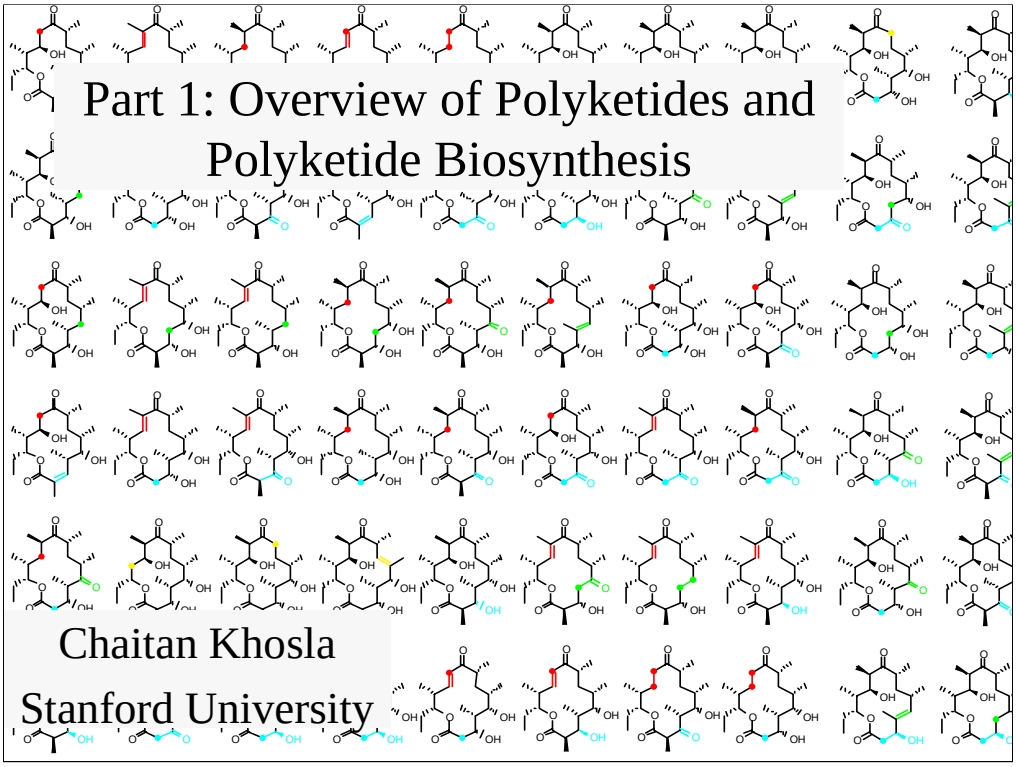
Part 1: Overview of Polyketides and Polyketide Biosynthesis
Chaitan Khosla
Stanford University

50 Years of Protein Biosynthetic Chemistry

- Remarkable catalytic properties of ribosomes
- Genetic code is modular
- Universality affords abundant access in *E. coli*
- Directed manipulation of protein biosynthesis
- Polypeptides became more accessible for therapeutic and other uses

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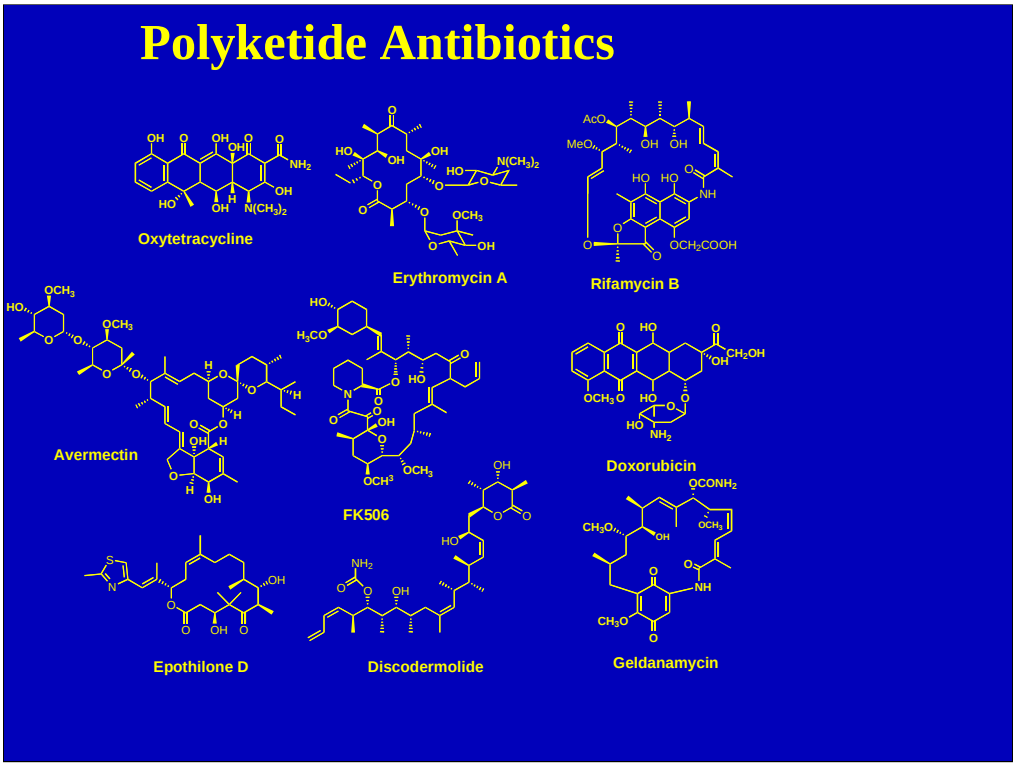
Impact of Studying Polyketide Biosynthesis Could be Similar

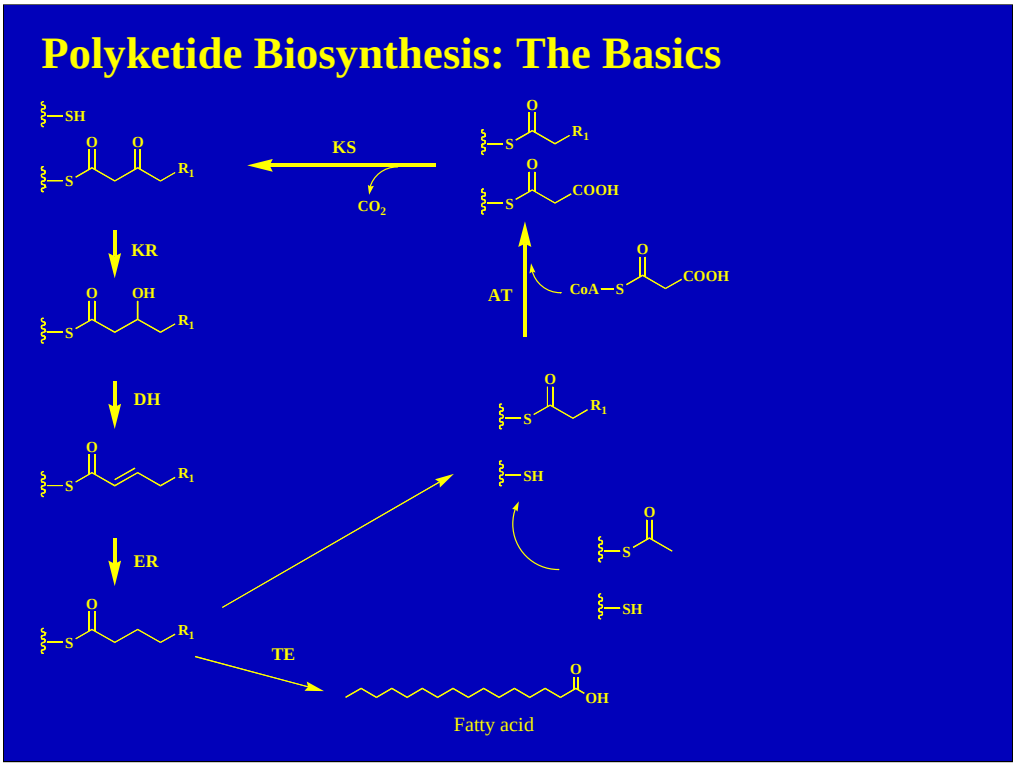

Polyketide Antibiotics
Oxytetracycline
Erythromycin A
Rifamycin B
Avermectin
FK506
Doxorubicin
Epothilone D
Discodermolide
Geldanamycin

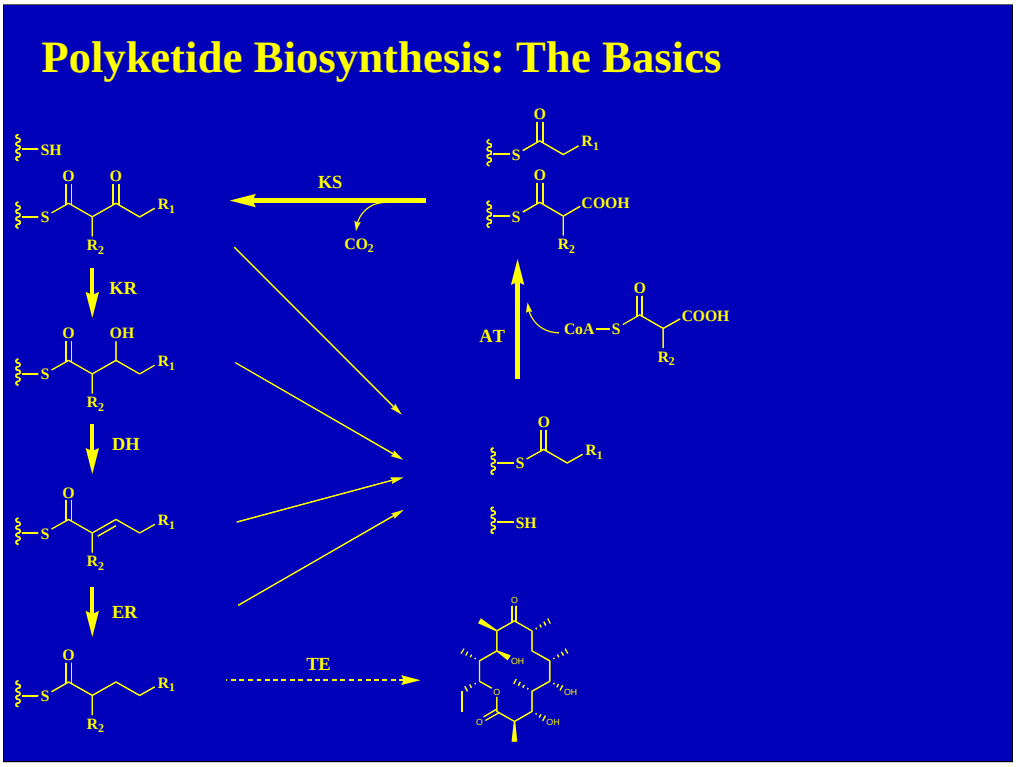
Polyketide Drug Development

- Polyketides are expensive
- Polyketides are difficult to analogue
- Technologies for discovering & making polyketides have not changed much in 50 years

Opportunities and Challenges

- Understand polyketide biosynthesis
- Engineer polyketide biosynthesis
- Connect polyketide chemistry to polyketide biology


Polyketide Biosynthesis: The Basics
KS
CO_2
KR
DH
ER
TE
AT
CoA—S
COOH
SH
OH
Fatty acid


Polyketide Biosynthesis: The Basics
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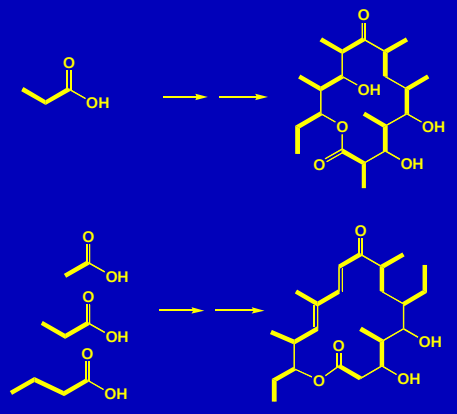
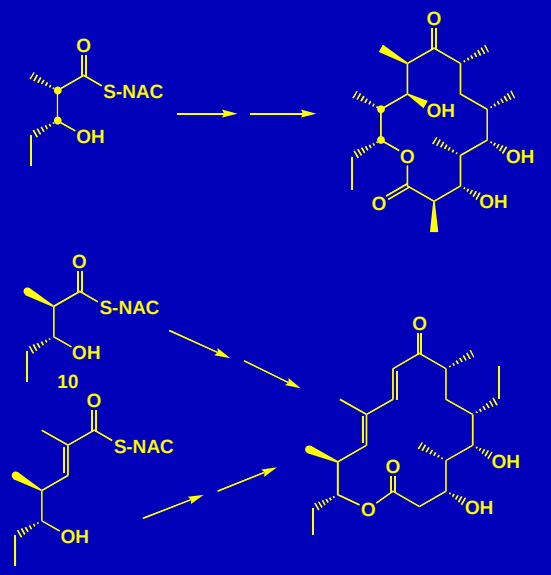
Polyketide Biosynthesis: The Basics

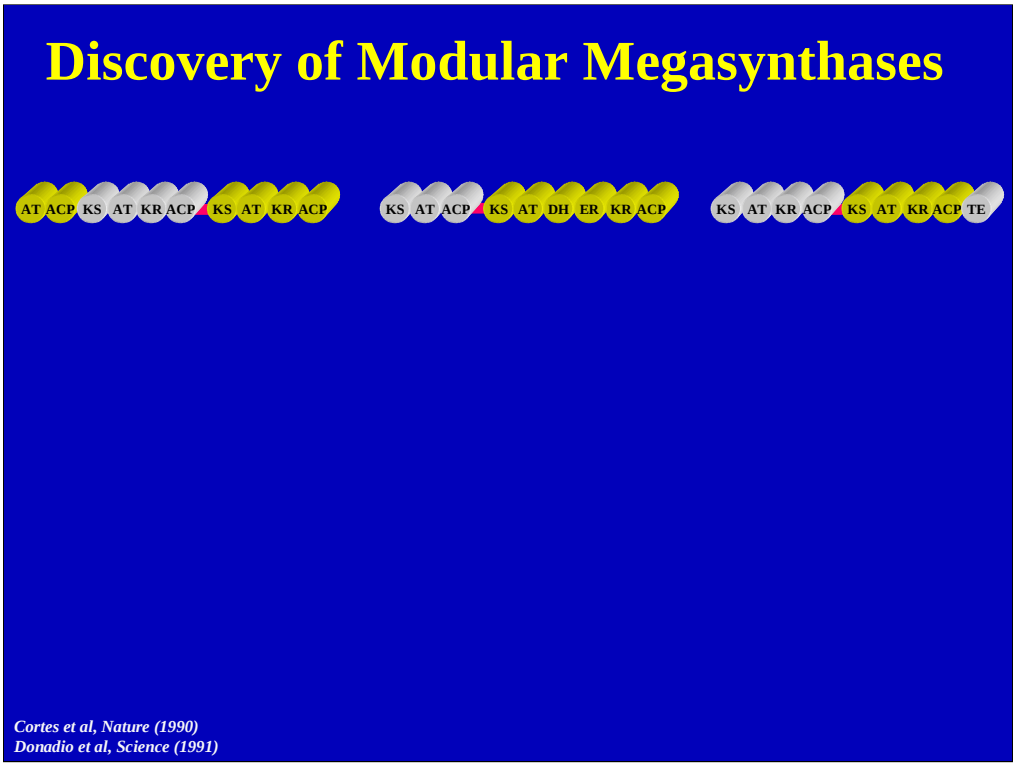


Gerzon et al, J. Am. Chem. Soc. (1956)

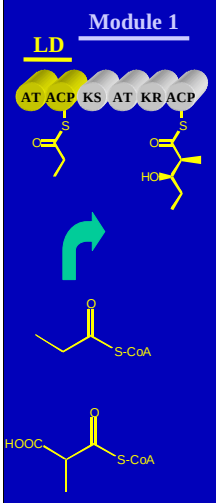
Polyketide Biosynthesis: The Basics



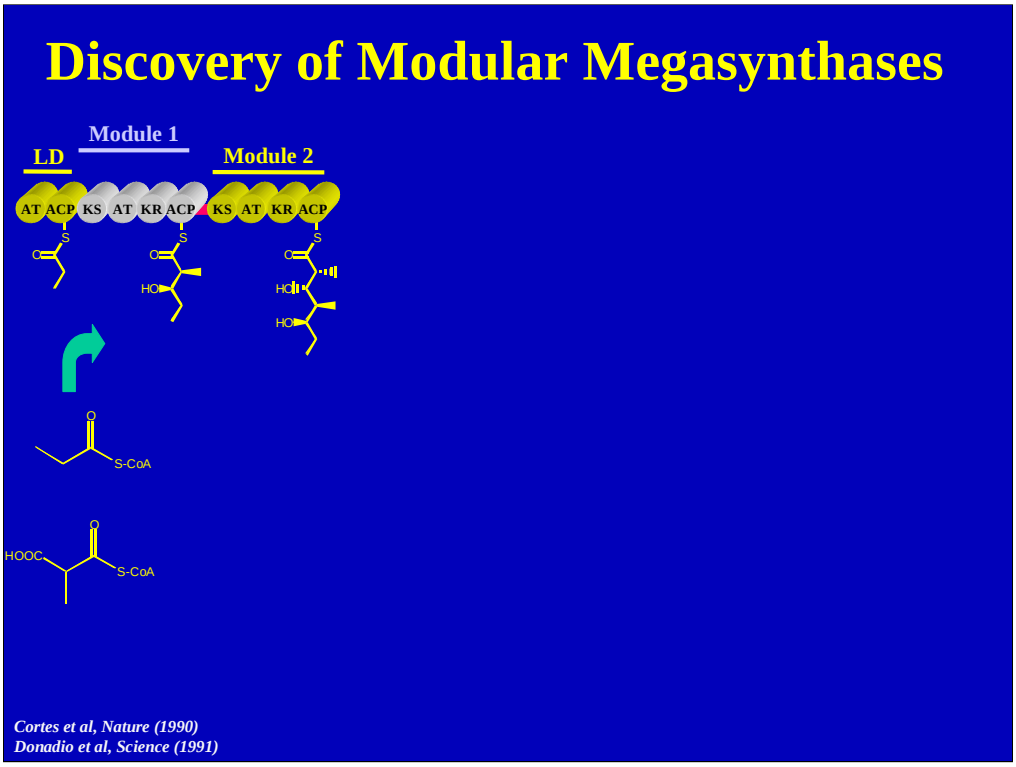
Cane & Yang, J. Am. Chem. Soc. (1987)
Yue et al, J. Am. Chem. Soc. (1987)

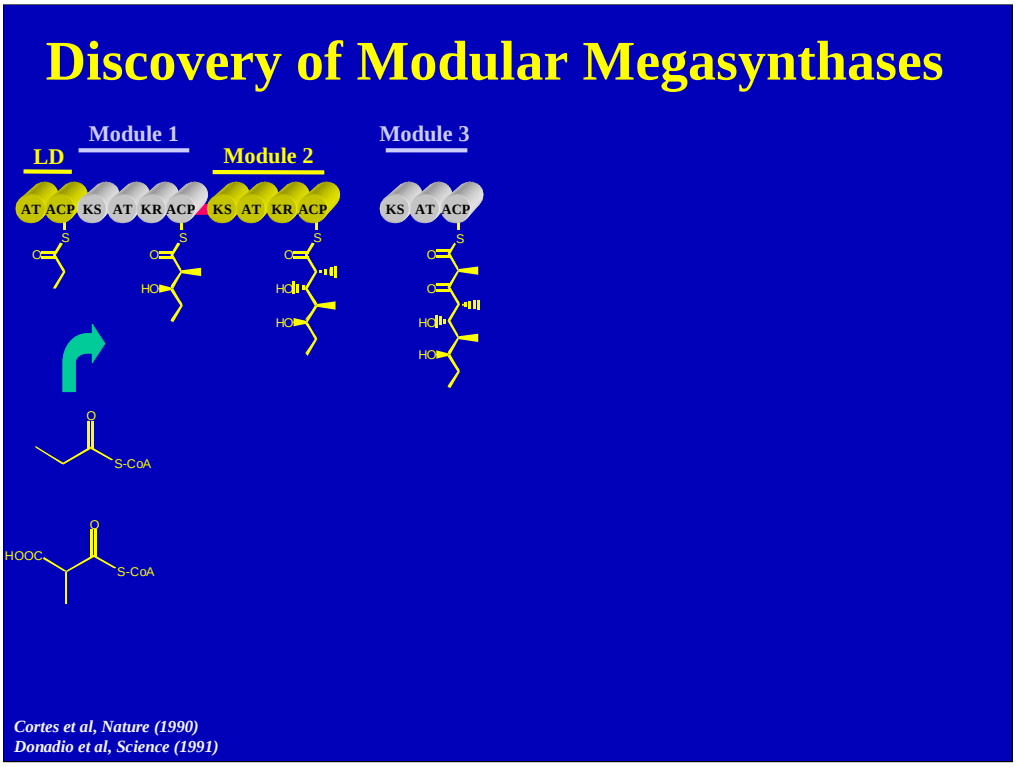

Discovery of Modular Megasynthases
AT ACP KS AT KR ACP KS AT KR ACP
KS AT ACP KS AT DH ER KR ACP
KS AT KR ACP KS AT KR ACP TE
Cortes et al, Nature (1990)
Donadio et al, Science (1991)

Discovery of Modular Megasynthases



Cortes et al, Nature (1990)
Donadio et al, Science (1991)


Discovery of Modular Megasynthases
Module 1
LD
Module 2
AT ACP KS AT KR ACP KS AT KR ACP
S-CoA
HOOC
Cortes et al, Nature (1990)
Donadio et al, Science (1991)


Discovery of Modular Megasynthases
LD
Module 1
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AT ACP KS AT KR ACP KS AT KR ACP
KS AT ACP
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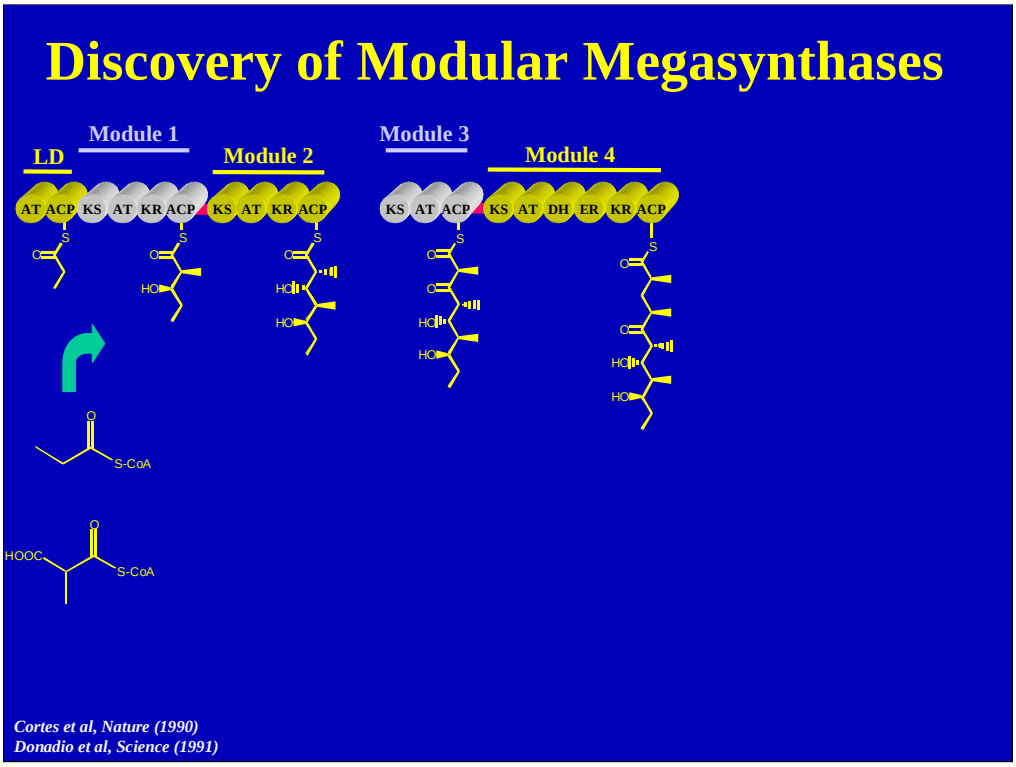
Discovery of Modular Megasynthases
LD
Module 1
Module 2
Module 3
Module 4
AT ACP KS AT KR ACP KS AT KR ACP
KS AT ACP KS AT DH ER KR ACP
S-CoA
HOOC
Cortes et al, Nature (1990)
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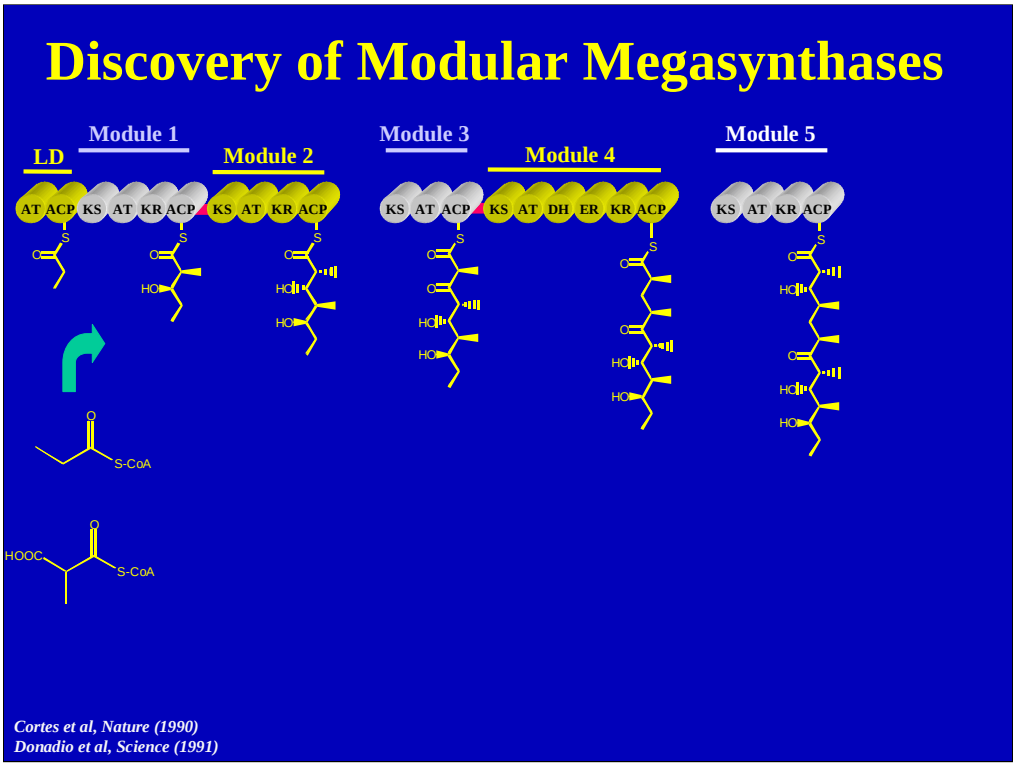
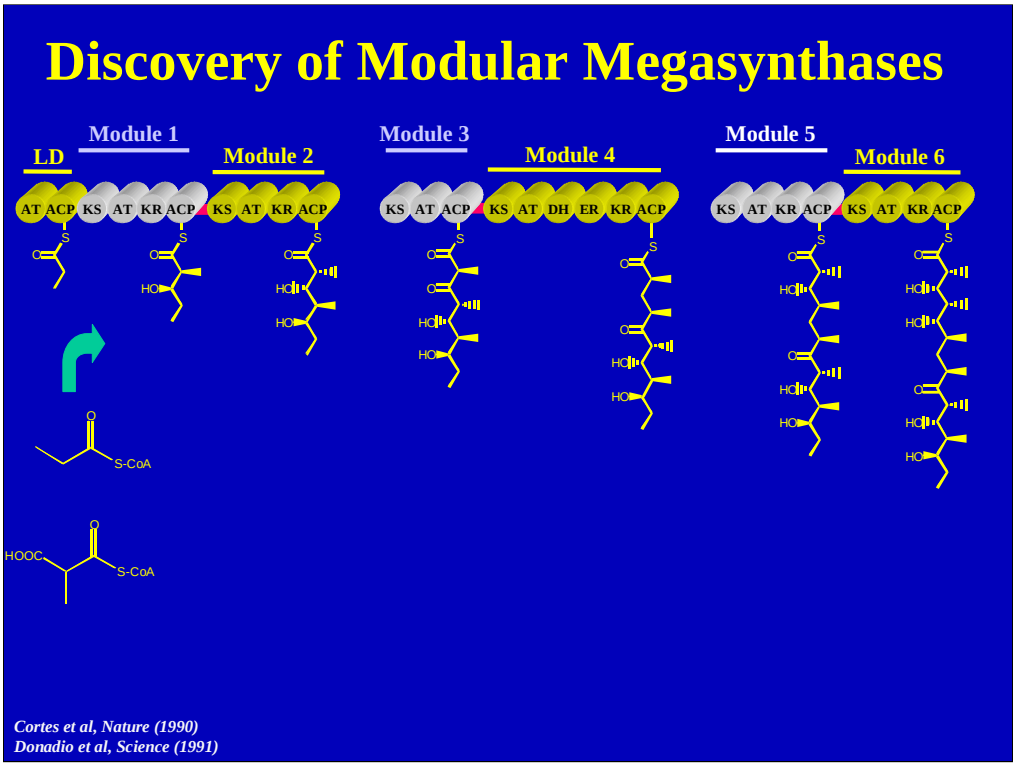
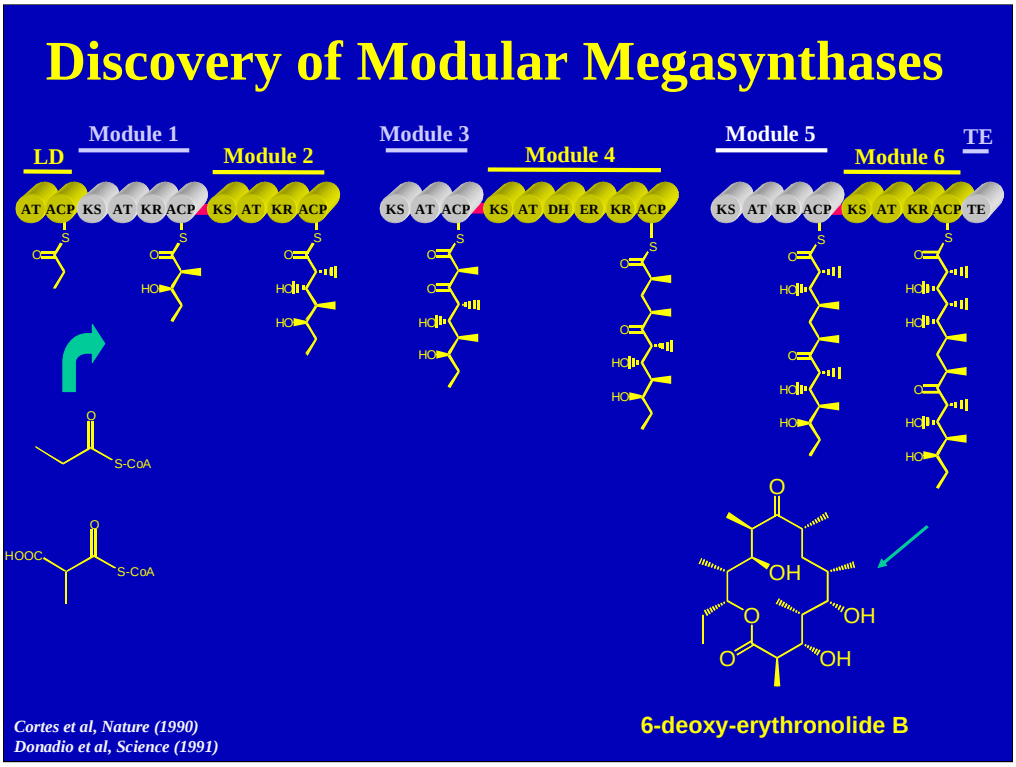
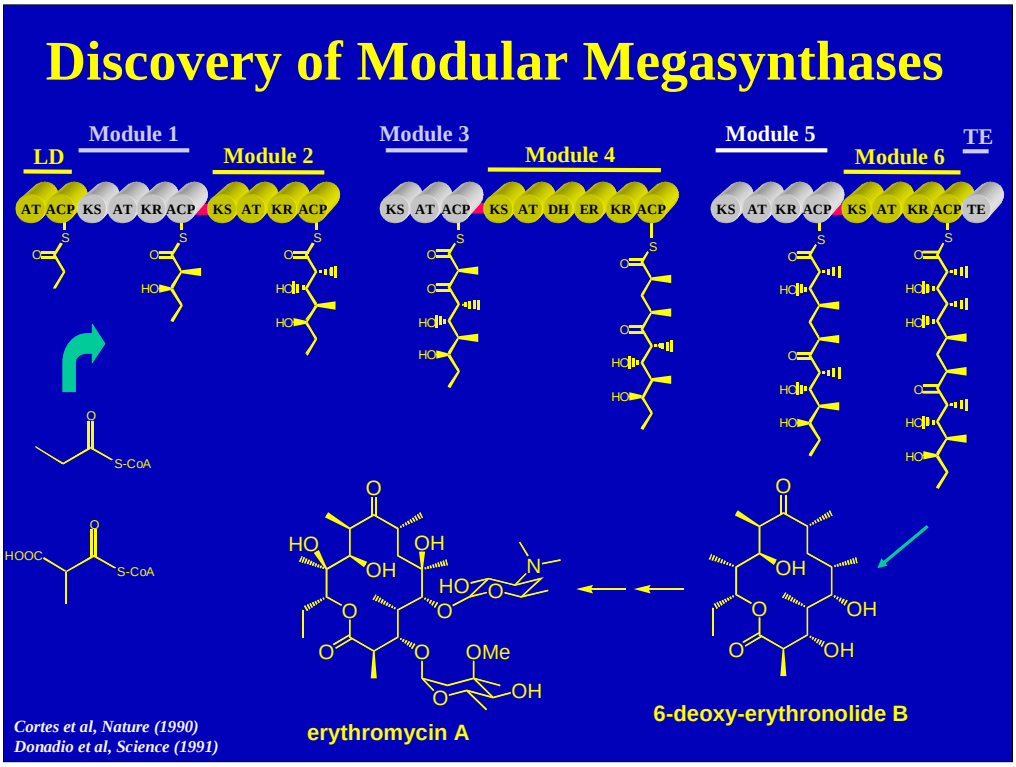

Discovery of Modular Megasynthases
LD
Module 1
Module 2
Module 3
Module 4
Module 5
AT ACP KS AT KR ACP KS AT KR ACP
KS AT ACP KS AT DH ER KR ACP
KS AT KR ACP
S-CoA
HOOC
Cortes et al, Nature (1990)
Donadio et al, Science (1991)


Discovery of Modular Megasynthases
LD
Module 1
Module 2
Module 3
Module 4
Module 5
Module 6
AT ACP KS AT KR ACP KS AT KR ACP
KS AT ACP KS AT DH ER KR ACP
KS AT KR ACP KS AT KR ACP
S-CoA
HOOC
S-CoA
Cortes et al, Nature (1990)
Donadio et al, Science (1991)


Discovery of Modular Megasynthases
LD
Module 1
Module 2
Module 3
Module 4
Module 5
Module 6
TE
AT ACP KS AT KR ACP KS AT KR ACP
KS AT ACP KS AT DH ER KR ACP
KS AT KR ACP KS AT KR ACP TE
S-CoA
HOOC
S-CoA
OH
OH
OH
Cortes et al, Nature (1990)
Donadio et al, Science (1991)
6-deoxy-erythronolide B


Discovery of Modular Megasynthases
LD
Module 1
Module 2
Module 3
Module 4
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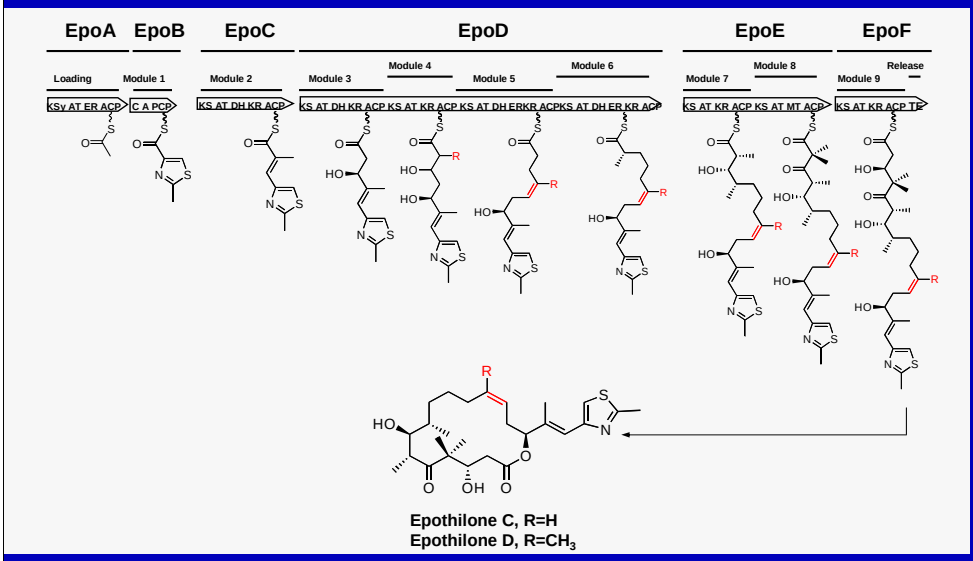
Module 6
TE
AT ACP KS AT KR ACP KS AT KR ACP
KS AT ACP KS AT DH ER KR ACP
KS AT KR ACP KS AT KR ACP TE
S-CoA
HOOC
S-CoA
erythromycin A
6-deoxy-erythronolide B
Cortes et al, Nature (1990)
Donadio et al, Science (1991)

The Epothilone Synthase



Tang et al, Science (2000)
Schupp et al, Gene (2000)

Summary

- Ca. 1990, convergence of genetic and chemical insights into polyketide biosynthesis
- Understanding and engineering modular megasynthases that make polyketides => new metabolic paradigm
- Erythromycin: excellent model system