Et$_3$P, MeCN/H$_2$O
4) LiOH, THF/H$_2$O

46% yield
1:1 dr
Amide Formation and Deprotection

Completion of the left half achieved via lactamization

1) FDPP, DIPEA
DMF, 0 -> 25 °C

2) TBSOTf,
lutidene

3) TMSOTf,
lutidene

70% yield
Synthesis of the Right Macrocycle

Fragment coupling completes the peptide chain

For synthesis of tripeptide, see Nicolaou *Classics II*, p. 268
**Synthesis of the Right Macrocycle**

- Triazene-activated ether formation favors unnatural atropisomer; thermal equilibration is possible

- Heating unnatural isomer at 140 °C provides 2:3 mix in 80-85% yield

![Chemical structure](image)
**Final Functionalizations**

- Triazene proves difficult to functionalize as phenol
**Final Functionalizations**

Triazene proves difficult to functionalize as phenol

1) Raney Ni, MeOH
2) H₂, Pd(OH)₂
3) HBF₄, iPrONO
4) KI, 25 °C
Final Functionalizations

- Triazene proves difficult to functionalize as phenol

1) Raney Ni, MeOH
2) H₂, Pd(OH)₂
3) HBF₄, iPrONO
4) KI, 25 °C
5) MeMgBr (30 eq) iPrMgBr (30 eq); B(OMe)₃ (100 eq); H₂O₂

32% yield
Final Functionalizations

- Phenol protection and introduction of methyl ester
Completion of the Natural Product

Desilylation is followed by global deprotection

Nicolaou, Takayanagi, Jain, Natarajan, Koumbis, Bando, Ramanjulu, *ACIEE*, 1998, 2717
Conclusions

While synthesis is not an issue in the supply of Vancomycin, fascinating chemistry has been discovered in pursuit of an expedient synthesis.

Evans - 36 steps
0.2% overall yield
84% average

Nicolaou - 36 steps
0.13% overall yield
82% average

Control over the wide variety of stereocenters in the context of a complex synthesis is most notable.