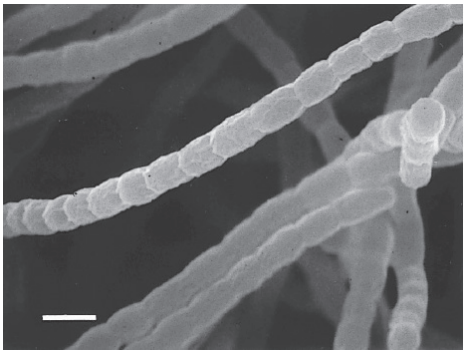
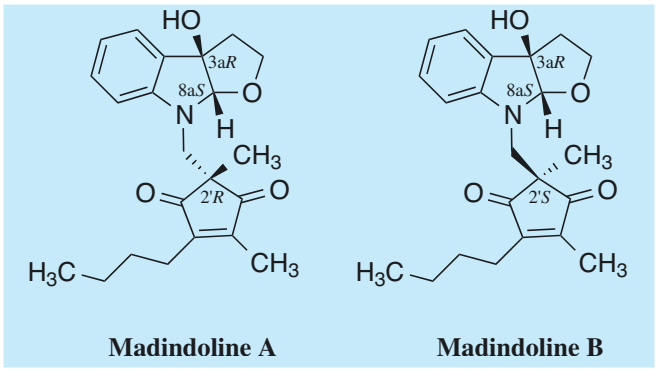
Madindoline ©

1. Discovery, producing organism and structures[1,2)]

Madindolines were isolated from the culture broth of *Streptomyces nitrosporeus* strain K93-0711 and found to be selective growth inhibitors of IL-6-dependent cells (MH-60)[1)]. Madindoline B (3a*R*, 8a*S*, 2'*S*) is a stereoisomer of madindoline A (3a*R*, 8a*S*, 2'*R*)[2,3)].



Streptomyces nitrosporeus K93-0711



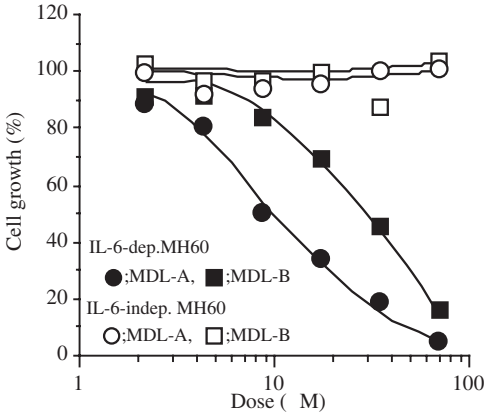
2. Physical data (Madindoline A)[2)]

Light yellow needles. $C_{22}H_{27}NO_4$; mol wt 370.20. Sol. in MeOH, EtOH, $CHCl_3$. Insol. in hexane.

3. Biological activity[1)]

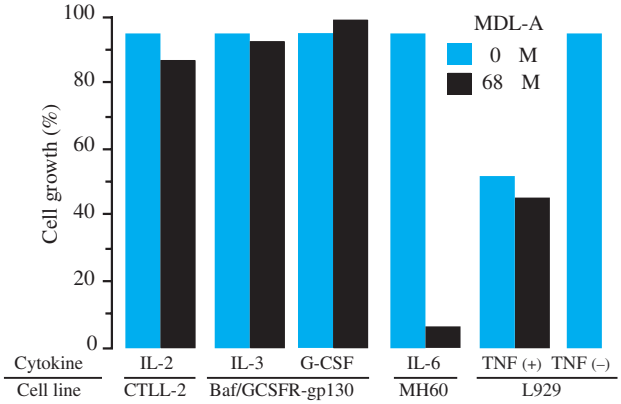
1) Growth inhibition of the IL-6-dependent MH60 cells

Madindolines A and B (MDL-A, B) showed potent growth inhibitory activity against IL-6 dependent MH60 cells with IC_{50} values of 8 and 30 μM, respectively. Madindolines did not show anti-microbial or cytocidal activity at 1000 μg/ml and 100 μg/ml, respectively.



2) Selectivity of madindoline A

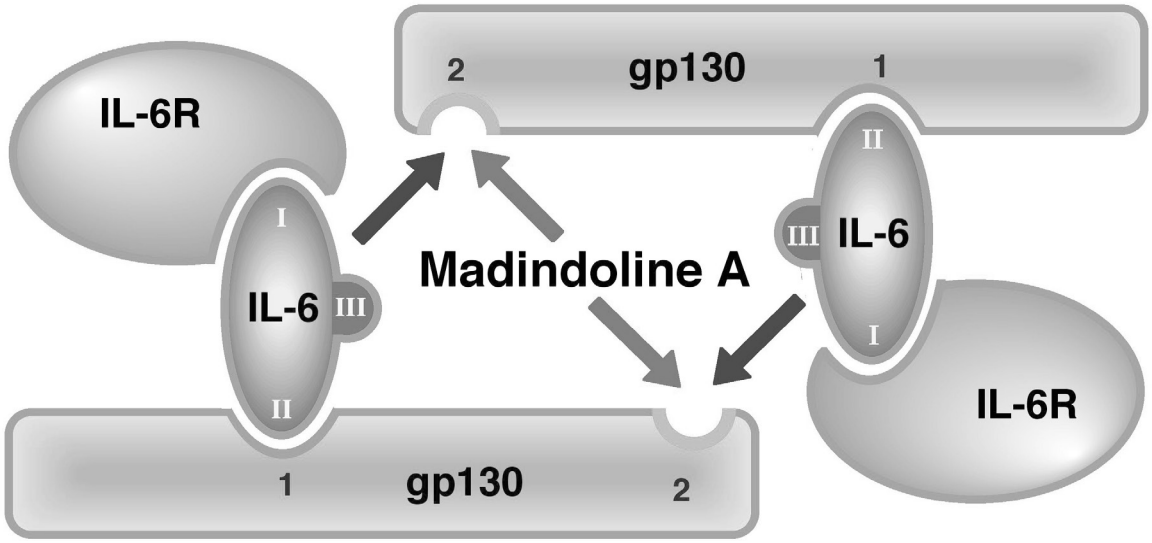
Selectivity against some cytokines was examined in cytokine-dependent or -sensitive cell lines. MDL-A inhibited growth of IL-6 dependent MH60 cells at 68 μM, but did not influence other cytokine activity.



3) Inhibitory mechanism of madindoline A[5)]

IL-6 has three topological binding sites (sites I, II, and III), and gp130 has two binding sites (sites 1 and 2)(29, 30); IL-6 first binds to the IL-6 receptor (IL-6R) at site I, IL-6 then binds to site I of the first gp130 at site II, forming a trimeric IL-6/IL-6R/gp130 complex. The trimeric complex then induces homodimerization of gp130 and forms a hexameric complex, activating the JAK/STAT signal transduction cascade.

MDL-A binds to gp130 and inhibits actions of IL-6 without inhibiting formation of the trimeric complex. Therefore, the MDL-A mechanism of action involves binding to gp130 site 2, the site for IL-6 site III, and inhibiting gp130 homodimerization, resulting in inhibition of IL-6 activity.

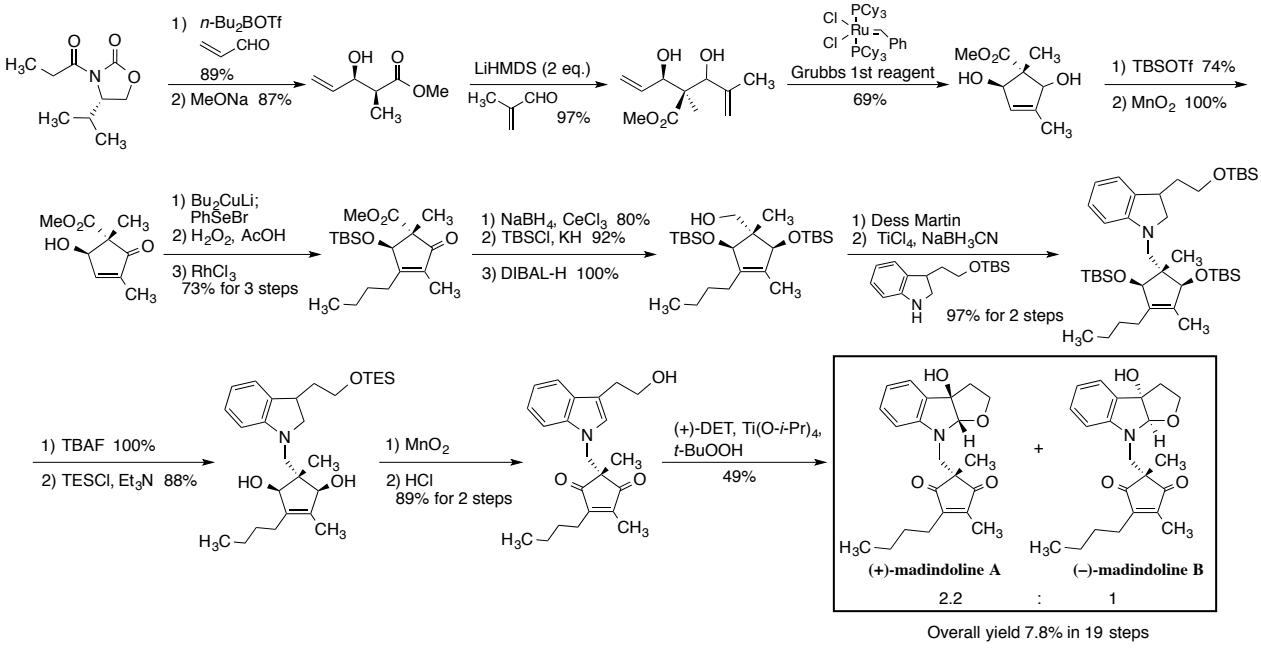


4. Madindoline A is commercially available as biological reagent.

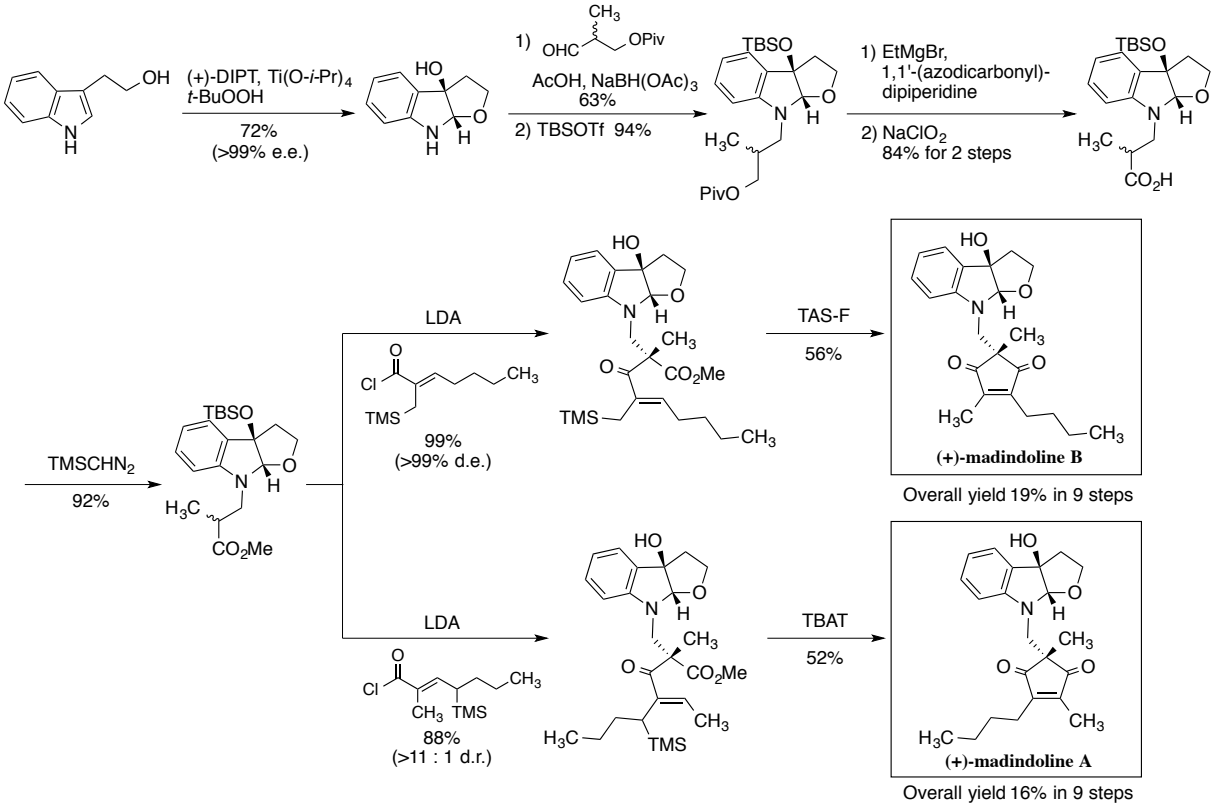
5. Total synthesis

The total syntheses of madindolines have been reported by several groups. Below are three schemes achieved by Ōmura's group (See Appendix-I).

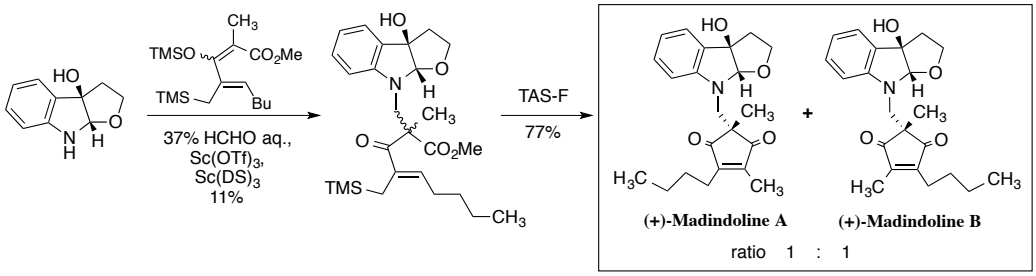
1) First total synthesis[3,6)]



2) Second total synthesis[4,6)]



3) Third total synthesis[7)]



6. References

1. [647] M. Hayashi *et al*., *J*. *Antibiot*. **49**, 1091-1095 (1996)
2. [688] S. Takamatsu *et al*., *J*. *Antibiot*. **50**, 1069-1072 (1997)
3. [745] T. Sunazuka *et al*., *J*. *Am*. *Chem*. *Soc*. **122**, 2122-2123 (2000)
4. [799] T. Hirose *et al*., *Org*. *Lett*. **4**, 501-503 (2002)
5. [813] M. Hayashi *et al*., *Proc*. *Natl*. *Acad*. *Sci*. *USA* **99**, 14728-14733 (2002)
6. [890] T. Hirose *et al*., *Tetrhedron* **61**. 3396-3403 (2005)
7. [917] T. Hirose *et al*., *Tetrhedron Lett*. **47**. 6761-6764 (2006)