Total Synthesis of (±)-Maoecrystal V

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Introduction

• Isolated in 2004 from leaves of Chinese medicinal herb *Isodon eriocalyx*
• Novel C₁₉ deterpenoid
• Potent & selective against HeLA cells (IC₅₀ = 60 nm)
• Challenging structure, attracted much synthetic attention
• Pentacyclic framework with six stereocentres
• 4 contiguous quaternary stereocentres
Previous Approach - Baran

Previous Approach—Controversy


Synthetic Study toward the Total Synthesis of Maoecrystal V
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Received 25 June 2009.


A Synthesis of the Carbon Skeleton of Maoecrystal V
Paul J. Krawczuk, Niklas Schne and Phil S. Baran*
Received 24 August 2009.

“This paper reports an early approach to 1 pursued in our laboratory from November 2007 to May 2008.3

3) During this period, one of the corresponding authors of the preceding paper was employed as a postdoctoral associate (C.-C. Li) in this laboratory: This work was reported in an NIH proposal (received 8/11/2008 and reviewed on 10/9/2008 by the BCMB-B study section) and a final report to the DFG (submitted 7/17/2009).”
Previous Approach - Danishefsky

\[
\text{Cyclonexanone} + \text{4-Bromo-3-methoxyphenol} \rightarrow \text{Product after Pd(OAc)}_2\text{ and TMSCHN}_2\text{, TMEDA treatment}
\]

\[
\text{Li, NH}_3\text{ (L)} \rightarrow \text{Product after Meerwein-Ponndorf-Verley reduction}
\]

\[
\text{Sealed tube at 180 °C} \rightarrow \text{Product after TBAF treatment}
\]

Previous Approach - Nicolaou

\[
\text{Chem. Commun. 2009, 46, 70.}
\]
Previous Approach - Singh

1) Zn-NH₄Cl, H₂O, MeOH
   93%

2) Jones ox., H₂O, THF, 140 °C
   66%

aq. NaIO₄, CH₃CN, 0 °C - rt
40%

C₆H₄Cl₂, 140 °C
75%

H₂, Pd/C, EtOH
90%

Previous Approach - Thomson

![Chemical Reaction Scheme]

1) KOH, 2) Jones Ox. (86%)

1) HMDS/TMSI, m-CPBA
2) H₂, Pd/C (88%)

1) DIBAL-H
2) O₂N
(44% over 2 steps)

1) H₂O₂, MeOH
2) NaBH₄
(75% over 2 steps)

Org. Lett. 2010, 12, 3010.
Previous Approach - Trauner

Org. Lett. 2010, 12, 5656.
Retrosynthesis

Maoecrystal V

\[ \text{IMDA} \rightarrow \text{oxidative dearomatization} \]

\[ \text{Pb(OAc)}_3 \]

\[ \text{CO}_2\text{Me} \]
Model Studies

Synthesis of substrate

\[
\begin{align*}
\text{B(OH)}_2 + \text{Pb(OAc)}_4 + \text{Hg(OAc)}_2 & \rightarrow \text{Pb(OAc)}_3 \\
& \text{CHCl}_3, 60^\circ C \\
\text{MeO} & \rightarrow \text{MeO}
\end{align*}
\]

\[
\begin{align*}
\text{Py, CHCl}_3 \text{ then } H^+ & \rightarrow 70\% \\
\text{MeO} & \rightarrow \text{MeO}
\end{align*}
\]

\textit{Org. Lett. 1999, 1, 1867.}

1) TMSCI, imid.
CH\textsubscript{2}Cl\textsubscript{2}, 0 °C

2) DIBAL-H, CH\textsubscript{2}Cl\textsubscript{2}
-78 °C to rt
then 3M HCl
85% (2 steps)

\[
\begin{align*}
\text{HO} & \rightarrow \text{HO} \\
\text{EDCI, DMAP} & \rightarrow 70\%
\end{align*}
\]

\textit{Org. Lett. 2009, 11, 4770.}
Other isomer 65% (3 : 1)
(also for free OH, 68% (3.8 : 1)

Synthesis

\[ \text{MeO}_2\text{C} \rightarrow \text{dimethyl carbonate, NaH, THF, reflux} \rightarrow \text{MeO}_2\text{C} \]

\[ \text{Pb(OAc)}_3 \rightarrow \text{Py, CHCl}_3, 60 \, ^\circ\text{C} \rightarrow \text{MeO}_2\text{C} \]

\[ \text{LiAlH}_4, \text{THF, rt} \rightarrow \text{HO} \]

\[ \text{R}_3\text{BH, NaBH}_4/\text{LA} \rightarrow \text{MeO}_2\text{C} \]

\[ (\text{Bu}_4\text{N})\text{BH}_4, \text{MeOH, 40 } ^\circ\text{C} \rightarrow \text{MeO}_2\text{C} \]

\[ \text{LiAlH}_4, \text{THF, rt} \rightarrow \text{HO} \]

\[ \text{65\% (89\% brsm) single isomer} \]

\[ \text{84\% (dr 6 : 1)} \]
Synthesis

1) HO₂C=P(O)(OE)₂
EDCI, DMAP
CH₂Cl₂, rt, 82%

2) TsN₃, DBU
0 °C, 81%

Rh₂(OAc)₄
PhMe, reflux
60%

1) t-BuOK, (HCHO)ₙ
THF, 0 °C 95%

2) TFA, CH₂Cl₂
rt, 90%

Pb(OAc)₄, AcOH, 0 °C
then PhMe 145 °C, 24 h

28%

12%

36%
**Synthesis**

1. NBS, (PhCO₂)₂, CCl₄, reflux, 2h, 90%
2. Bu₃SnH, TEMPO, PhH, reflux, 2 h, 75%

1. Zn, AcOH, THF, H₂O, 70 °C, 2h, 85%
2. Sml₂, THF, MeOH 10 min, 88%

H₂, Lindlar cat. MeOH, THF, rt, 2h 92%

DMP, CH₂Cl₂, rt, 1 h, 88%

DBU, PhMe, 100 °C, 1 h 48% (90% brsm)

C16-epi-Maoecrystal V

Maoecrystal V
Summary

First reported total synthesis of Maoecrystal V

17 linear steps

Employs Wessely Oxidative dearomatisation, IMDA & Rh cat. O-H bond insertion