Total Synthesis of Manzamine A and related Alkaloids

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Outline

- Isolation, structure and biological activity
- The family of manzamine alkaloids
- Biosynthesis proposal
- Previous synthesis
- Synthesis of the Dixon group
- Conclusion
Isolation, Structure and biological activity

- Manzamine A was discovered in the sponge *Haliclona* occurring in the Okinawan sea

- Pentacyclic core comprising 6-, 6-, 5-, 13- and 8-membered rings, two Z-olefins, two tertiary amines and five stereocenters

- It shows insecticidal, anti-bacterial, anti-inflammatory, anti-cancer and anti-malarial activity.

The family of Manzamine Alkaloids

Biosynthesis proposal of Manzamine Alkaloids

Biosynthesis proposal of Manzamine Alkaloids

Previous synthesis

Previous synthesis

The total synthesis of Dixon’s group
The total synthesis of Dixon’s group

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\begin{align*}
8 & \xrightarrow{a} 9 \xrightarrow{b} 10 \\
6 & \xrightarrow{e} 12 \xleftarrow{d} 11
\end{align*}
\]

Reagents and conditions: (a) KOAc, Aliquat 336, 120 °C, 16 h; (b) K₂CO₃, MeOH, RT, 1 h, 49% (84% brs) (over two steps); (c) COCl₂, DMSO, Et₃N, CH₂Cl₂, −78 °C to RT, 0.5 h; (d) CH₃NO₂, EtOH, 0 °C, 2 h, 90% (over two steps); (e) MsCl, Et₃N, CH₂Cl₂, −15 °C to RT, 15 min, 90%.
The total synthesis of Dixon’s group

Reagents and conditions: (a) KHMDS, 18-crown-6, -94 °C, THF, 1 h, 65% of 5, 21% of minor isomer 5’.
Nitro-Mannich/Lactamization cascade

The total synthesis of Dixon’s group

(a) CH₂O, hex-5-en-1-amine, MeOH, reflux, 10 h, 88%
(b) AIBN, Bu₃SnH, toluene, reflux, 30 min, 77%
(c) TMSCl, KI, 4 Å MS, MeCN, RT, 50 min, 81%
(d) AgNO₂, Et₂O, RT, 48 h, 63%
(e) DIBAL, toluene, -78 to -20 °C, 1 h, 74%
The total synthesis of Dixon’s group

(f) Ti(OiPr)$_4$, Ph$_2$SiH$_2$, hexane, 0°C, 2 h, 81% (dr 83:17)
(g) TiCl$_3$, THF, water, RT, 5 h, 56% of 3, 21% of 20
(h) 3-butenylmagnesium bromide, THF, CeCl$_3$, 0°C, 0.5 h then HCl, 40 h, RT, 91%
(i) TMSOTf, Et$_3$N, Et$_2$O, RT, 30 min, 72%
(j) Commins’ reagent, KHMDS, THF, -78°C, 20 min, 90%
(k) Grubbs’ first-generation catalyst (20 mol %), DCM, reflux, 3 h, 73%, 70:30 Z/E
The total synthesis of Dixon’s group

Reagents and conditions: (a) Pd(PPh₃)₄ (12 mol %), 29, DMF, 60 °C, 1 h, 52%; (b) Pd(OAc)₂ (18 mol %), PPh₃ (40 mol %), CO, Et₃N, MeOH, DMF, 60 °C, 1 h, 78%; (c) DIBAL, toluene, −78 °C, 2 h, 82%; (d) Pd(PPh₃)₄ (10 mol %), CO, LiCl, Bu₃SnH, toluene, 50 °C, 30 min, 58%.
Conclusion

- Development of a short and stereoselective synthesis of manzamine A (18 steps longest linear sequence).

- Overall yield of 0.73% for manzamine A

- Late stage synthesis of the 13-membered ring by ring closure methathesis.

- Introduction of the β-carboline by cross-coupling strategy.

- Key late stage enol triflate intermediate enables the synthesis of different family members of manzamine alkaloids.
Thank you for your attention
Nef reaction

Previous synthesis

Previous synthesis

Previous synthesis


\textsuperscript{a} Reaction conditions: (a) tryptamine·TFA, CH\textsubscript{2}Cl\textsubscript{2}, MS3A, rt. (b) TFA, CH\textsubscript{2}Cl\textsubscript{2}, rt. (c) DDQ, CH\textsubscript{2}Cl\textsubscript{2}/benzene, rt, 75\% (three steps).