Christian Gloor
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Total Synthesis of Manzamine A and related Alkaloids

Pavol Jakubec, Alison Hawkins, Wolfgang Felzmann, Darren J. Dixon

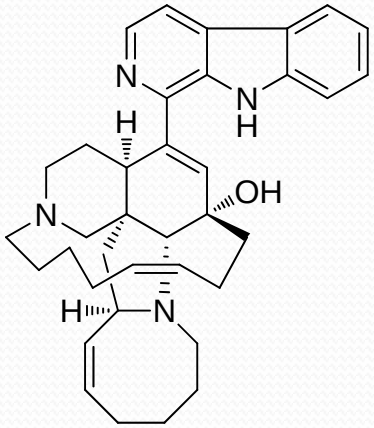
JACS **2012**, *134*, 17482-17485

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

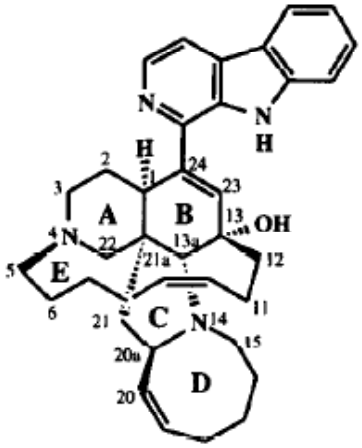


- Pentacyclic core comprising 6-, 6-, 5-, 13- and 8-membered rings, two *Z*-olefins, two tertiary amines and five stereocenters

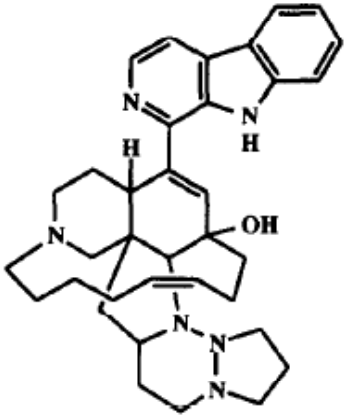
- It shows insecticidal, anti-bacterial, anti-inflammatory, anti-cancer and anti-malarial activity.

Sakai, R.; Higa, T. *J. Am. Chem. Soc.* **1986**, *108*, 6404

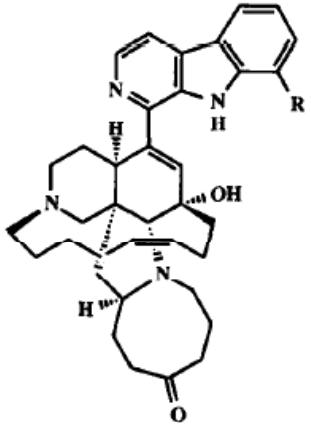
The family of Manzamine Alkaloids



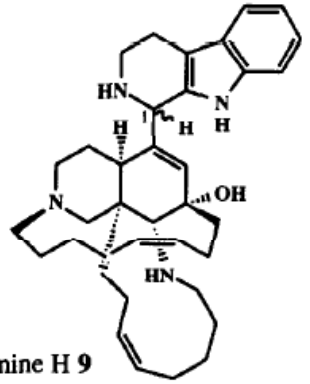
manzamine A **1**
(keramamine A)



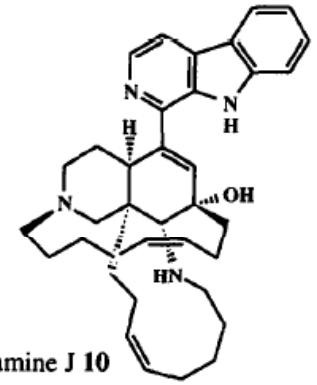
keramamine B **2**
(proposed structure)



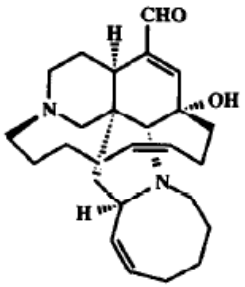
R= H : manzamine E **5**
R= OH : manzamine F **6**
(revised structure for **2**)



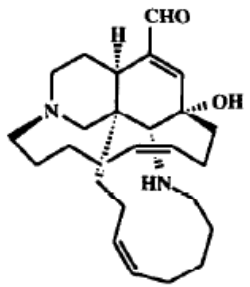
manzamine H **9**



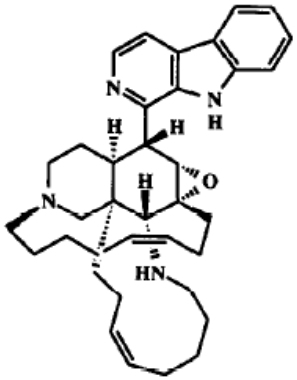
manzamine J **10**



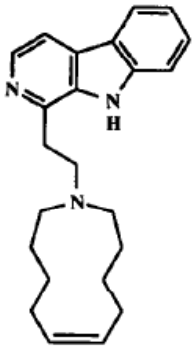
ircinal A **7**



ircinal B **8**



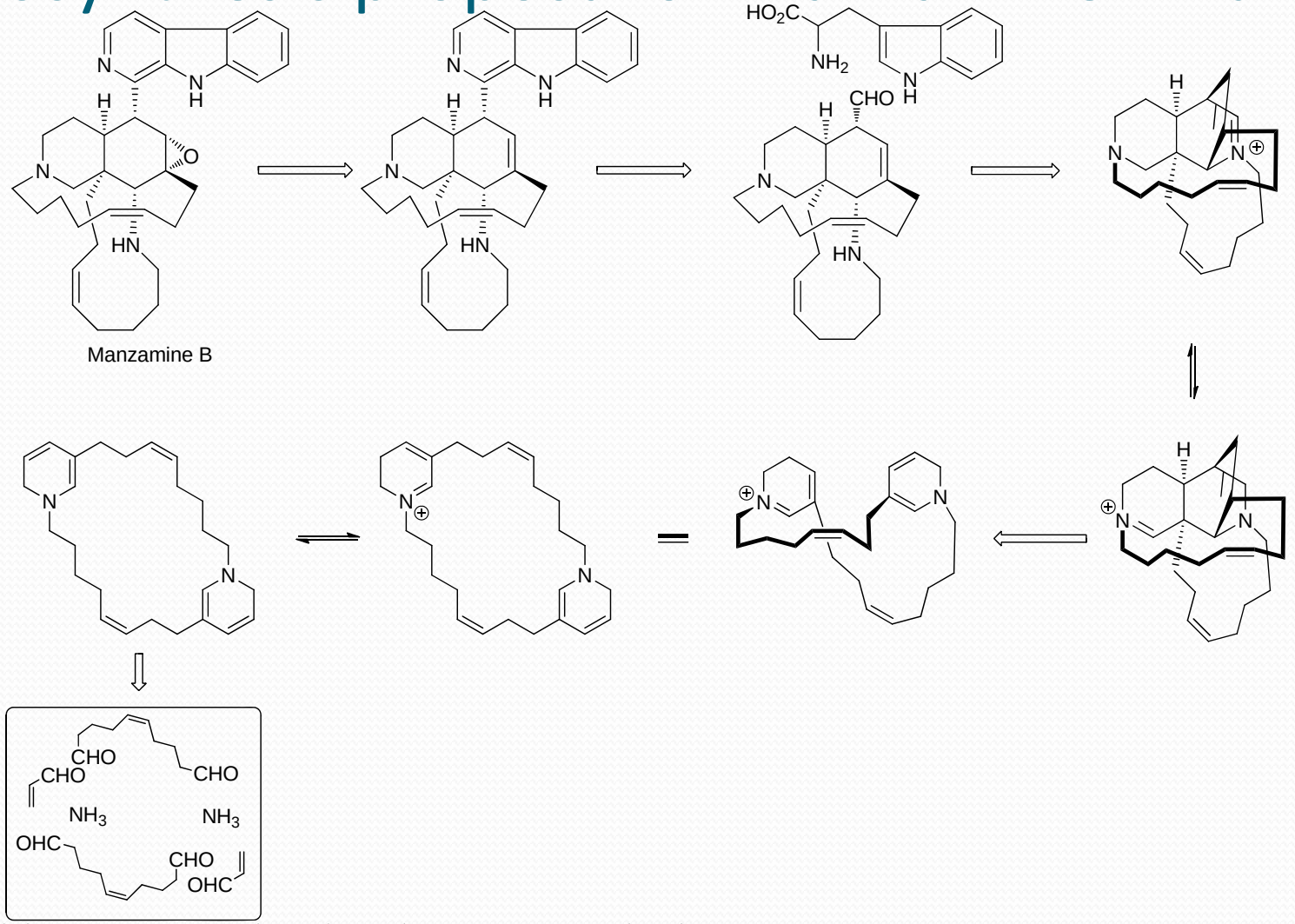
manzamine B **3**



manzamine C **4**

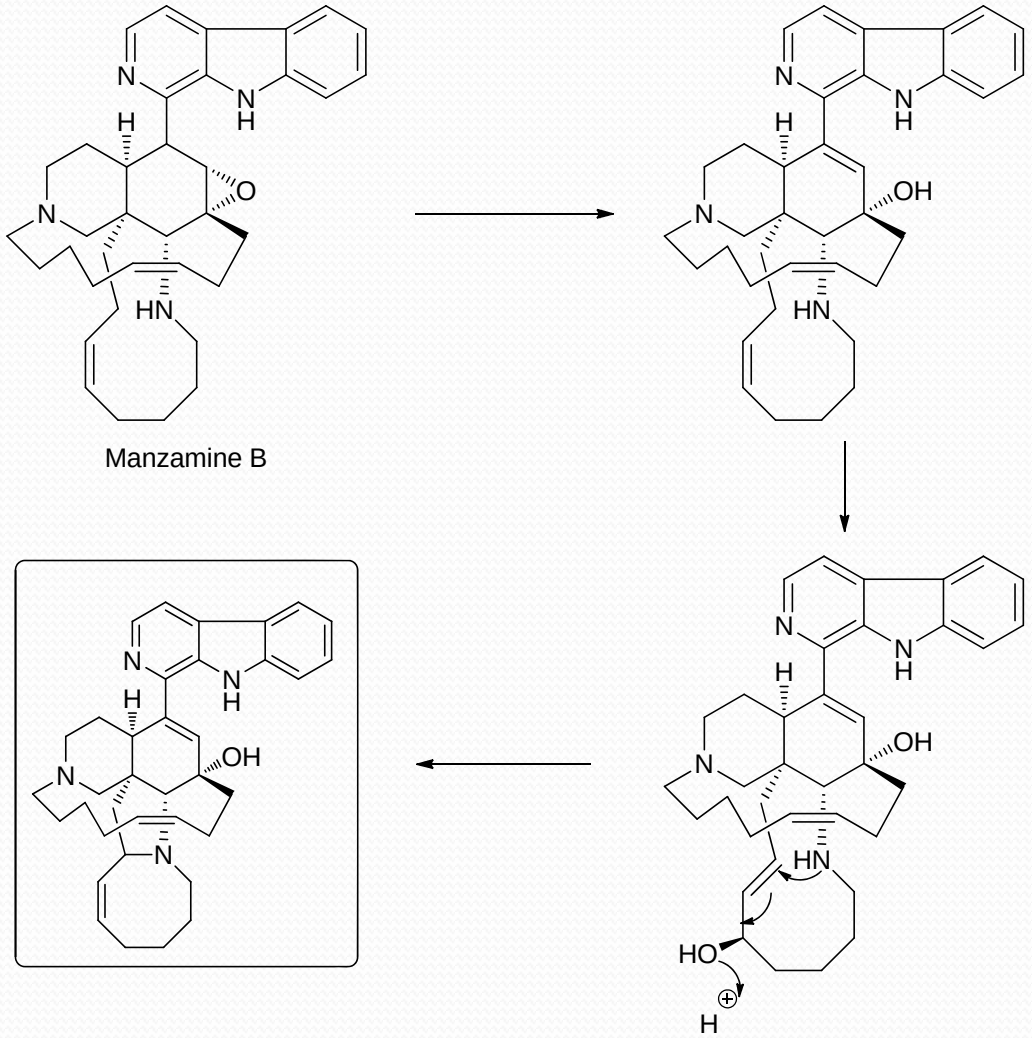
Magnier, E.; Langois, Y. *Tetrahedron* **1998**, *54*, 6201

Biosynthesis proposal of Manzamine Alkaloids



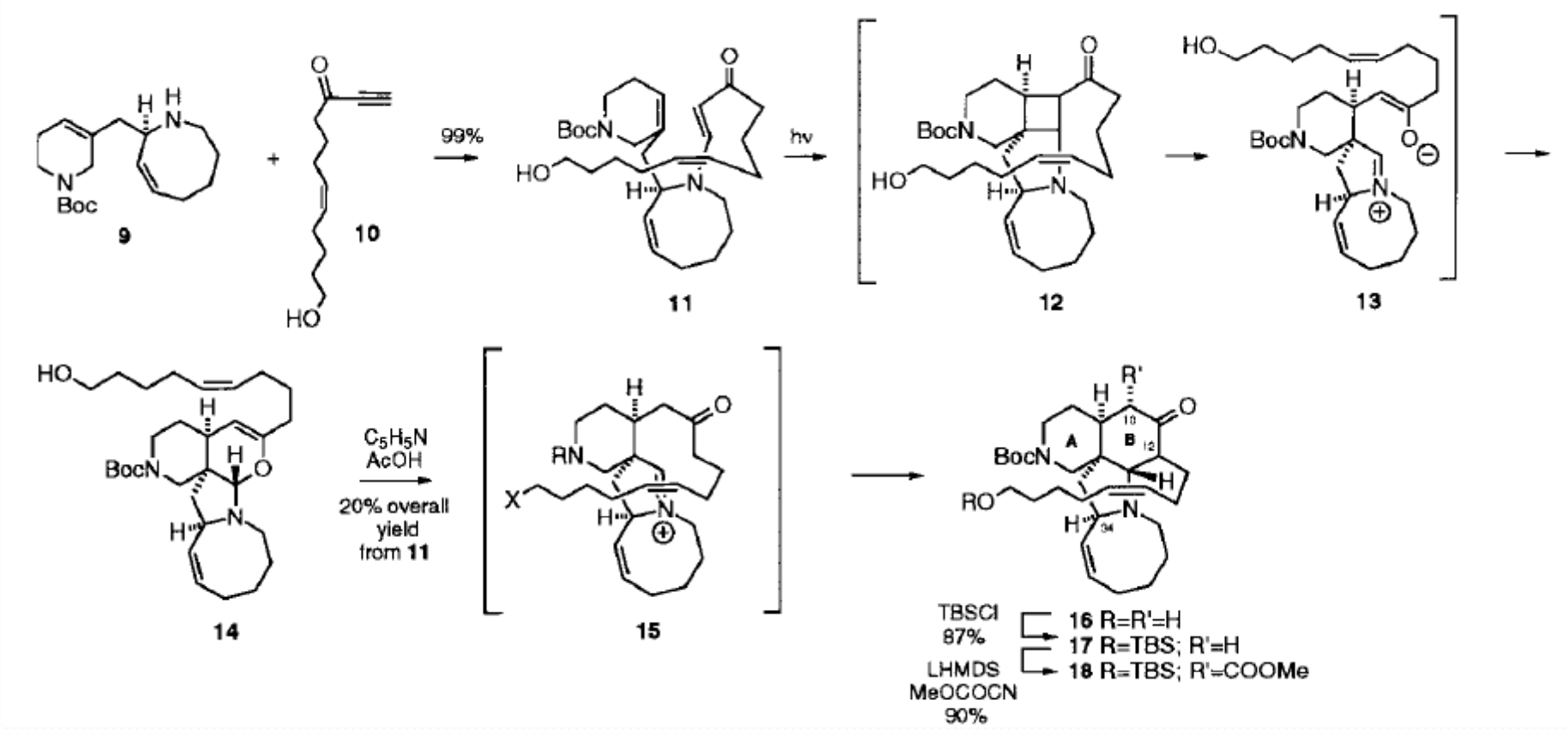
Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, 5, 2059

Biosynthesis proposal of Manzamine Alkaloids



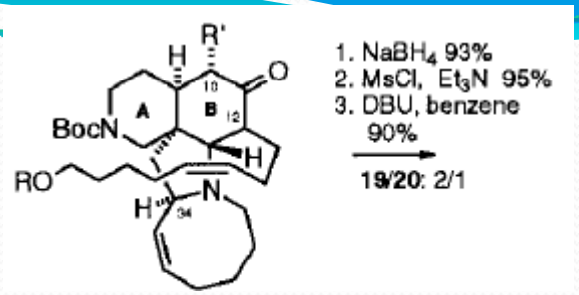
Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, 5, 2059

Previous synthesis

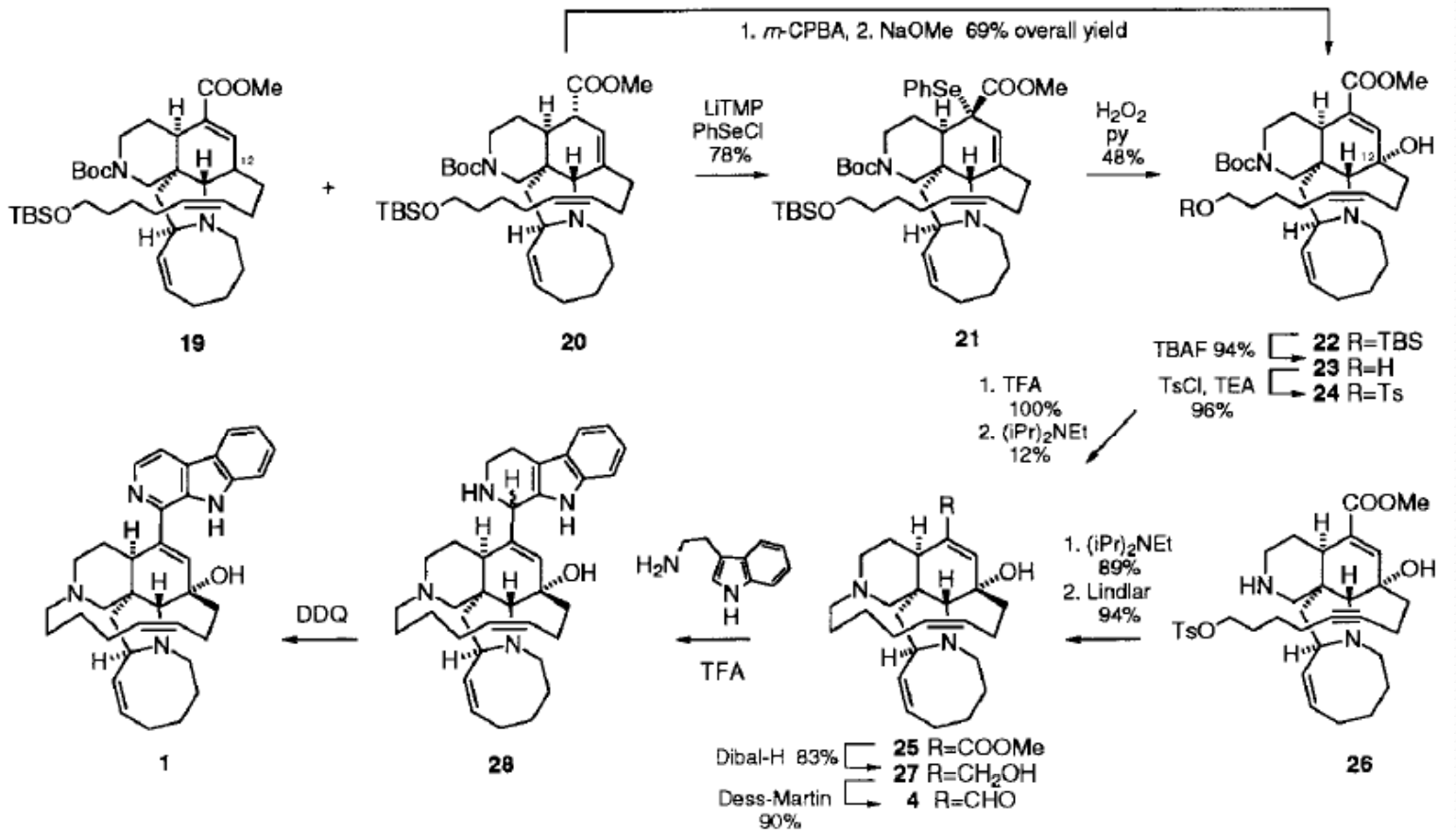


Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425

Previous synthesis

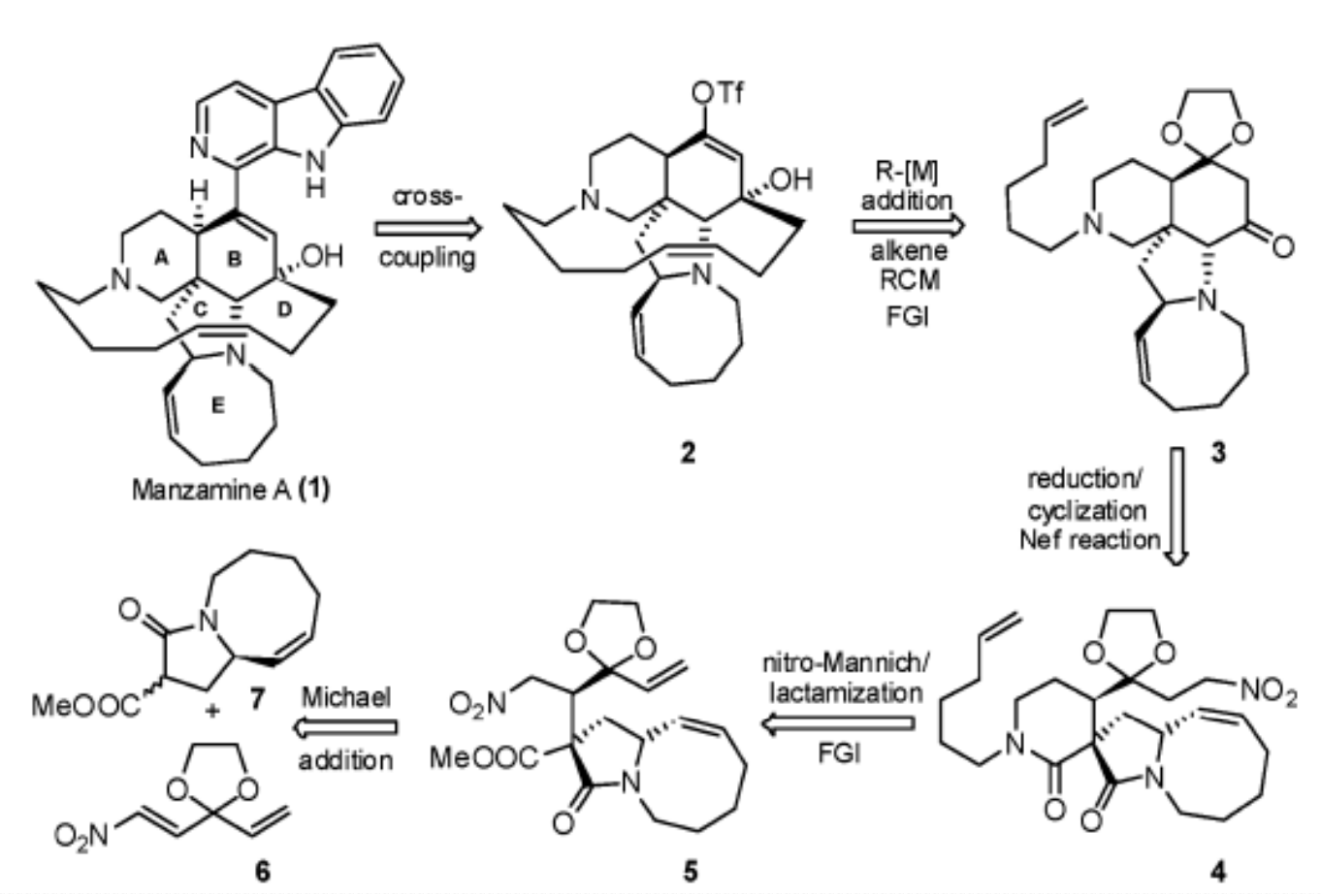


R=TBS; R'=COOMe

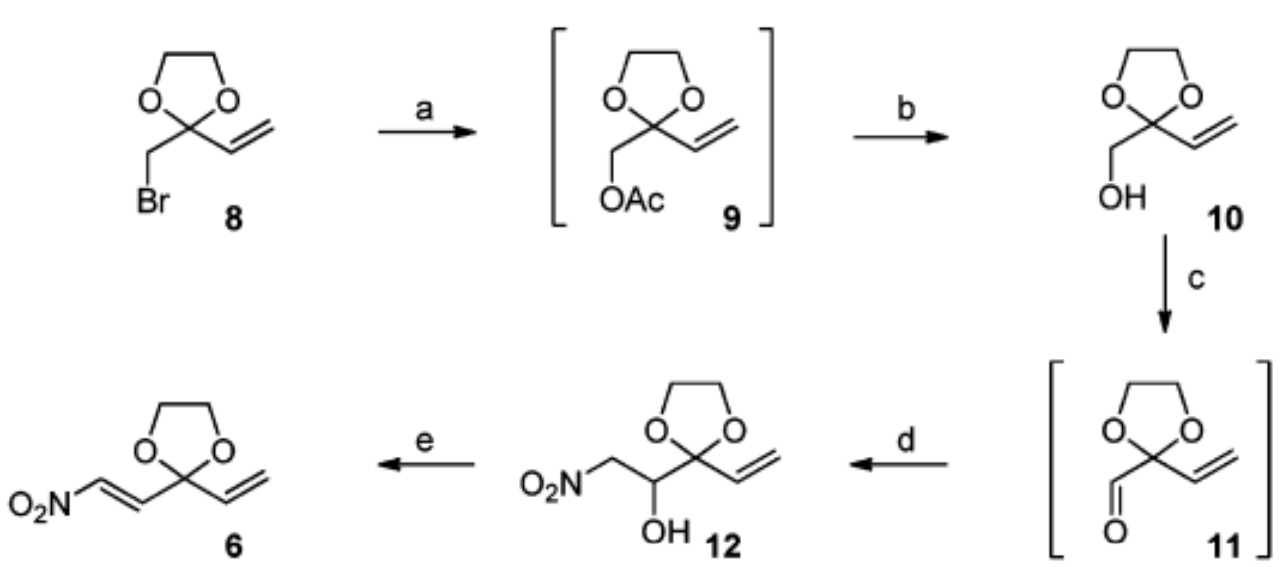


Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425

The total synthesis of Dixon's group

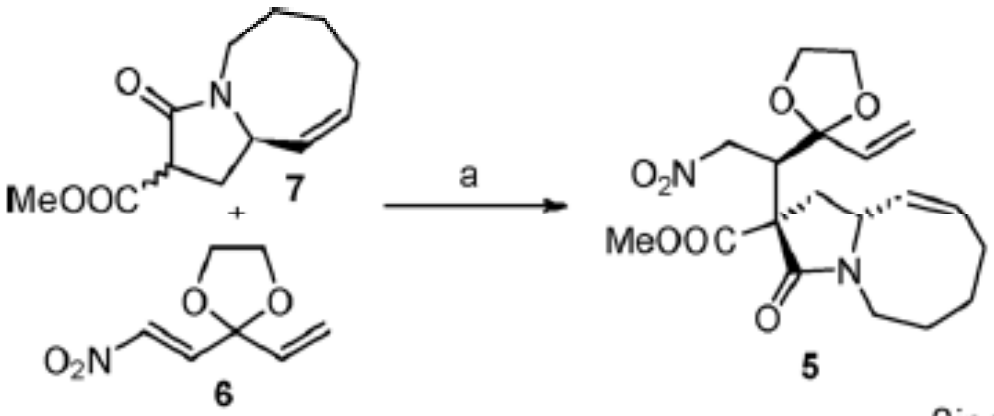


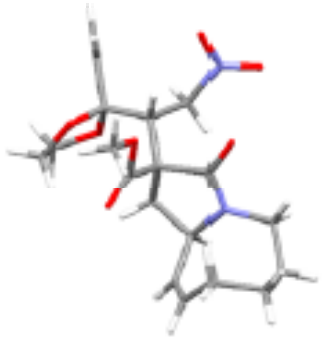
The total synthesis of Dixon's group



[a]Reagents and conditions: (a) KOAc, Aliquat 336, 120 °C, 16 h; (b) K_2CO_3, MeOH, RT, 1 h, 49% (84% brs) (over two steps); (c) $COCl_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to RT, 0.5 h; (d) CH_3NO_2, EtOH, 0 °C, 2 h, 90% (over two steps); (e) MsCl, Et_3N, CH_2Cl_2, −15 °C to RT, 15 min, 90%.

The total synthesis of Dixon's group

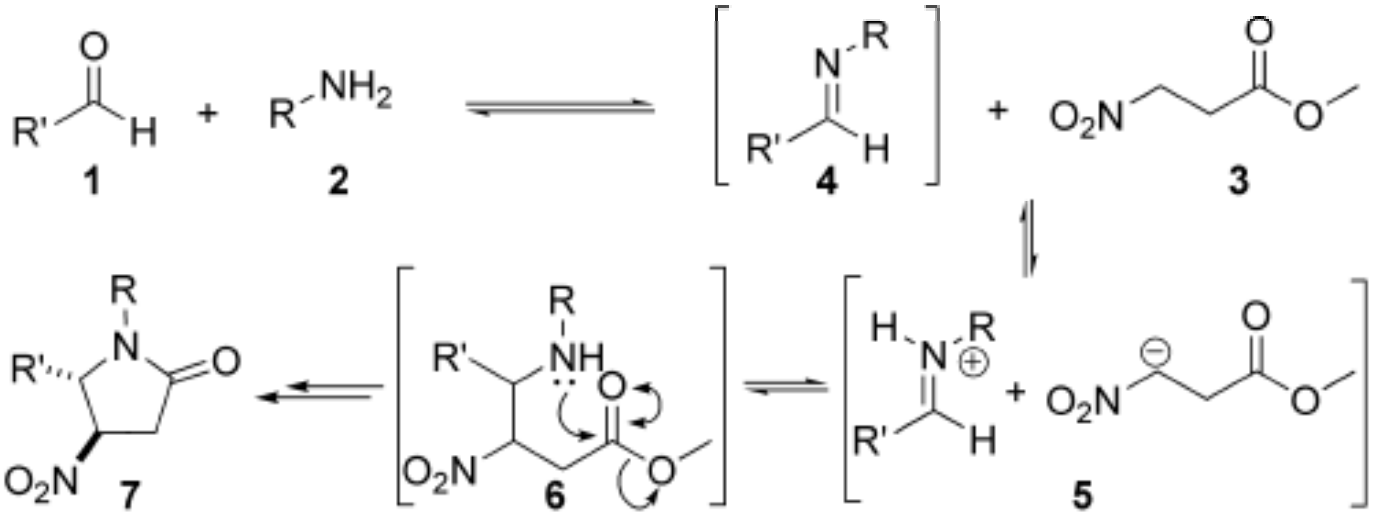




Single crystal X-ray analysis of **5**

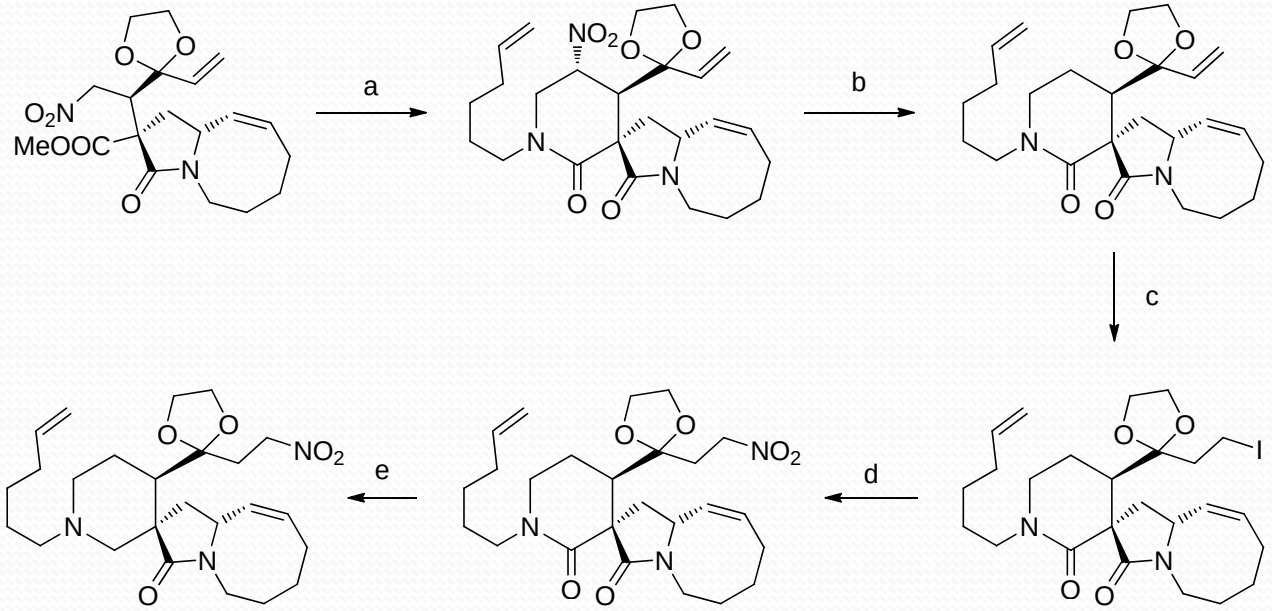
[a]Reagents and conditions: (a) KHMDS, 18-crown-6, −94 °C, THF, 1 h, 65% of 5, 21% of minor isomer 5′.

Nitro-Mannich/Lactamization cascade



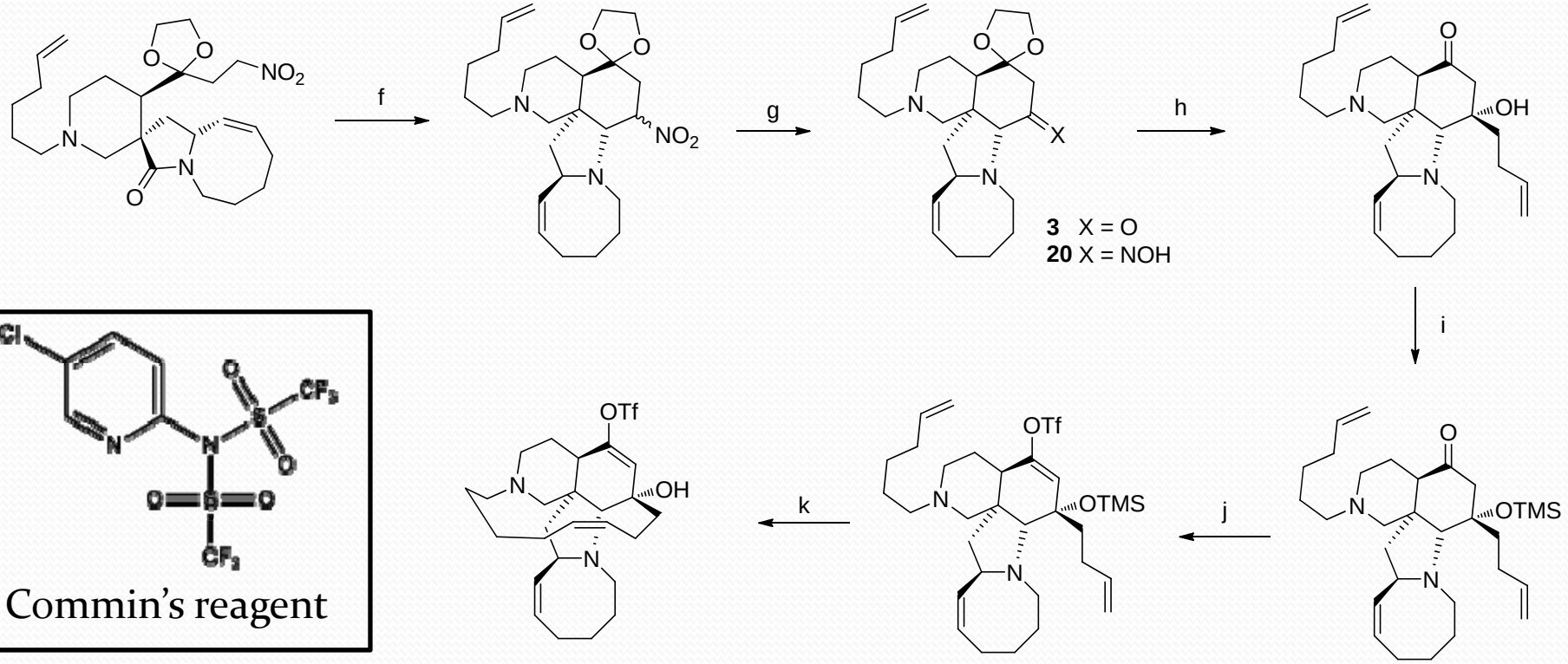
Dixon D. J. et al. *Org. Lett.* **2009**, *11*, 4512

The total synthesis of Dixon's group



(a) CH_2O, hex-5-en-1-amine, MeOH, reflux, 10 h, 88%
(b) AIBN, Bu_3SnH, toluene, reflux, 30 min, 77%
(c) TMSCl, KI, 4 Å MS, MeCN, RT, 50 min, 81%
(d) $AgNO_2$, Et_2O, RT, 48 h, 63%
(e) DIBAL, toluene, -78 to -20 °C, 1 h, 74%

The total synthesis of Dixon's group

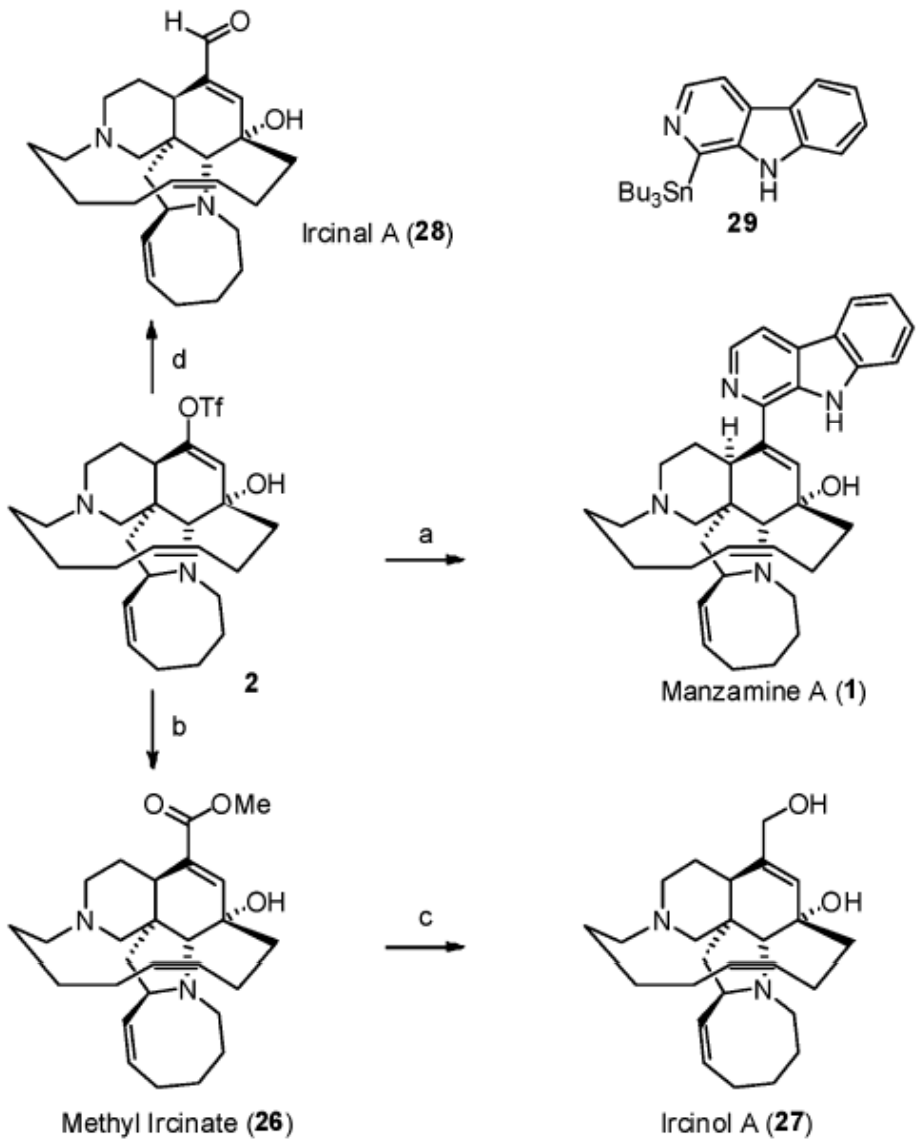


Commin's reagent

(f) $Ti(OiPr)_4$, Ph_2SiH_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_3N, Et_2O, 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

[a]Reagents and conditions: (a) $Pd(PPh_3)_4$ (12 mol %), **29**, DMF, 60 °C, 1 h, 52%; (b) $Pd(OAc)_2$ (18 mol %), PPh_3 (40 mol %), CO, Et_3N, MeOH, DMF, 60 °C, 1 h, 78%; (c) DIBAL, toluene, −78 °C, 2 h, 82%; (d) $Pd(PPh_3)_4$ (10 mol %), CO, LiCl, Bu_3SnH, 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

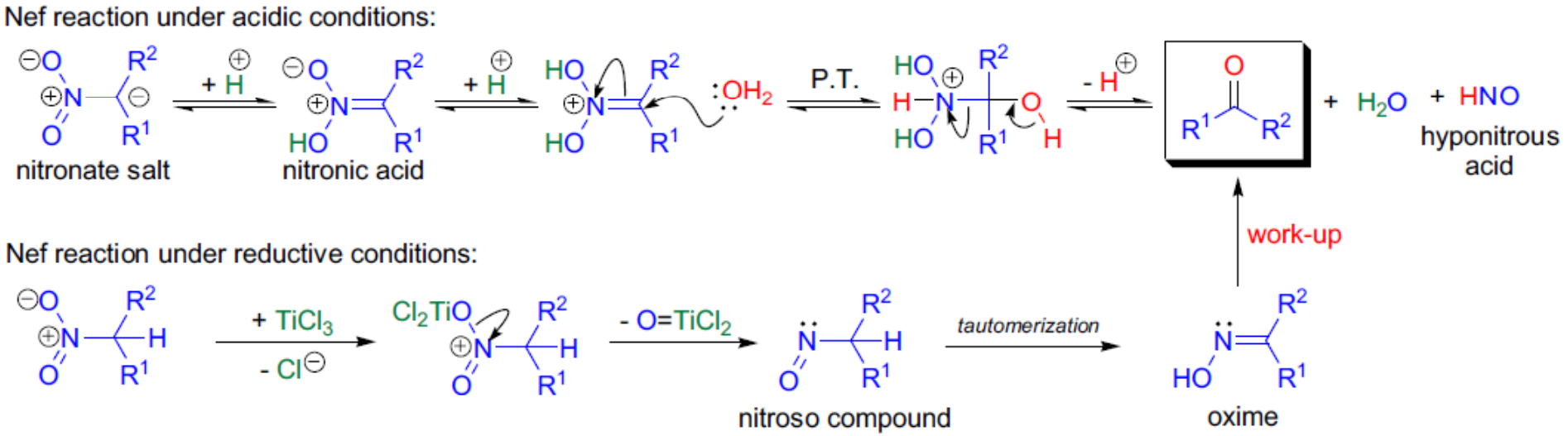
-Late stage synthesis of the 13-membered ring by ring closure methathesis.

-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.

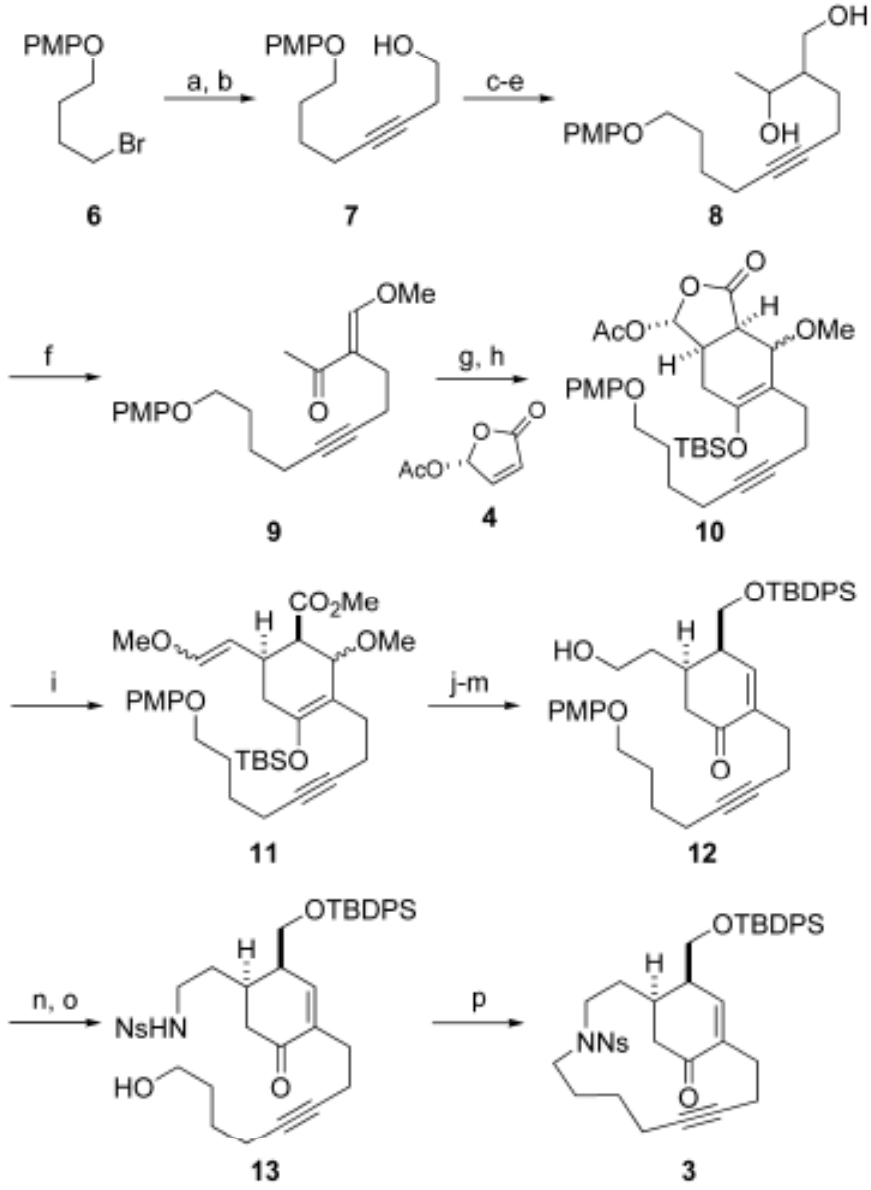
Thank you for your attention

Nef reaction



Kürti, L.; Czakó, B. Strategic Applications of named reactions in organic synthesis, Elsevier Inc. London **2005**, p. 308

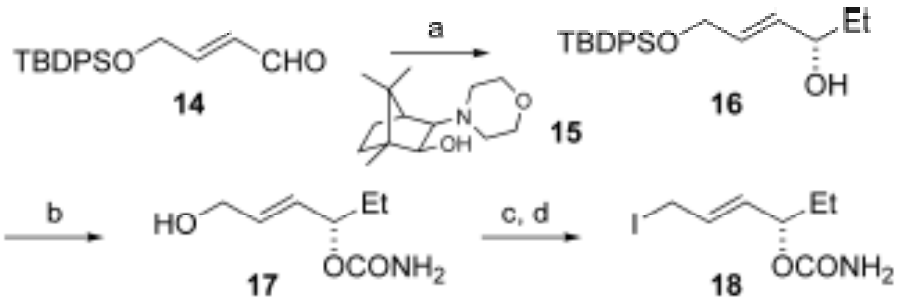
Previous synthesis



[a] Reaction conditions: (a) *n*-BuLi, $THPO(CH_2)_2CCH$, TMEDA, *n*-Bu_4NI, THF/HMPA, −78 °C to rt, 91%. (b) CSA, MeOH, rt, 93%. (c) I_2, PPh_3, imidazole, CH_3CN/Et_2O, 0 °C to rt, 97%. (d) Methyl acetoacetate, NaH, THF, reflux, 86%. (e) $LiAlH_4$, THF, rt, 91%. (f) Dess−Martin periodinane, *t*-BuOH, CH_2Cl_2, rt; *p*-TsOH·H_2O, Na_2SO_4, MeOH, rt, 66%. (g) TBSOTf, Et_3N, Et_2O, 0 °C. (h) **4**, NaOAc, toluene, MS3A, reflux, 97% (two steps, endo/exo = 2:1). (i) Et_3N, MeOH, rt; evaporation; $MeOCH_2PPh_3Cl$, KHMDS, THF, −78 to 0 °C; MeI, *i*-Pr_2NEt, DMF, 0 °C, 89% (*E*/*Z* = 1:1 for endo, 1:4 for exo). (j) $LiAlH_4$, Et_2O, 0 °C, 99%. (k) TBDPSCl, imidazole, CH_2Cl_2, rt, 99%. (l) *p*-TsOH·H_2O, acetone, rt, 97%. (m) $NaBH(OAc)_3$, AcOH, benzene, 40 °C, 88%. (n) NsNHBoc, DEAD, PPh_3, benzene, rt, 97%. (o) TFA, rt; evaporation; CAN, CH_3CN/H_2O, 0 °C, 81%. (p) DEAD, PPh_3, toluene (0.01M), rt, 85%.

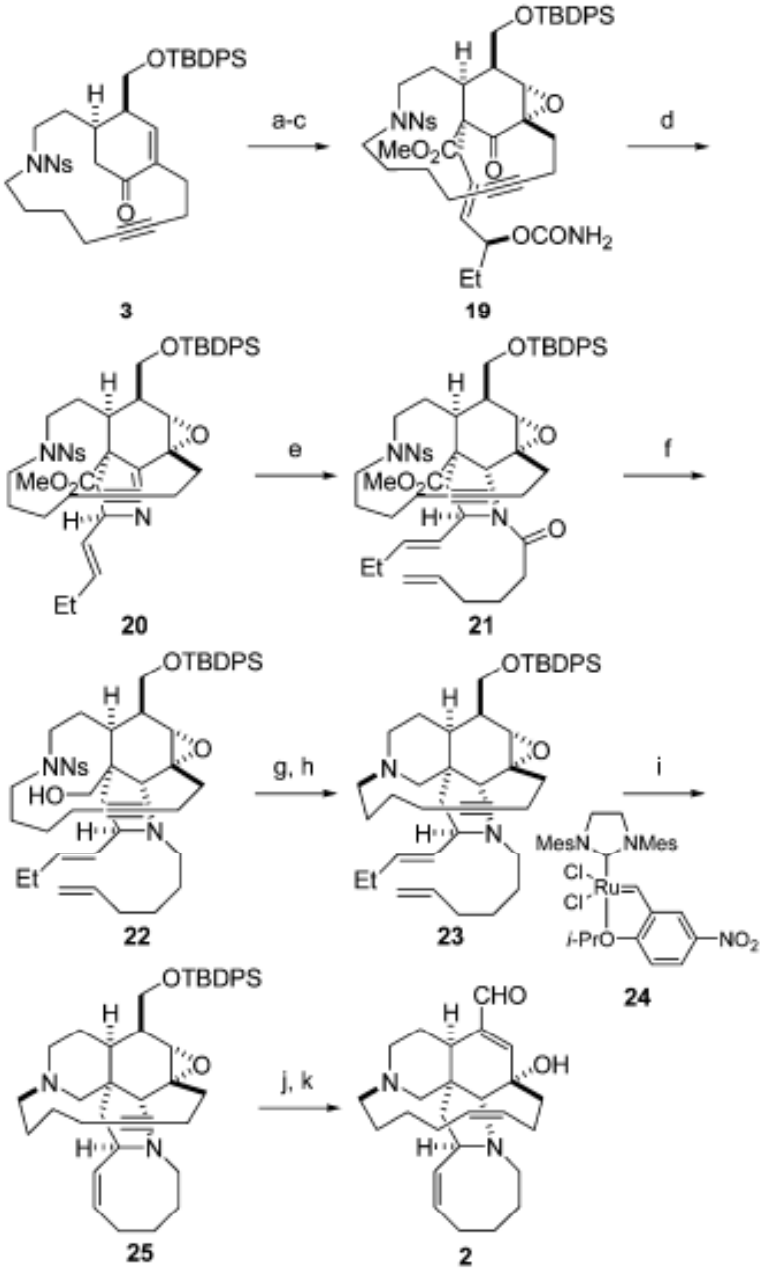
Toma, T.; Kita, Y. Fukuyama T. *J. Am. Chem. Soc.* **2010**, *132*, 10233

Previous synthesis



[a] Reaction conditions: (a) **15** (8 mol %), Et_2Zn, hexane/toluene, −10 °C, 75%, 93% ee. (b) $Cl_3CCONCO$, CH_2Cl_2, 0 °C; evaporation; Et_3N, MeOH, rt; evaporation; TBAF, THF, 50 °C, 99%. (c) MsCl, Et_3N, CH_2Cl_2, 0 °C. (d) NaI, acetone, 50 °C, 51% (two steps), >99% ee.

[a] Reaction conditions: (a) LHMDS, THF, −78 °C; $NCCO_2Me$, −78 °C to rt. (b) **18**, K_3PO_4, DMF, rt, 69% (two steps). (c) TBHP, Triton B, CH_3CN/benzene, rt, 62%. (d) TFAA, Et_3N, CH_2Cl_2, 0 °C; evaporation; AcOH, $Mg(ClO_4)_2$, benzene, 40 °C. (e) $NaBH(OCOCF_3)_3$, THF, rt; TFA; 5-hexenoyl chloride, Et_3N, 0 °C, 80% (two steps). (f) $LiAlH_4$, $AlCl_3$, Et_2O, −20 to −10 °C, 93%. (g) IBX, *t*-BuOH, 70 °C. (h) PhSH, Cs_2CO_3, CH_3CN, 50 °C; $NaBH(OCOCF_3)_3$, THF, rt, 89% (two steps). (i) **24** (1.0 equiv), PMPOH, CH_2Cl_2 (1 mM), rt, 41%. (j) TBAF, THF, 50 °C; evaporation; H_2, Lindlar's catalyst, quinoline, MeOH, rt, 84%. (k) Dess−Martin periodinane, CH_2Cl_2, rt, 87%.



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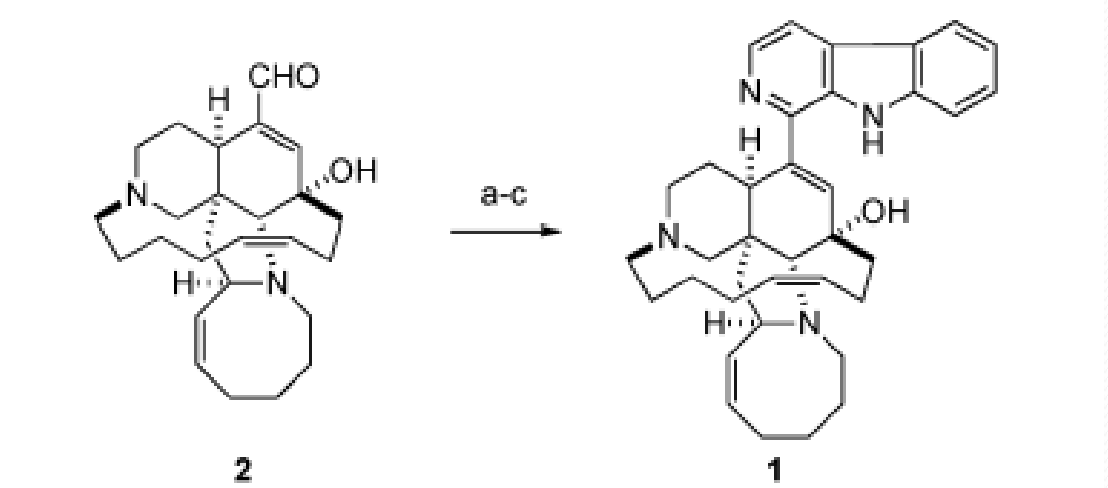
Previous synthesis



2 1

[a] Reaction conditions: (a) tryptamine·TFA, CH_2Cl_2, MS3A, rt. (b) TFA, CH_2Cl_2, rt. (c) DDQ, CH_2Cl_2/benzene, rt, 75% (three steps).

Toma, T.; Kita, Y. Fukuyama T. *J. Am. Chem. Soc.* **2010**, *132*, 10233