Total Synthesis of Sieboldine A

Denksport, 16.06.2011
Introduction:

- *Lycopodium* alkaloid
- isolated from the club moss *Lycopodium sieboldii*
- native in Japan
- structure elucidation in 2003 by Kobayashi *et al.*
- up to now 2 total synthesis published
  (Overman *et al.*, Tu *et al.*)

Sieboldine A
Biological activity:

- cytotoxicity against murine lymphoma L1210 cells (IC$_{50}$ 5.1 µg/mL)
- acetylcholinesterase inhibitor (IC$_{50}$ 2.0 µg/mL)
  comparable to huperzine A (IC$_{50}$ 1.6 µg/mL)
(huperzine A: clinical evaluation for treatment of Alzheimer’s disease and schizophrenia (NCT00083590))
Acetylcholinesterase:

... family of enzymes that catalyze the hydrolysis of acetylcholin

\[
\text{O} - \text{N}^+ + \text{H}_2\text{O} \rightarrow \text{OH} - \text{N}^+ + \text{AcOH}
\]

acetylcholin acts as neurotransmitter for the:

- PNS (peripheral nervous system)
- CNS (central nervous system)
Acetylcholinesterase

Mode of action: • PNS (peripheral nervous system)

- Acetylcholin binds to acetylcholine receptors on skeletal muscle fibers
- Ligand-gated sodium channels is opened
- Muscle contraction
- Acetylcholinesterase hydrolizes acetylcholin
- Muscle relaxation
Acetylcholinesterase

**Mode of action:**

- PNS (Peripheral Nervous System)

acetylcholin binds to acetylcholine receptors on skeletal muscle fibers

\[ \downarrow \]

ligand-gated sodium channels is opened

\[ \downarrow \]

muscle contraction

\[ \downarrow \]

Inhibition $\rightarrow$ muscle spasm, ultimately death

acetylcholinesterase hydrolizes acetylcholin

\[ \downarrow \]

muscle relaxation
Acetylcholinesterase

Acetylcholinesterase Inhibition:

**Sarin**
- Developed in the late 1930s
- Originally used as pesticides
- Extremely high toxicity
- Penetrates skin

**VX**
- Weapon of mass destruction:
- Developed in the late 1930s
- Originally used as pesticides
- Extremely high toxicity
- Penetrates skin
**Mode of action:**

- CNS (central nervous system)

- inhibition of AChE reduces memory deficits, if the cholinergic (acetylcholine-producing) system is damaged → application against Alzheimer disease

- important role in the enhancement of sensory perceptions

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**Sieboldine A**

**Huperzine A**
Sieboldine A

1st Total Synthesis by Overman et al.:
1st Total Synthesis by Overman et al.: 

\( \text{Sieboldine A} \)

Sieboldine A

Summary:

- 20 steps
- 3% overall yield

2nd Total Synthesis by Tu et al.:

???
Sieboldine A

A

N₂ \rightleftharpoons CO₂Et
BF₃*Et₂O
Et₂O, -30°C
55%

B

K₂CO₃ aq
THF, rfx
75%

C

NaBH₄, CeCl₃
MeOH, 0°C
quant.

D

Me₃Si(allyl),
BF₃*Et₂O
DCE, 60°C
75%

E

Ac₂O, Et₃N,
DMAP
DCM, RT
97%

F

tert-BuLi, CeCl₃
then B
Et₂O, -78°C

G

mCPBA,
NaHCO₃
DCM, 0°C
66% over 2 steps

H

BF₃*Et₂O
Et₂O, -30°C
45%

I

1) MOMCl, DIPEA,
TBAI
2) O₃
DCM
86% over 2 steps

J

Sml₂,
HMPA
THF, 0°C
60%

K

1) 6N HCl, THF
2) (Boc)₂O, Et₃N, MeOH
80% over 2 steps
Sieboldine A

K → TPAP, NMO, DCM, RT → L → TFA, DCM, RT → M

Alopecuridine

mCPBA, DCM, RT → N → HgO, MeOH, 35°C → O → Sieboldine

55% 96%

(not isolated)
Sieboldine A

\[
\text{O} \xrightarrow{\text{N}_2=\text{CO}_2\text{Et}} \text{BF}_3\cdot\text{EtO}_2 \xrightarrow{\text{EtO}_2, -30^\circ\text{C}} \text{55\%} \xrightarrow{\text{K}_2\text{CO}_3 \text{aq}} \xrightarrow{\text{THF, rfx}} \text{75\%} \]

(+/-) \xrightarrow{\text{NaBH}_4, \text{CeCl}_3, \text{MeOH, 0$^\circ$C}} \text{quant.} \xrightarrow{\text{Ac}_2\text{O, Et}_3\text{N, DMAP}} \xrightarrow{\text{DCM, RT}} \text{97\%} \xrightarrow{\text{Me}_3\text{Si(allyl), BF}_3\cdot\text{EtO}_2}} \xrightarrow{\text{DCE, 60$^\circ$C}} \text{75\%}

\text{tert-BuLi, CeCl}_3 \text{then B} \xrightarrow{\text{Et}_2\text{O, -78$^\circ$C}} \text{66\% over 2 steps}

\text{mCPBA, NaHCO}_3 \xrightarrow{\text{DCM, 0$^\circ$C}} \text{60\%}

\text{1) MOMCl, DIPEA, TBAI} \xrightarrow{\text{O}_3} \xrightarrow{\text{DCM}} \text{86\% over 2 steps}

\text{1) 6N HCl, THF} \xrightarrow{\text{2) (Boc)_2O, Et}_3\text{N, MeOH}} \text{80\% over 2 steps}
Sieboldine A

\[
\begin{align*}
\text{HO} & \quad \text{NBoc} \\
& \xrightarrow{\text{TPAP, NMO}} \\
& \quad \text{NBoc} \\
& \xrightarrow{\text{TFA}} \\
& \quad \text{N}\text{H} \\
\end{align*}
\] 96%

Alopecuridine

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
& \xrightarrow{\text{mCPBA, DCM}} \\
& \quad \text{NOH} \\
& \xrightarrow{\text{HgO, MeOH, 35°C}} \\
& \quad \text{N}\text{O}^- \\
\end{align*}
\]
(not isolated)

60% over 2 steps

Sieboldine