Approaches to the Total Synthesis of the Manzamine Alkaloids

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Leading References:
Manzamine A: Discovery and Structural Elucidation


• Structure of manzamine A was assigned by X-ray crystal analysis of the hydrochloride salt.

• Manzamine A shown to have significant in vitro activity, with an IC$_{50}$ of 0.07 µg/mL against P388 mouse leukaemia cells.

• Subsequently, many cogeners of the manzamine family of alkaloids have been isolated (Magnier et al, Tetrahedron 1998, 54, 6201).

• ".....the structure of manzamine A hydrochloride is unprecedented in nature. Moreover, its provenance is problematic as there appears to be no obvious biogenetic pathway..." Higa (1986)

The Manzamine Family of Alkaloids: Representative Members

Manzamine C

Manzamine A

Manzamine B

Ircinal A

ent-Ircinol A? (absolute configuration not unambiguously assigned yet)

Keramaphidin B (isolated as a racemic mixture)

Kauluamine

Magnier et al, Tetrahedron 1998, 54, 6201
Biosynthesis of Manzamine C


- Despite the rather simple structure, some biological activity is retained in this molecule.

- For total syntheses, see:
  - Nakagawa et al, Tetrahedron 1991, 47, 8067
Manzamine B Biosynthesis

Manzamine Biosynthesis: Both Antipodes Produced by Nature?

- (-) Keramaphidin B
- Ircinal A, B
- Manzamine A, B
- Ircinol A, B???
- (+) Keramaphidin B
**Baldwin: A Biomimetic Approach**

- **1.** $\text{Ph}_3\text{P} \rightarrow \text{KHDM}\text{S} \rightarrow \text{PH}_3\text{P}$
- **2.** $\text{TsCl, Et}_3\text{N, CH}_2\text{Cl}_2, 95\%$

- **1.** $\text{NaI, Butanone}$
- **2.** $\text{NaBH}_4, \text{MeOH}$
  - 56\% (two steps)

- **1.** $\text{m-CPBA, CH}_2\text{Cl}_2$
  - 98\%
- **2.** $\text{TFAA, CH}_2\text{Cl}_2$
  - 100\%

- **MeOH, aq. TRIS buffer (1:1), pH = 7.3**
- **then**
- **NaBH}_4, \text{MeOH}$
  - 0.2-0.3\%

**TRIS = tris(hydroxymethyl)aminomethane**

- **(±) Keramiphidin B**


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**Note:** The image contains chemical structures and reactions, along with a diagram illustrating the synthetic process. The text explains the steps involved in the synthesis of the compound, highlighting key reagents and yields at each step. The final structure is labeled as (±) Keramiphidin B.
Hart: Radical Cyclization Approach Towards the ABC Core

\[
\text{HO}_2\text{C} \xrightarrow{\text{Li, NH}_3} \text{HO} \xrightarrow{\text{Et}_3\text{N}, \text{PhO}^+\text{P}^\text{N}_3} \text{SePh} \\
\text{Br} \quad \text{OMe} \quad \text{PhO} \quad \text{N}_3 \quad \text{PhO} \quad \text{95\%} \quad \text{87\% (two steps)} \\
\text{HN} \xrightarrow{\text{SePh}} \text{Ac} \xrightarrow{\text{Bu}_3\text{SnH, AIBN}} \text{Me} \\
\text{NH} \xrightarrow{\text{I}_2, \text{K}_2\text{CO}_3} \text{NCO}_2\text{Et} \\
\text{I} \xrightarrow{\text{DBU}} \text{Ac} \\
\text{NHCO}_2\text{Et} \\
\text{H} \xrightarrow{\text{Ph}_3\text{P, H}_2\text{O, THF}} \text{Ac} \\
\text{2) ClCO}_2\text{Et, Et}_3\text{N} \\
\text{70\% (two steps)} \\
\text{H} \xrightarrow{\text{I}_2, \text{K}_2\text{CO}_3} \text{NCO}_2\text{Et} \\
\text{H} \xrightarrow{\text{DBU}} \text{Ac} \\
\text{Hart et al, Tetrahedron Lett., 1989, 30, 2611} \]
Pandit: Synthesis of the ABC Core

Pandit: Synthesis of the ABC Core

1. **BnNH₂**
   2. CbzCl, NaHCO₃
   88% (two steps)

1. O₃, then Zn, HOAc
   2. Ph₃P=CO₂Me
   76% (two steps)

HBr, HOAc
92%

HBr, HOAc
92%

BnNH₂
88% (two steps)

Ph₃PCO₂Me
76% (two steps)

OsO₄, py.

p-TsOH, benzene
78% (2 steps)

1. OsO₄, py.
2. p-TsOH, benzene
78% (2 steps)

Pandit's Synthesis of the ABCD System


1. LiBH₄
2. TBDPSCI, Im, DMF
70% (two steps)

1. Li/NH₃, Bn₂O quench
2. I
KOH, DMSO
77% (two steps??)

1. 9-BBN, then H₂O₂
2. Dess-Martin
3. Ph₃P=CH₂
48% (three steps)

1. 1 equiv.
Pd₆-benzene
5 days
30%
(selectivity ???)

Leonard : A Sulfolene-based Diels-Alder

For synthesis, see:
McIntosh et al,
**Leonard : A Sulfolene-based Diels-Alder**


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**Diagram:**

- LiBHEt₃, THF then MsCl, Et₃N → 82% (one pot)
- Toluene, ↑↓, 72h → 82%
- "one isomer" (Diels-Alder is slow step)

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**Structure:**

- Epimeric product
- Undesired product

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Notes:

- Reaction details and product structures are shown in the diagram.
- The synthesis involves a Diels-Alder reaction followed by further transformations to yield the target compound.
- The undesired product is formed during the synthesis.

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References:

Nagakawa: An Intermolecular Diels-Alder Approach

1. LiHDMS, THF, -60 °C
2. Bu3SnH, AIBN
   benzene, ↑↓
   80% (two steps)

1. PhSSPh, KHDMS, THF, -30 °C
2. m-CPBA, CH2Cl2
   77% (two steps)

45% (two steps) (desired diastereomer)
40% (two steps) (undesired diastereomer)

Nagakawa et al., Tetrahedron Lett. 1999, 40, 113
Nagakawa: Further Elaboration Towards the ABCD Ring System

PhO2SN O

1N HCl
THF, ↑↓

PhO2SN O

1N HCl (yield??)

PhO2SN

1. TBDPSCI, Im, DMF
2. HO-CHO

p-TsOH, benzene, ↑↓
83% (two steps)

1. Na, naphthalene
DME, -65 °C
2. Boc2O, NaOH
92% (two steps)

Na, anthracene
DME, -65 °C
94%

1. TBAF, THF
2. Dess-Martin oxidation
96% (two steps)

HN CO2K

toluene

(E:Z 1:5)

HN O

1. TFA, CH2Cl2
2. BOP-Cl, Et3N, CH2Cl2
32% (three steps)

OHC

Nagakawa et al, Tetrahedron Lett. 1999, 40, 113
Overman: Mannich Ring Closure Approach

from D-(-) quinic acid

88% "stereoselective"

"one isomer"

"axial addition of imminium favored stereoelectronically"

Overman : Mannich Ring Closure Approach

1. MMPP, MeOH, 23 °C
2. CSA, CHCl₃, 50 °C
59% (two steps)

(BnOCH₂)₂CuLi, TMSCl, THF
-78 °C → 0 °C
Pd(OAc)₂, MeCN, 80 °C
55% (one pot)

1. BCl₃, -78 °C → 0 °C
then MeOH
-78 °C → 0 °C
2. Dess-Martin oxidation
65% (two steps)

• Addition of β-carboline unit directly was unsuccessful.
• 2-naphthyl and 2-pyridyl cuprates also reacted with similar yields.

Hart's Synthesis of the ABCE Ring System

1. Li, NH₃, Br⁻, OMe
2. Et₃N, PhO⁺, P₅N₃⁻, pyrrolidine
3. I₂, THF, H₂O
70% (three steps)

1. PMBNHMgBr
2. Ac₂O, DMAP, Py
91% (two steps)

1. cat. OsO₄, NaIO₄
2. NaBH₃CN, TFA
65% (two steps)

1. BBr₃
2. Swern oxidation
77% (two steps)

1. Pd/BaSO₄, Py, H₂
100%

Hart's Synthesis of the ABCE Ring System

1. HN(SES)CO\textsubscript{2}tBu, Ph\textsubscript{3}P, DEAD
2. CH\textsubscript{3}SiCl\textsubscript{3}, NaI, CH\textsubscript{3}CN
3. TsCl, Et\textsubscript{3}N, DMAP, CH\textsubscript{2}Cl\textsubscript{2}

74% (three steps)

Mistusobu proceeds with retention at C\textsubscript{38}.


KH, TBAI
18-crown-6 toluene, ↑↓
(0.005M)
91%

1. LiOH
2. VO(acac\textsubscript{2}), tBuOOH, ∆

diastereoselectivity??
64% (two steps)

Brands et al., Tetrahedron Lett. 1998, 39, 1677
Coldham: An Azamethine Ylide Cycloaddition Approach

three steps, 55% from 2-arecoline

LiAlH₄ (THF, 0 °C) 85%

1. CBr₄, Ph₃P, CH₂Cl₂
2. NaI, acetone 96% (two steps)

EtO₂C

n-BuLi, THF, HMPA

-78 °C -> RT 82%

OEt

NHMe

• HCl

iPr₂NEt, toluene, Δ 45%

“one diastereomer”

Yamamura's Synthesis of the ABCE System

\[
\text{[Structural diagram showing the synthesis and products as per the text]}\]

Yamamura et al., *Tetrahedron* 1998, 54, 8691
Yamamura's Synthesis of the ABCE System

1. OsO₄, NMO
2. NaIO₄, THF
3. NaBH₄, MeOH
4. MOMCl, iPr₂NEt
65% (five steps)

1. 2N LiOH, MeOH
2. PCC, NaOAc, CH₂Cl₂
3. CSA, CHCl₃

1. OsO₄, NMO
2. CSA, CHCl₃
36% (five steps)

1. BH₃•SMe₂, THF, 0 °C then H₂O₂, NaOH
2. Swern Oxidation
3. Ph₃P = OTBDPS
THF, -78 °C
66% (three steps), E:Z??

Yamamura et al, Tetrahedron 1998, 54, 8691
Yamamura's Synthesis of the ABCE System

Yamamura et al., Tetrahedron 1998, 54, 8691
**Winkler : Synthesis of AE Precursor**

1. **Step 1:**
   - **Starting Material:** 
     - 
   - **Conversion:** 
     - LDA, LiCl, THF
   - **Product:** 
   - **Yield:** 87% (two steps)
   - **Remarks:** diastereoselectivity??

2. **Step 2:**
   - **Starting Material:** 
     - 
   - **Conversion:** 
     - NaOH, MeOH
   - **Product:** 
   - **Yield:** 71% (two steps)

3. **Step 3:**
   - **Starting Material:** 
     - 
   - **Conversion:** 
     - EtOCOCl, NMM, HN(Me)OMe•HCl, CH₂Cl₂
   - **Product:** 
   - **Yield:**

4. **Step 4:**
   - **Starting Material:** 
     - 
   - **Conversion:** 
     - PPTS, MeOH, 98%
   - **Product:** 
   - **Yield:** 88%

5. **Step 5:**
   - **Starting Material:** 
     - 
   - **Conversion:** 
     - NaH, THF, 79%
   - **Product:** 
   - **Yield:**

6. **Step 6:**
   - **Starting Material:** 
     - 
   - **Conversion:** 
     - (Ph₃P)₄Pd, dimedone, 90%
   - **Product:** 

**References:**
Winkler : Synthesis of ABCE Ring System

\[
\begin{align*}
\text{BocN} & \quad \text{BocN} \\
\text{H} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{99%} & \\
\end{align*}
\]

\[ \text{[2+2]} \]

\text{hv}

\text{one isomer}

\text{BocN}

\text{BocN}

\text{AcOH, Py}

\text{20%}

\text{20%}

\text{20%}

\text{20%}

\text{C}_{12} \text{ stereochemistry not assigned}

\text{Winkler et al, J. Am. Chem. Soc. 1998, 120, 25, 6425}

\text{MM2 calculations show that the C}_{32}-C_{33} \text{ olefin is crucial for observed [2+2] diastereoselectivity. See : Winkler et al, Tetrahedron 1998, 54, 7045}
Winkler : Elaboration of ABCE Tetracycle

1. TBSCI, 87%
2. LiHDMS, MeOCOCN, 90%
"one isomer"

1. NaBH₄, 93%
2. MsCl, Et₃N, 95%
3. DBU, Benzene, 90%

LiTMP, PhSeCl
40%

H₂O₂, Py, 48%

Winkler: Completion of Synthesis

1. TBAF, 94%
2. TsCl, Et₃N, 96%

Note: cyclization of the corresponding C₁₅⁻C₁₆ alkyne proceeded in 89% yield

1. TFA, 100%
2. ³Pr₂NET, 12%

1. DIBAL-H, 83%
2. Dess-Martin oxidation, 90%

Martin: Diels-Alder Approach to the ABC Core

Three steps, 71% from methyl pyro-D-glutamate

Martin et al, J. Am. Chem. Soc. 1999, 121, 866
Martin : Elaboration of ABC Core

\[
\begin{align*}
\text{R} &= \text{TBDPSO(CH}_2\text{)}_5 \\
\text{1. DMSO, (COCl}_2, \text{Et}_3\text{N} & \quad 47\% \text{ (three steps)} \\
\text{2. Ph}_3\text{P} = \text{CH}_2 & \\
\text{1. excess DIBAL-H} \quad \text{53}\% \text{ (two steps)} \\
\text{2. Dess-Martin oxidation} & \\
\text{MeOH} & \quad \text{55}\% \text{ (two steps)} \\
-78 \, ^\circ\text{C} \rightarrow \text{RT} & \quad \text{"stereoselective"}
\end{align*}
\]

Martin: Completion of Synthesis

![Chemical Structures and Reactions]

1. DIBAL-H
2. Dess-Martin
56% (two steps)

1. KOH, MeOH, \(\Delta\)
2. Et\(_3\)N, \(\text{CH}_2\text{Cl}_2\)
75% (two steps)

1. Cl\(_2\)Ru(Cy)\(_3\)
2. Et\(_3\)N,
0.005M in CH\(_2\)Cl\(_2\)
67%
E:Z 1:8

1. Cl\(_2\)Ru(Cy)\(_3\)
2. Et\(_3\)N, \(\text{CH}_2\text{Cl}_2\)
0.004M in benzene
the 1N HCl
26%

Manzamine A

Martin et al, J. Am. Chem. Soc. 1999, 121, 866
Summary: Where They Left Off........

Pandit :

Hart :

Brands :

Leonard :

Nagakawa :

Coldham :

Overman :

Yammamura :

Scorecard:

Winkler, Martin :

Winkler      35 steps (longest linear)                      0.020% overall (89% per step)
Martin        23 steps (longest linear)                      0.061% overall (88% per step)