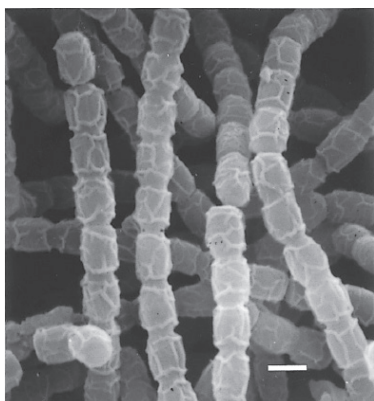


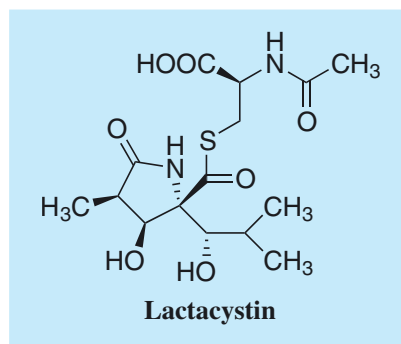
Lactacystin[©]

1. Discovery, producing organism and structure¹⁻⁴⁾

Lactacystin was originally isolated from a broth of *Streptomyces lactacystinicus* strain OM-6519^T while screening for neurite outgrowth inducers in Neuro 2a, a cell line of murine neuroblastoma cells. The absolute configuration of the structure was confirmed by X-ray crystallographic analysis²⁾.



Streptomyces lactacystinicus OM-6519^T

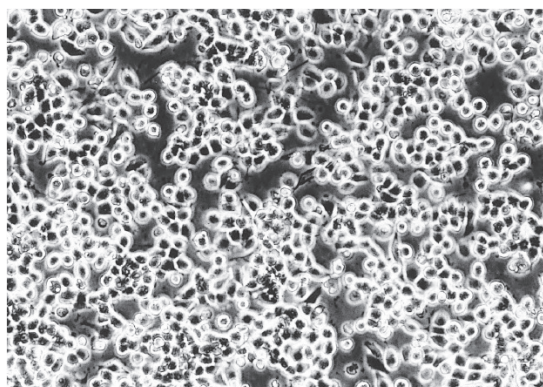


2. Physical data

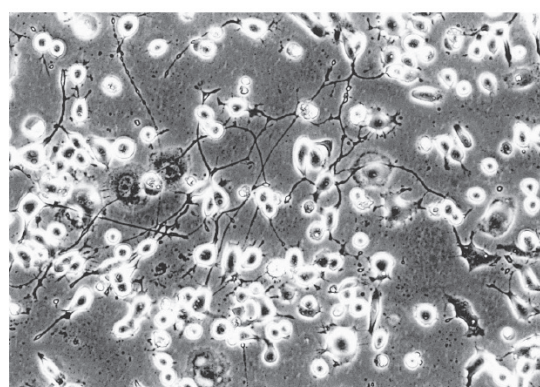
Colorless crystal. C₁₅H₂₄N₂O₇S; mol wt 376.13. Sol. in H₂O, MeOH, DMSO, pyridine. Insol. in benzene, EtOAc, CHCl₃.

3. Biological activity⁵⁻⁹⁾

1) Lactacystin inhibits cell cycle progression⁵⁾ and induces neurite outgrowth in Neuro 2a cells¹⁾.



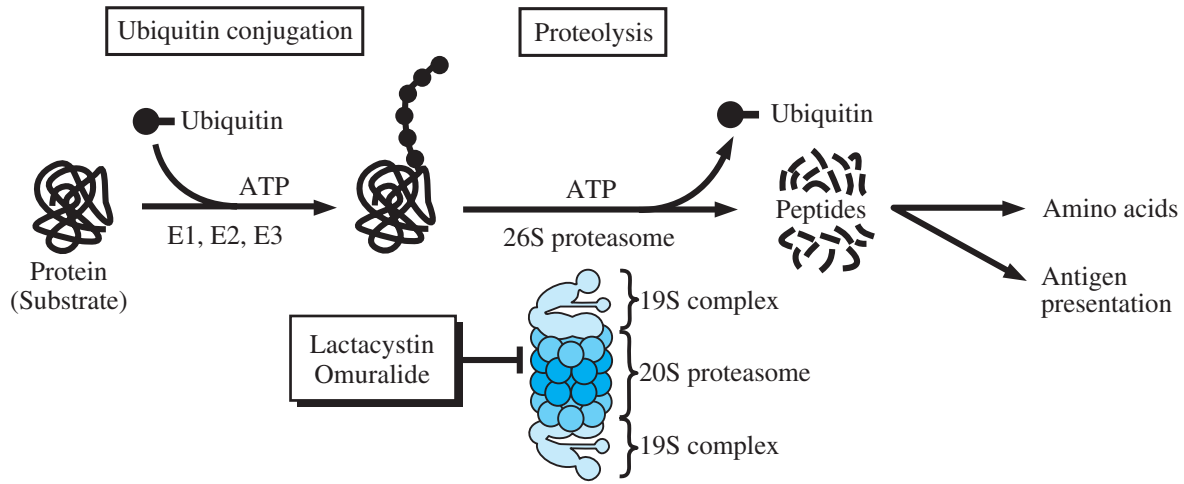
Control (day 4)



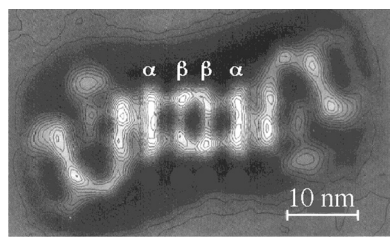
Lactacystin (1.3 μM, day 4)

Photomicrographs of morphological changes induced by lactacystin in Neuro 2a cells

2) Lactacystin inhibits proteasome activity⁶⁾. Proteasome exhibits three protease activities, of the three, lactacystin inhibits chymotrypsin-like activity most potently, followed by trypsin-like activity, but its inhibitory activity against peptidylglyutamylpeptide hydrolytic activity is relatively weak.

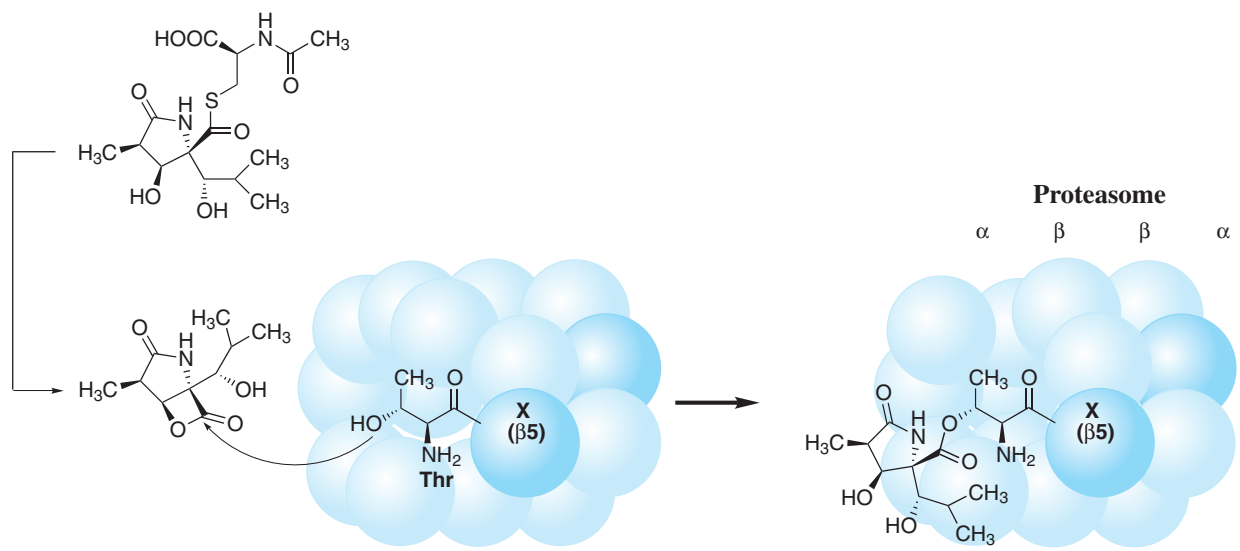


The molecular structure of rat liver 26S proteasome based on electron microscopy⁶⁾



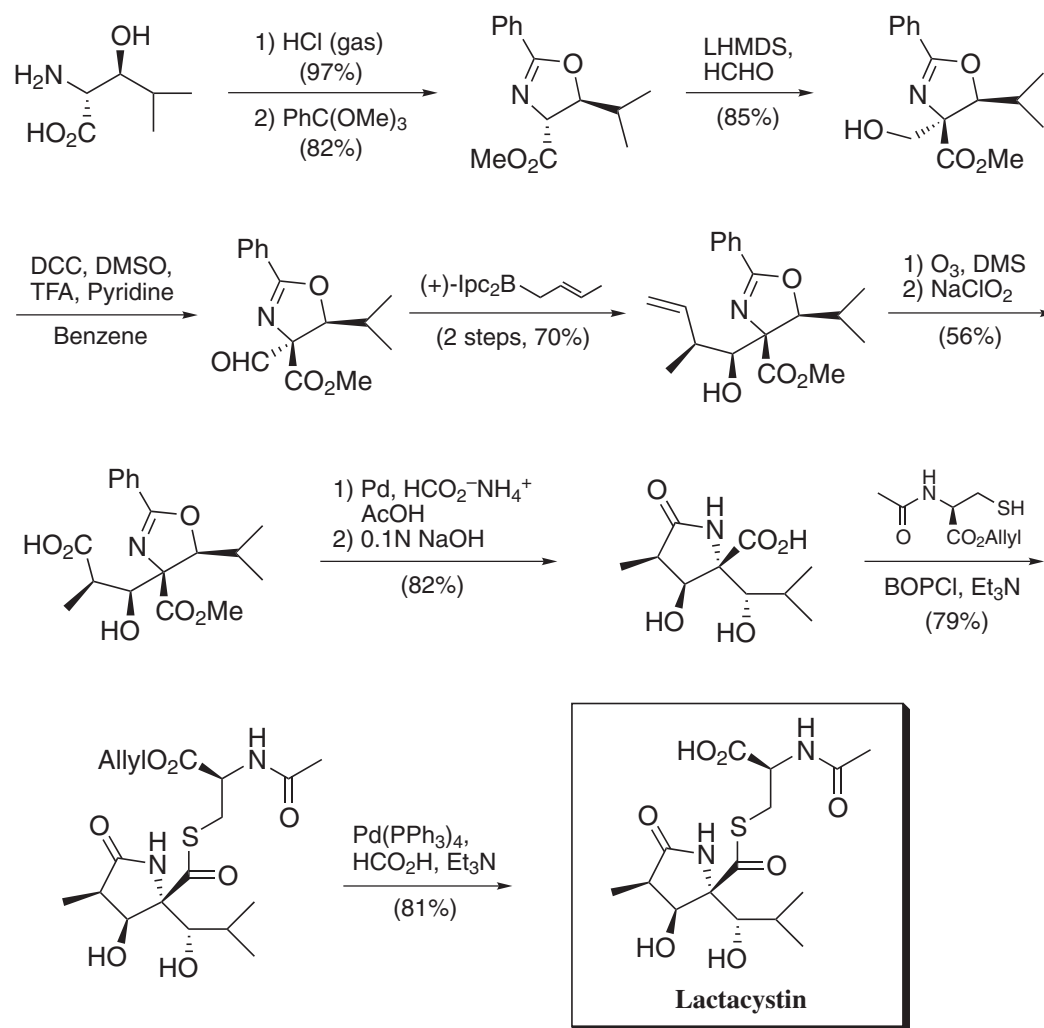
Model of intracellular protein degradation mediated by the ubiquitin-proteasome system

Lactacystin is specifically bound to the *N*-terminal threonine residue of certain β subunits (subunit X for mammalian cells⁶⁾ and subunit $\beta 5$ for yeast⁸⁾). Recently, it has been proposed that lactacystin is converted non-enzymatically to the β -lactone derivative (Omuralide), which reacts directly with the threonine active site.



6. Total synthesis

The total synthesis of lactacystin has been reported by several groups. The following scheme is Ōmura's approach¹³⁻¹⁵.



7. Application

Lactacystin is recognized as the most specific inhibitor of proteasome due to its mode of action. Therefore, lactacystin has been used to reveal and support the cellular proteasome functions.

- 1) Cell cycle: [571], [642], [667], [719], [735]
- 2) Apoptosis: [599], [676], [691], [692], [713], [716], [739]
- 3) Immunoantigen processing: [666], [667]
- 4) Protein degradation on ER: [593]
- 5) Receptor degradation: [594], [606], [653]
- 6) Transcription factor degradation: [643], [674], [769],
- 7) Other regulatory protein degradation: [618], [627], [641], [654], [670], [678], [698], [704], [752], [756], [770], [771], [780], [783], [818]
- 8) Anti-tumor: [750],
- 9) Anti-malaria: [830]
- 10) Anti-angiogenesis: [697]

The above brackets [] show references for the applications (See Publications).

8. Lactacystin is commercially available from Kyowa Medex.

9. References

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