Nine-Step Enantioselective Total Synthesis of (-)-Vincorine

Benjamin D. Horning and David W. C. MacMillan
Merck Center for Catalysis at Princeton University
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vincorine (1)

Joseph Salamoun
Wipf Group
Current Lit. 05/11/13
Vincorine

- Isolated from *Alstonia vitiensis* in 1975.
- Indole alkaloids are of interest for cancer research and drug discovery.
- Belongs to the akuammiline alkaloid family.

Vincorine

Aspidophylline A
See Liming's CL 06/18/11 for total synthesis.

Scholarisine A
See Filip's CL 02/18/12 for total synthesis.

(+)-Minfiensine
See Kara's CL 11/12/09 for total synthesis.
The Challenge

- Contains a pentacyclic caged structure.
- Installation of a strained seven-membered azepanyl ring system (red).
- Enantioselective synthesis.
Previous Syntheses

• Total synthesis of Vincorine completed by:
  – Qin group, 31 steps, racemic, 1% overall yield
    • J. Am. Chem. Soc. 2009, 131, 6013-6020
  – Ma group, 18 steps, 5% overall yield
    • J. Am. Chem. Soc. 2012, 134, 9126-9129
  – MacMillan group, 9 steps, 9% overall yield
    • Title Paper, 2013
Key Steps from Qin Group

(±)-Vincorine

Condensation of carboxylic acid and amine with Mukaiyama’s reagent to form lactam.

1:5 ratio of ketone:enol isomers

Cu(I) catalyzed cyclization

Formation of keto-ester with Meldrum’s Acid

Regitz Diazo Transfer

Johnson-Claisen Rearrangement

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Key Steps from Ma Group

1. TMSOTf, 2,6-lutidine, CH₂Cl₂, r.t.
2. K₂CO₃, KI, CH₃CN, 60 °C

12 Steps, ~19%

LiHMDS, I₂, THF
-40 °C to rt
67%

KCN, H₂O, DMF, 100 °C
65%

37% aq. HCHO, NaBH₃CN
CH₃CN, AcOH
68%

(-)-Vincorine

MacMillan’s Strategy

1. Radical Cyclization

2. Diels-Alder
   Imminium cyclization cascade

3. Resulting structure

4. Final product
MacMillan’s Earlier Methodology

Total Synthesis of Solanapyrone D, 2005 (9 steps)

\[
\begin{align*}
\text{CHO} & \quad \text{Me} \\
\text{Ph} & \quad \text{N} \\
& \quad \text{Me} \\
& \quad \text{Me} \\
\text{H} & \quad \text{Me} \\
\end{align*}
\]

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

71%, >20:1 dr, 90% ee

5 Steps

Solanapyrone D


Total Synthesis of Minfiensine, 2009 (9 steps, 21% overall yield)

\[
\begin{align*}
\text{NHBoc} & \quad \text{SMe} \\
\text{PMB} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{NHBoc} & \quad \text{SMe} \\
\text{PMB} & \quad \text{Me} \\
\end{align*}
\]

87%, 96% ee

5 Steps

(+)-Minfiensine


Total Synthesis of Six Natural Products, 2011

(-)-Strychnine, 12 steps, 6.4% overall yield.

(-)-Akuammicine, 10 steps, 10% overall yield.

(+)-Vincadifformine, 11 steps, 8.9% overall yield.

(+)-Aspidospermidine, 9 steps, 24% overall yield.

(-)-Kopsinine, 9 steps, 14% overall yield.

(-)-Kopsanone, 11 steps, 10% overall yield.

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MacMillan’s Synthesis

1. NaH, DMF, 0 °C; MeI
2. n-BuLi, DME, -40 °C;
   ZnCl₂, -78 °C to rt;
   XPhos precatalyst, vinyl iodide
   67%

MeO

10

NHBOc

MeO

NHBoc

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   ZnCl₂, -78 °C to rt;
   XPhos precatalyst, vinyl iodide
   67%

MeO

NHBoc

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MeO

NHBoc

1. NaH, DMF, 0 °C; MeI
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   ZnCl₂, -78 °C to rt;
   XPhos precatalyst, vinyl iodide
   67%
Enantioselective Organocatalytic Cascade

\[
\text{cat. 6} \quad \text{endo [4+2]}
\]

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

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

20 mol\% catalyst 6-HBF$_4$

\[
\begin{align*}
\text{MeO}_2C & \quad \text{C} \\
\text{C} & \quad \text{O}
\end{align*}
\]

MeO$_2$C

Boc

7

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MacMillan’s Synthesis Cont’d

1. TFA, rt
2. 4-(tert-Butylthio)but-2-ynal

1.2-Dichlorobenzene, 200 °C

84%
65%
51%
Mechanism of Single-Electron Mediated Cyclization

1,2-Dichlorobenzene, 200 °C

51%

13

14

5/31/2013
MacMillan’s Synthesis Cont’d

\[ \text{Pd/C, } H_2, \text{ THF, } -15 \, ^\circ C \rightarrow \text{80\%} \]

14

\[ \text{(-)-vincorine} \]
Conclusions

• 9 step, 9% overall yield, enantioselective synthesis.
• Stereoselective organocatalyzed Diels-Alder, iminium cyclization cascade sequence builds the tetracyclic core structure in one step.
• Seven member azepanyl ring constructed by single electron-mediated cyclization.