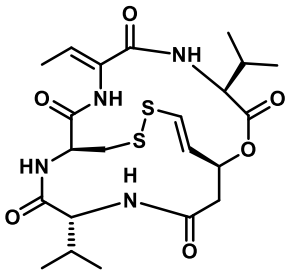
Drug of the week: *Romidepsin*

Romidepsin (*Istodax* ®)



Drug for treatment of cutaneous and peripheral T-cell lymphomas (licensed by FDA in Nov 2009)

Mechanism of action

The prodrug is reduced in the organism to form a dithiol which than reversibly interact with zinc atom in Zn-dependent histone deacetylaze (fig. 1) and inhibits it thus inducing apoptosis
Causes arrest of the cell cycle at both G_1 and G_2/M phases and induction of internucleosomal breakdown of chromatin

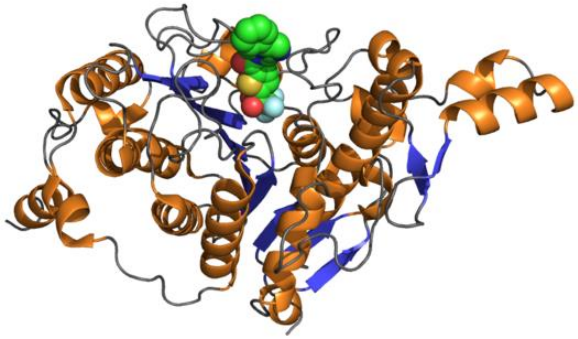


Fig. 1: Catalytic domain of human histone deacetylaze with bound inhibitor (PDB 2vqj)

Isolation

First isolated in 1994 in 1 g quantities from a broth culture of *Chromobacterium Violaceum* and was assigned a code of FR901228. It was tested by the same authors and they found it to be of very promising anti-cancer activity.

J. of Antibiotics **1994**, *47*, 301

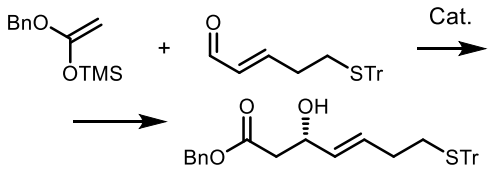
Total syntheses

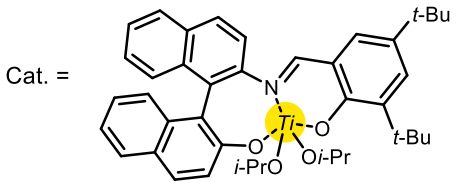
#	Citation	LLS	Yield %	Yield mg*
1	*JACS* **1996**, *118*, 7237	14	18	8
2**	*JOC* **2003**, *68*, 8902	6	26	8
3	*JACS* **2004**, *126*, 1030	9	10	11
4	*OL* **2008**, *10*, 613	12	23	8
5	*JOC* **2008**, *73*, 9353	11	2	30

* for the final step
** analogous molecule (one different amino acid)

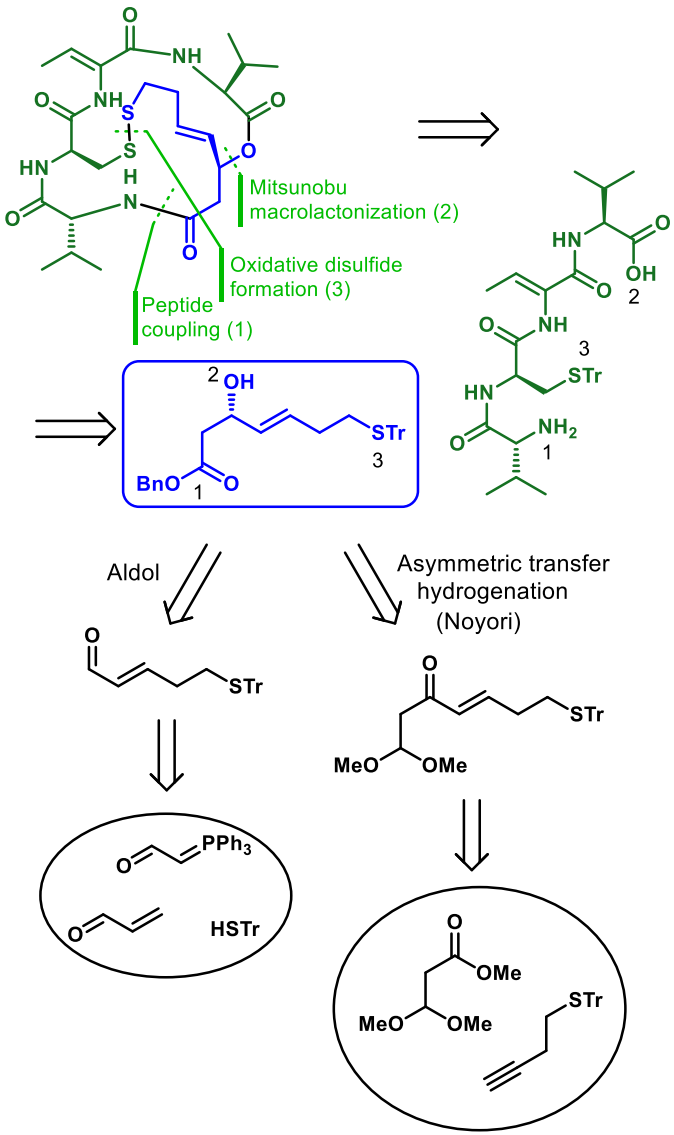
Aldol reaction issues

Groups 2 and 3 mentioned that they failed to reproduce aldol reaction *ee* (>98%) obtained in the first synthesis





Retrosynthesis



Drug of the week: *Romidepsin*