Asymmetric [C+NC+CC] Coupling Entry to the Naphthyridinomycin Natural Product Family: Formal Total Synthesis of Cyanocycline A and Bioxalomycin β2

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Wipf Group Current Literature
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Napthyridinomycin Family

- Belongs to a family of tetrahydroisoquinoline alkaloids
- Isolated primarily from different species of *Streptomyces*
- Members of family are known “antitumor antibiotics”

Key Features:
- Hexacyclic core framework
- Quinone functionality
- Piperazine system
- Oxazolidine fragment

Cyanocycline A and Bioxalomycin β2

- 2 prior total syntheses of cyanocycline A have been completed:
  - Evans (1985 and 1987)
  - Fukuyama (1987 and 1992)
  - Wipf (partial – 2006)
Evans’ Total Synthesis of Cyanocycline A

- 31 steps, 1.8% overall
- Key Reactions:
  - Pictet Spengler and epoxide opening

Fukuyama’s Total Synthesis of Cyanocycline A


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Fukuyama’s Completion of Cyanocycline A

- 29 steps, 1.1% overall

- Key Reactions:
  - Zinc di-enolate coupling
  - Nitrosyl chloride oxidation/oxime formation
  - Carbamate protecting group
  - Pictet-Spengler
Wipf Approach Towards Diazabicyclo[3.2.1]octane Core

Garner’s Retrosynthetic Scheme
Key Asymmetric [C+NC+CC] Coupling

Garner’s Total Synthesis of Cyanocycline A

\[
\text{BnO} \quad \text{MeO} \quad \text{Br} \quad \text{MeO} \quad \text{OMe}
\]

\[
\text{BnO} \quad \text{MeO} \quad \text{BnO} \quad \text{MeO}
\]

\[
\text{Mg}^0, \text{cat. C}_2\text{H}_4\text{Br}_2 \rightarrow \text{THF, reflux; } 1, -50^\circ \text{C} \rightarrow \text{MeO} \quad \text{NOH}
\]

\[
\text{Zn, EtOH} \rightarrow \text{sat'd aq. NH}_4\text{Cl} \rightarrow 90^\circ \text{C}
\]

\[
\text{CBzCl} \rightarrow \text{aq. NaHCO}_3\text{-dioxane} \rightarrow 85\% \text{ over 2 steps}
\]

\[
\text{Dess-Martin periodinane} \rightarrow \text{CH}_2\text{Cl}_2, \text{rt} \rightarrow \text{85\%}
\]

\[
\text{cat. TsOH} \rightarrow \text{MeOH, rt} \rightarrow \text{(71\%, 80\% brsm)}
\]
Garner’s [C+NC+CC] Coupling

\[
\text{BocHN, CHO} + \text{CO}_2\text{Me} \xrightarrow{10 \text{ mol\% AgOAc, rt}} (73\%, \text{dr} = 4:1) \rightarrow \text{BocHN, CO}_2\text{Me} + \text{BocHN, CO}_2\text{Me}
\]

\[
\text{Sm(OTf)}_3, \text{MeOH, rt} \rightarrow (62\%)
\]

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Garner’s End Game

[Chemical structures and reactions depicted in the image]

1. Swern oxidation
2. TMSCN, ZnCl₂
   (45%)

1. Lawesson’s reagent
   C₆H₆, reflux
2. Raney-Ni/acetone, rt
   (63%)

LiAlH₄
THF, 0°C
(61%)

BnBr, K₂CO₃
DMF, 50°C
(81%)

BnOCH₂CHO
AcOH, 4 Å MS
CH₂Cl₂, rt
(86% over 2 steps)

TFA
CH₂Cl₂, rt

H₂ atm, Pd/C
MeOH, rt
(57%)

CbzCl, DIEA
THF, 0°C
(85%)

BnOCH₂CHO
AcOH, 4 Å MS
CH₂Cl₂, rt
(86% over 2 steps)
Garner’s Formal Completion of Cyanocycline A

- 22 steps, 0.3% overall

- Key Reactions:
  - Stereoselective Grignard addition
  - [C+NC+CC] coupling
  - Pictet-Spengler
  - Late stage “D” ring closure
Conclusions

- Formal synthesis of bioxalmycin β2 and 3rd completed synthesis (formal) of cyanocycline A

- Currently the shortest synthesis although lower yielding than previous syntheses

- Novel [C+CN+CC] coupling reaction utilized