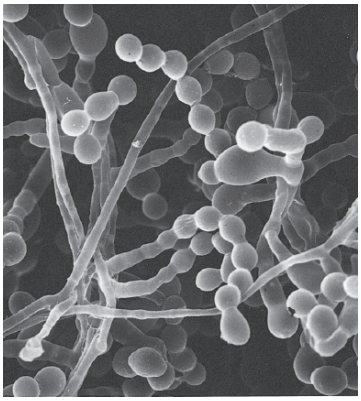
# Hymeglusin© (1233A, F-244)

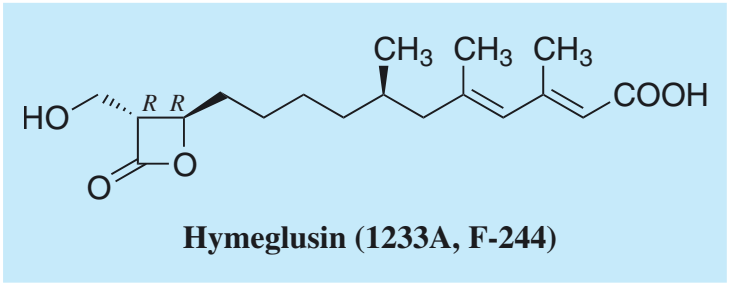
## 1. Discovery, producing organism and structure[1-4)]

Specific inhibitors of mevalonate biosynthesis were screened with an intact mammalian cell assay (Vero cells). Hymeglusin (1233A, F-244 or L-659,699) was isolated from the culture broth of *Scopulariopsis candida* strain F-244 and found to be an inhibitor of Vero cell groth in MEM medium containing 2% calf serum, but not in the above medium supplemented with 1 mM mevalonate[2)].

The absolute configuration was determined by Chiang *et al.*[3)] The total synthesis of hymeglusin has been reported by several groups. The first total synthesis was reported by Mori *et al.*[5)] (See Appendix-I).



*Scopulariopsis* sp. F-244
(*Scopulariopsis candida* F-244)
Bar: 5 μm



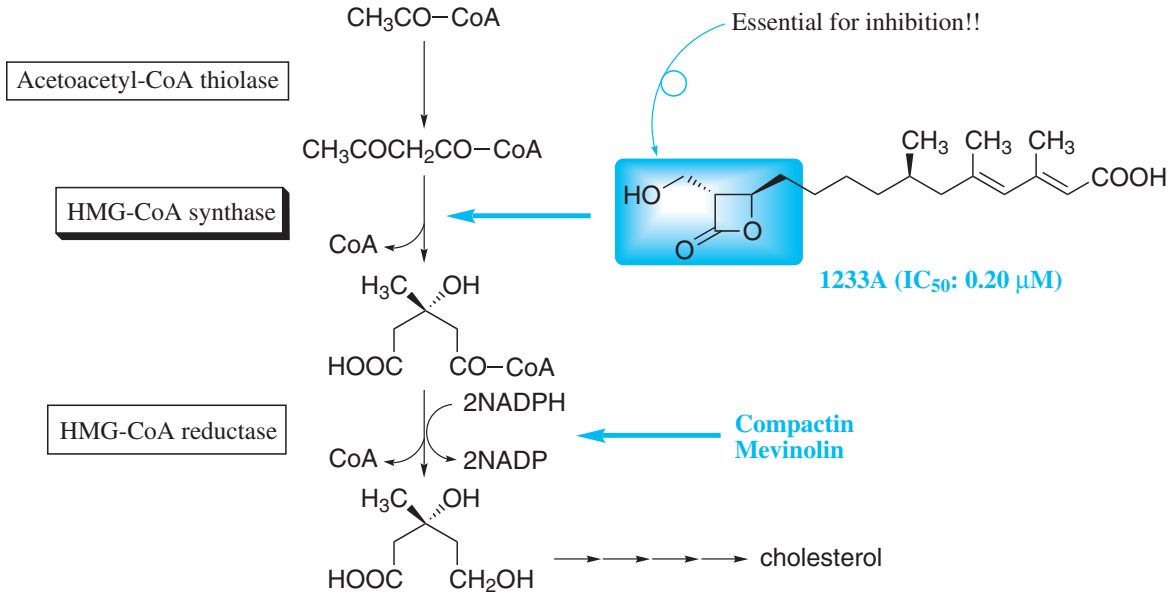

**Hymeglusin (1233A, F-244)**

## 2. Physical data[1)]

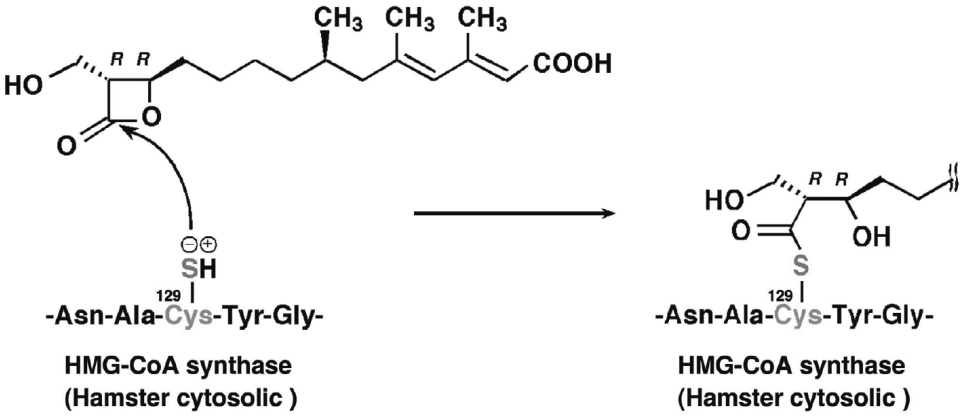
White amorphous powder. $C_{18}H_{28}O_5$; MW 324.19. Sol. in MeOH, EtOH, $CH_3CN$, EtOAc, $CHCl_3$. Insol. in $H_2O$, hexane. Store at –20°C.

## 3. Biological activity[1,6–9)]

1) Specific and irreversible inhibition of HMG-CoA synthase *in vitro*[6-8)] and *in vivo*[9)].



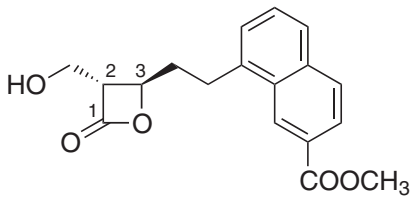
2) Mede of action (or Meohanism of action)
Hymeglusin was bound to the active centor 129 Cys of hamster HMG-CoA synthase. It is speculator that the hymeglusin β-lactone ring reacts with the thiol group of the Cys residue as shows below.




Recemly, X-ray arystalography of hymeglush: HMG CoA synthase complex was defined to demonstrate the speculation was correct.

3) Antimicrobial activity[1)]
Hymeglusin showed antifungal activity against *Candida albican*s (MIC: 12.5 μg/ml), *Penicillium herquei* (25) and *Pyricularia oryzae* (6.25).

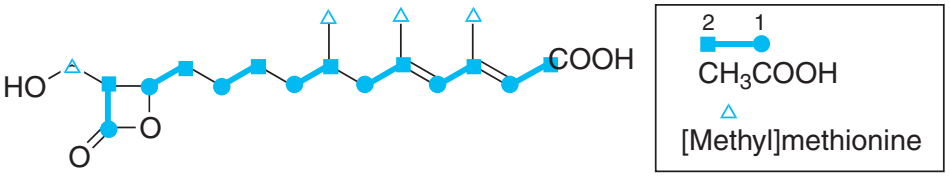
**4. Importance of β-lactone geometry for specific HMG-CoA synthase inhibition**[10–15,17,18)]
Two kinds of natural β-lactones have been reported; (2*R*,3*R*)-β-lactone as a HMG-CoA synthase inhibitor and (2*S*,3*S*)-β-lactone as a lipase (esterase) inhibitor. During our synthetic study of β-lactone analogs, four optically active DU-6622s were synthesized to discriminate between the inhibitory activity of the two. Consequently, (2*R*,3*R*)-β-lactone was found to be responsible for specific inhibition of HMG-CoA synthase, whereas (2*S*,3*S*)-β-lactone was responsible for pancreatic lipase inhibition.



**DU-6622**

| Configuration (C-2, C-3) | $IC_{50}$ ($\mu$M) | | L/H |
|---|---|---|---|
| | HMG-CoA synthase (H) | Pancreatic lipase (L) | |
| (*R*,*R*) | 0.098 | 270 | 2700 |
| (*S*,*S*) | 31 | 27 | 0.87 |
| (*R*,*S*) | 360 | >300 | >0.83 |
| (*S*,*R*) | 9.4 | >300 | >32 |
| (*R*,*R*)+(*S*,*S*) | 0.15 | 120 | 800 |

**5. Biosynthesis**[16)]



## 6. References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