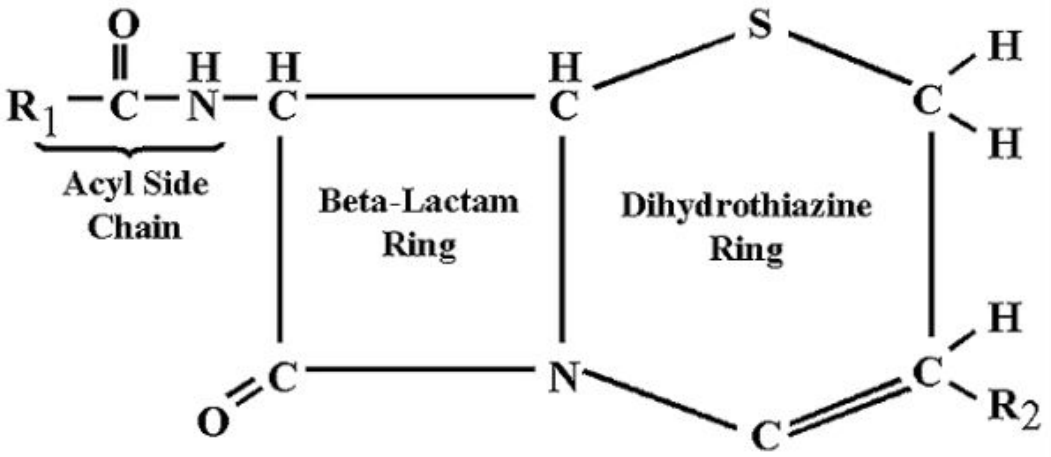
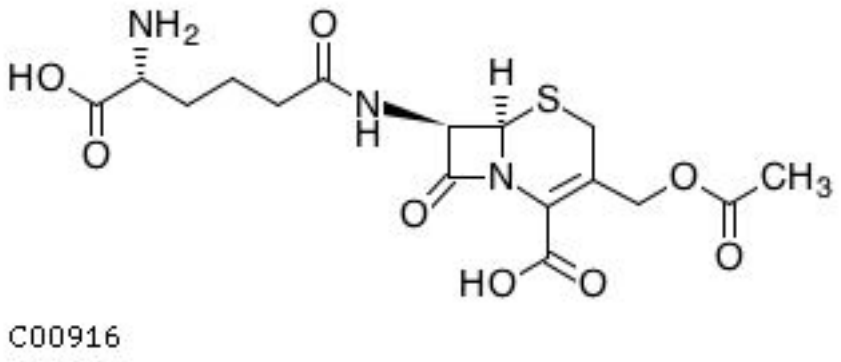
Cefalosporin Production

Agneyo Ganguly

Cefalosporins



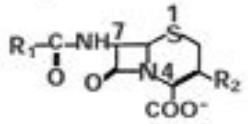
General Structure of Cephalosporins



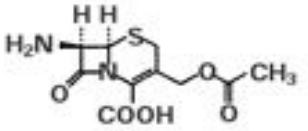
Cefalosporin C

Semisynthetic Cefalosporins

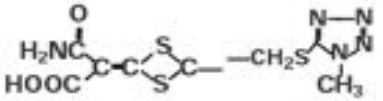
Cephem nucleus



7-ACA

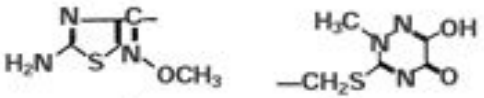


Cefotetan



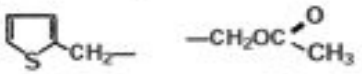
R_1 R_2

Ceftriaxone



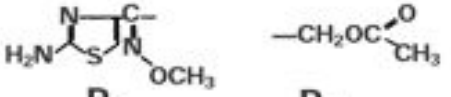
R_1 R_2

Cephalothin



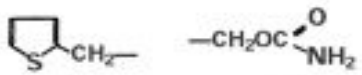
R_1 R_2

Cefotaxime



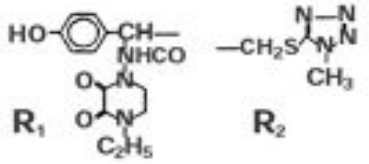
R_1 R_2

Cefoxitin



R_1 R_2

Cefoperazone

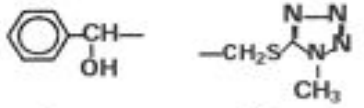


R_1 R_2

Ceftazidime

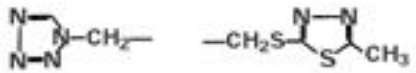
R_1 R_2

Cefamandole



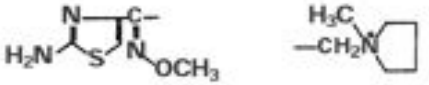
R_1 R_2

Cefazolin



R_1 R_2

Cefepime



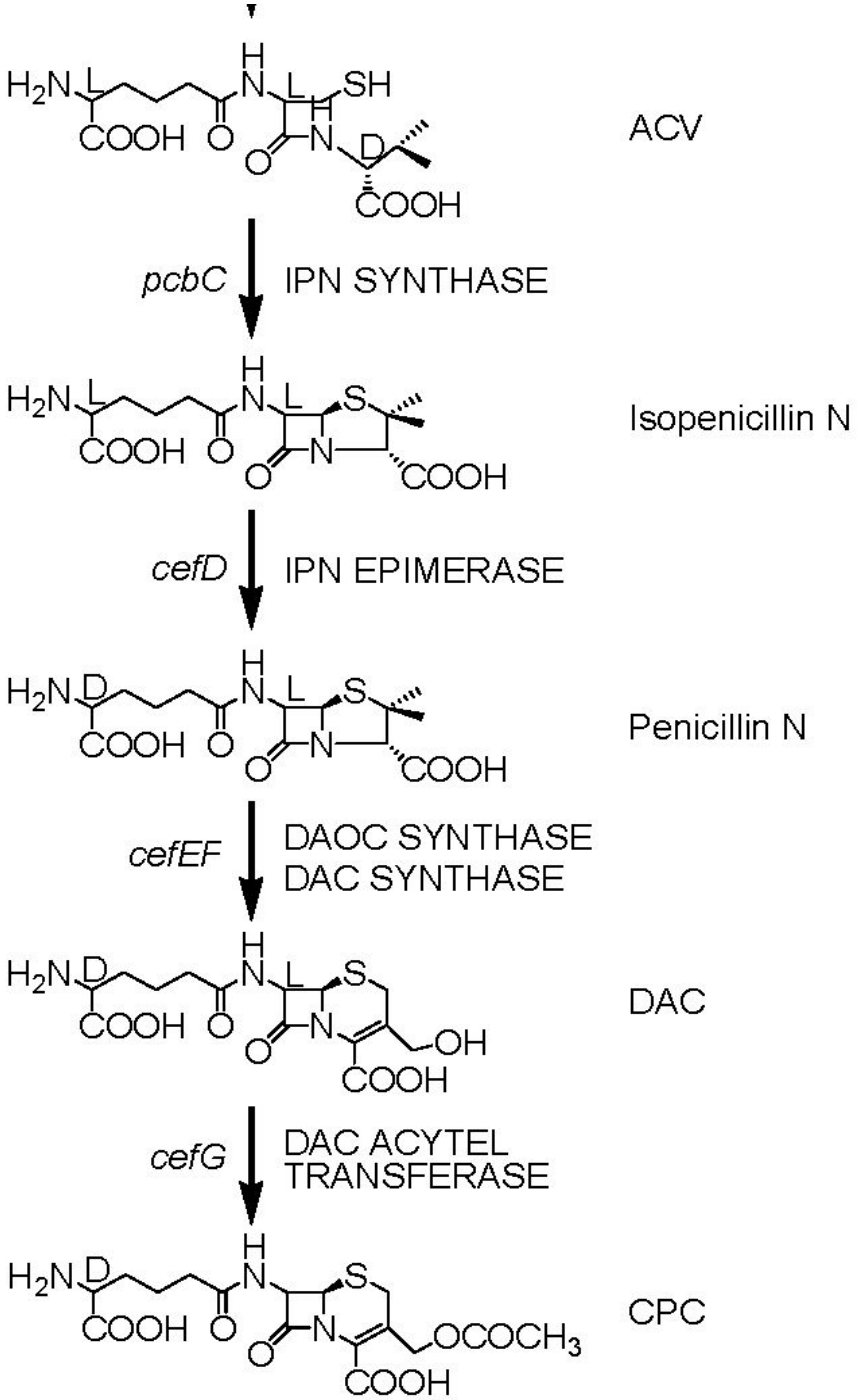
R_1 R_2

Cefalosporin biosynthesis

Genes involved

deacetoxyCefC (DAOC)

deacetylCefC (DAC)



Cefalosporin gene cluster

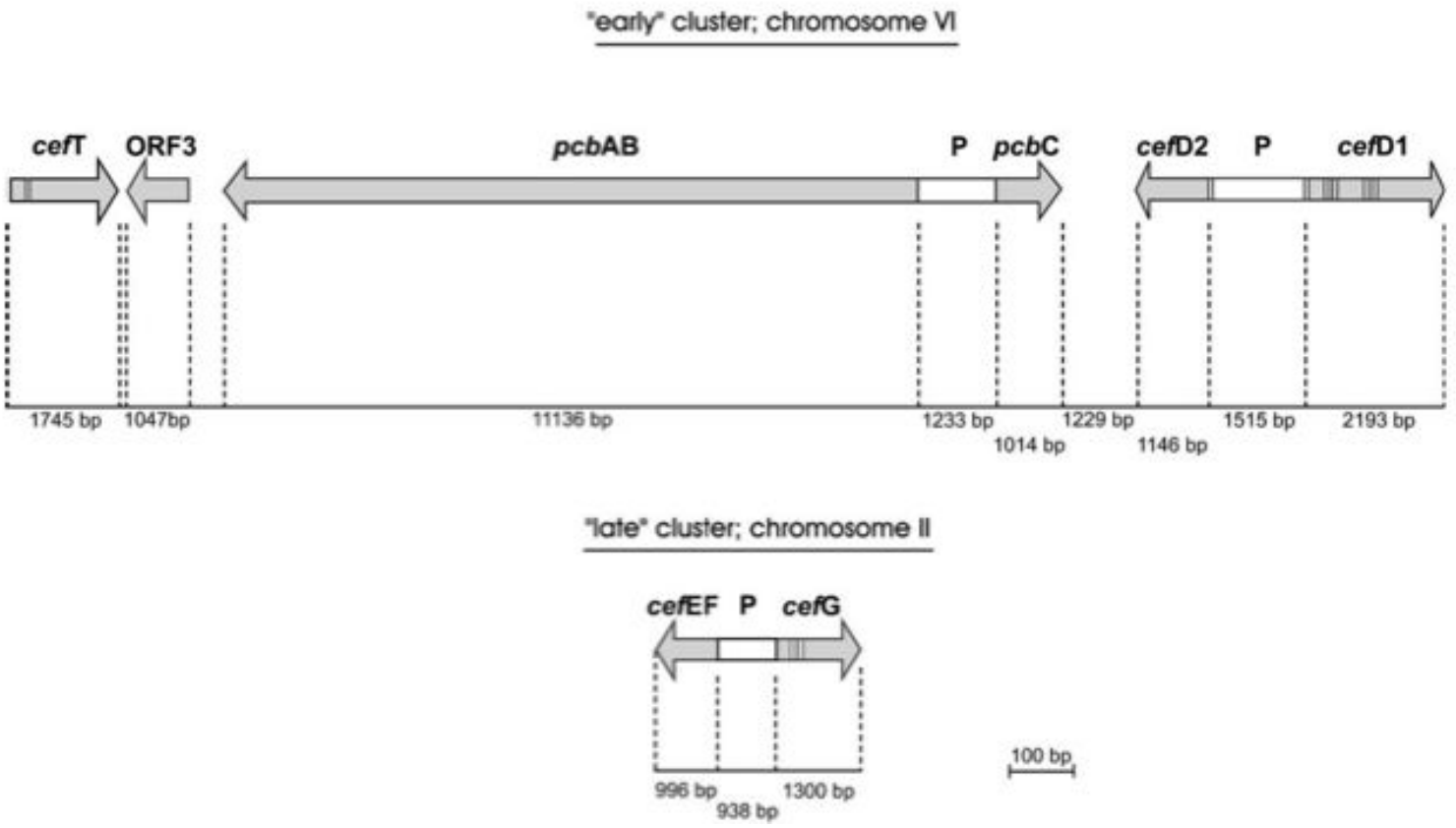
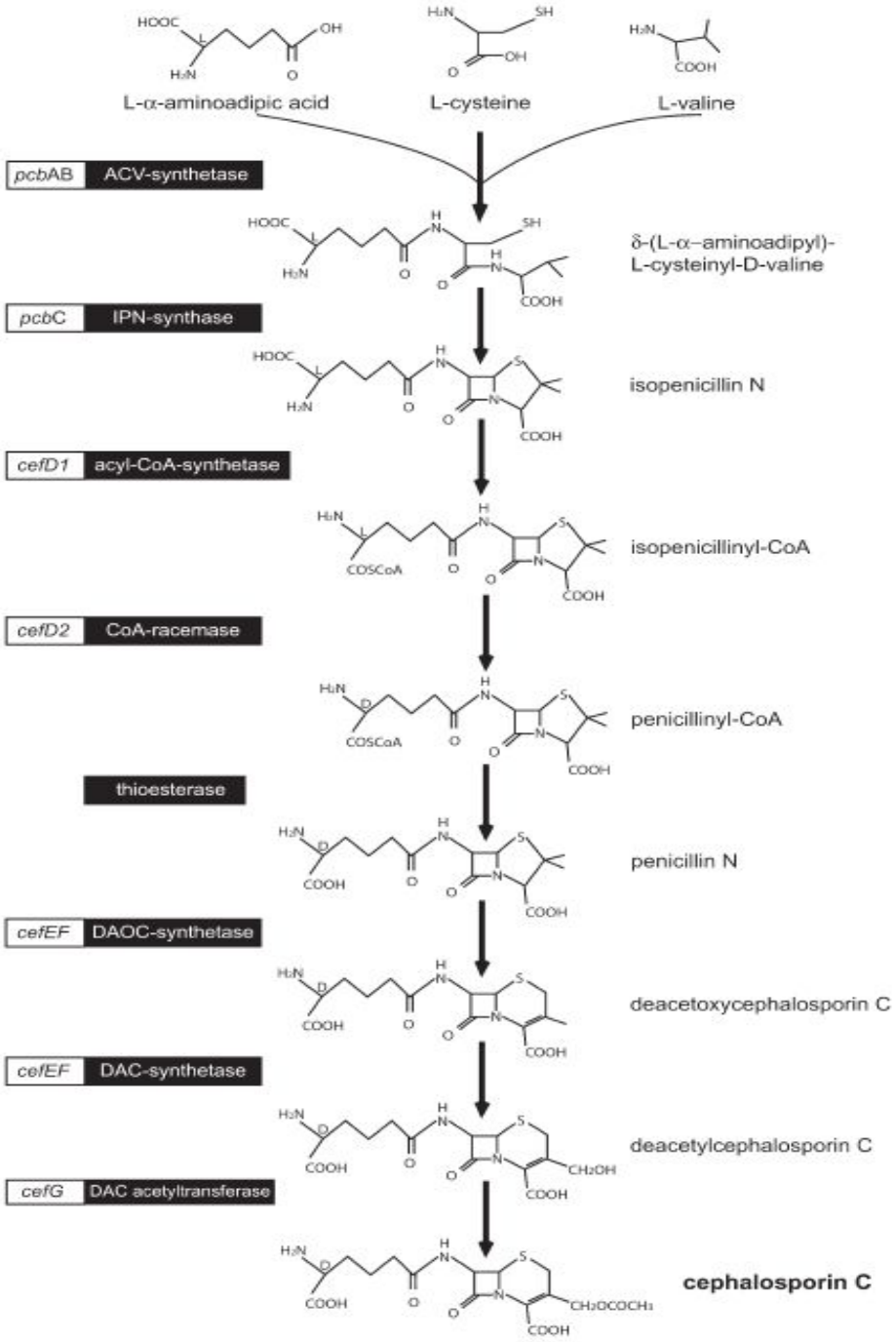
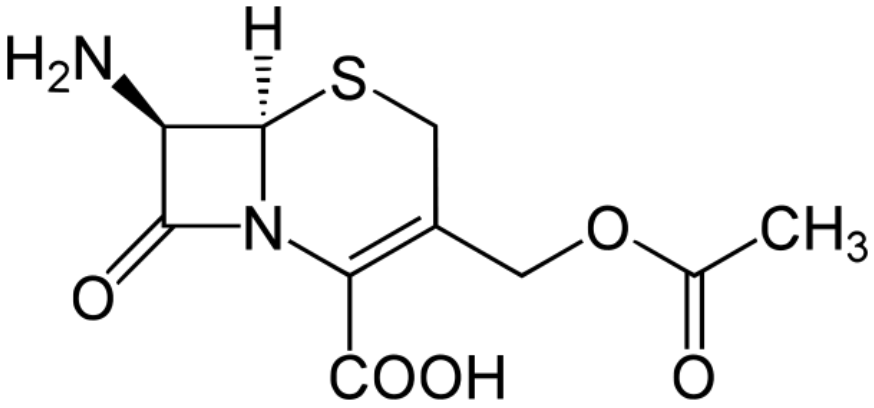


Table 1 Designation of genes, which have been isolated and characterized from *Acremonium chrysogenum*

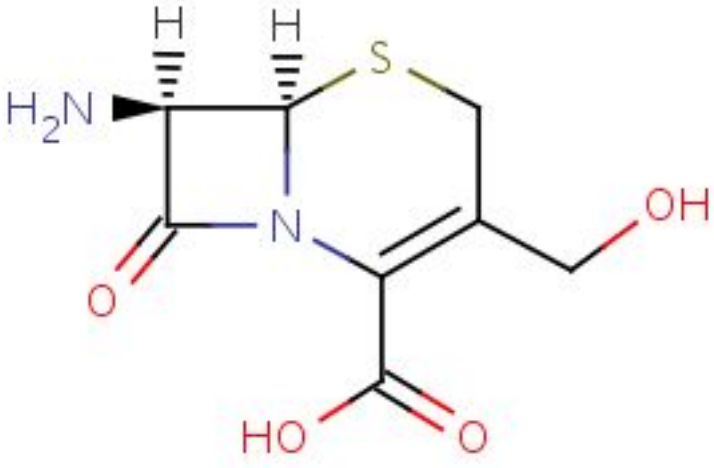
Gene abbreviation	Product
pcb AB (syn. *acvA*)	δ-(L-α-aminoadipyl)-L-cysteinyl-D-valine synthetase
pcbC (syn. *ipnA*)	isopenicillin N synthase
cefD1	acyl-CoA-synthetase
cefD2	acyl-CoA-racemase
cefEF	deacetoxycephalosporin C/deacetylcephalosporin C synthetase
cefG	acetyl-CoA: deacetylcephalosporin C acetyltransferase
lys2	α-aminoadipate reductase
mecB	cystathionine-γ-lyase
cpcR1	cephalosporin C regulator 1
cre1	carbon catabolite repressor CRE1
pacC	pH-dependent transcription factor PACC


L-α-aminoadipic acid
L-cysteine
L-valine
pcbAB
ACV-synthetase
δ-(L-α–aminoadipyl)-
L-cysteinyl-D-valine
pcbC
IPN-synthase
isopenicillin N
cefD1
acyl-CoA-synthetase
isopenicillinyl-CoA
cefD2
CoA-racemase
penicillinyl-CoA
thioesterase
penicillin N
cefEF
DAOC-synthetase
deacetoxycephalosporin C
cefEF
DAC-synthetase
deacetylcephalosporin C
cefG
DAC acetyltransferase
cephalosporin C

Industrial intermediates

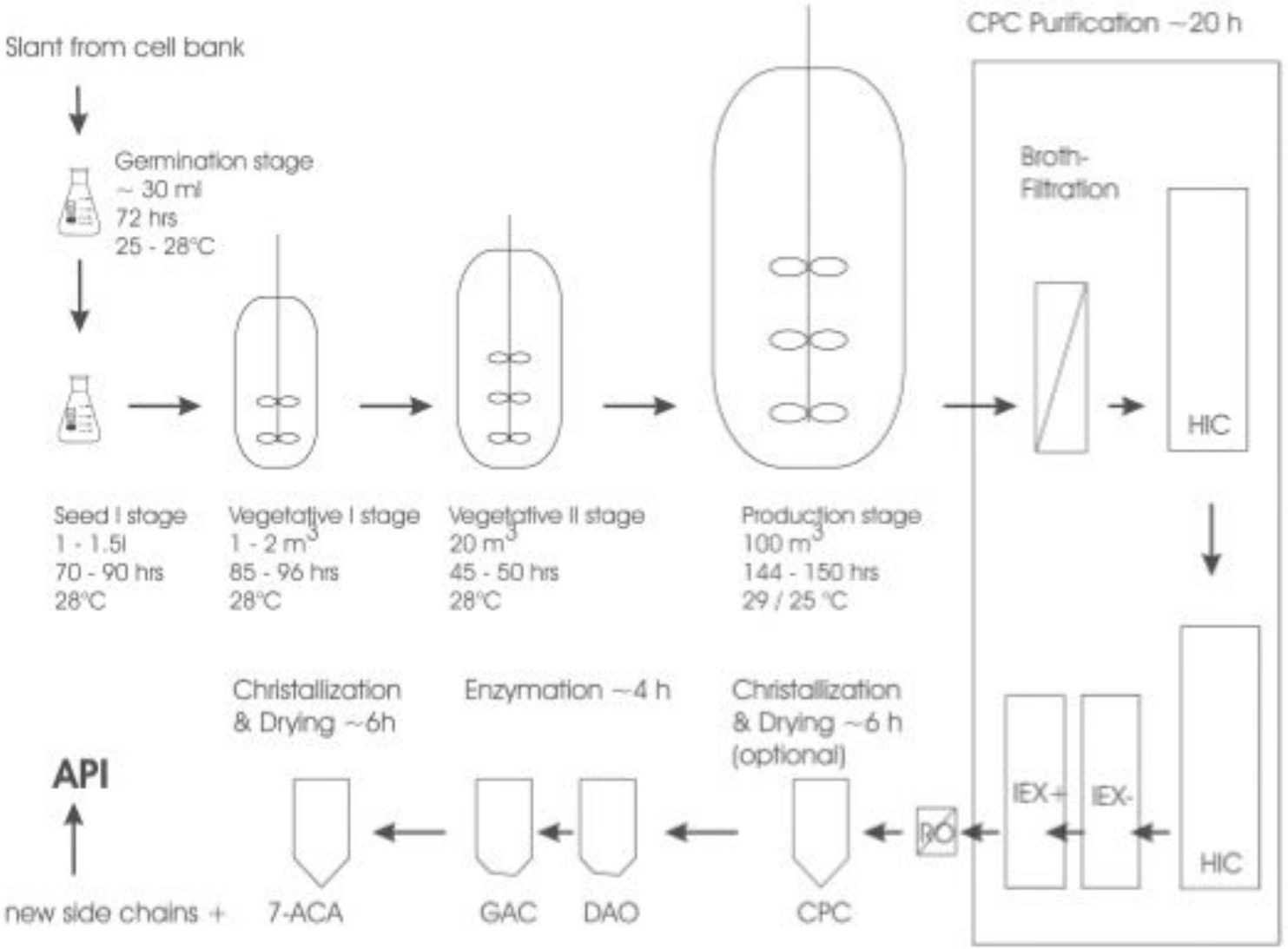


7-aminocefalosporanic acid (7-ACA)



Deacetyl-7-aminocefalosporanic acid (7-ADCA)

Cefalosporin prodution : Steps Involved



Purification of CPC

A.Chrysogenum fermentation broth

↓

Filtration

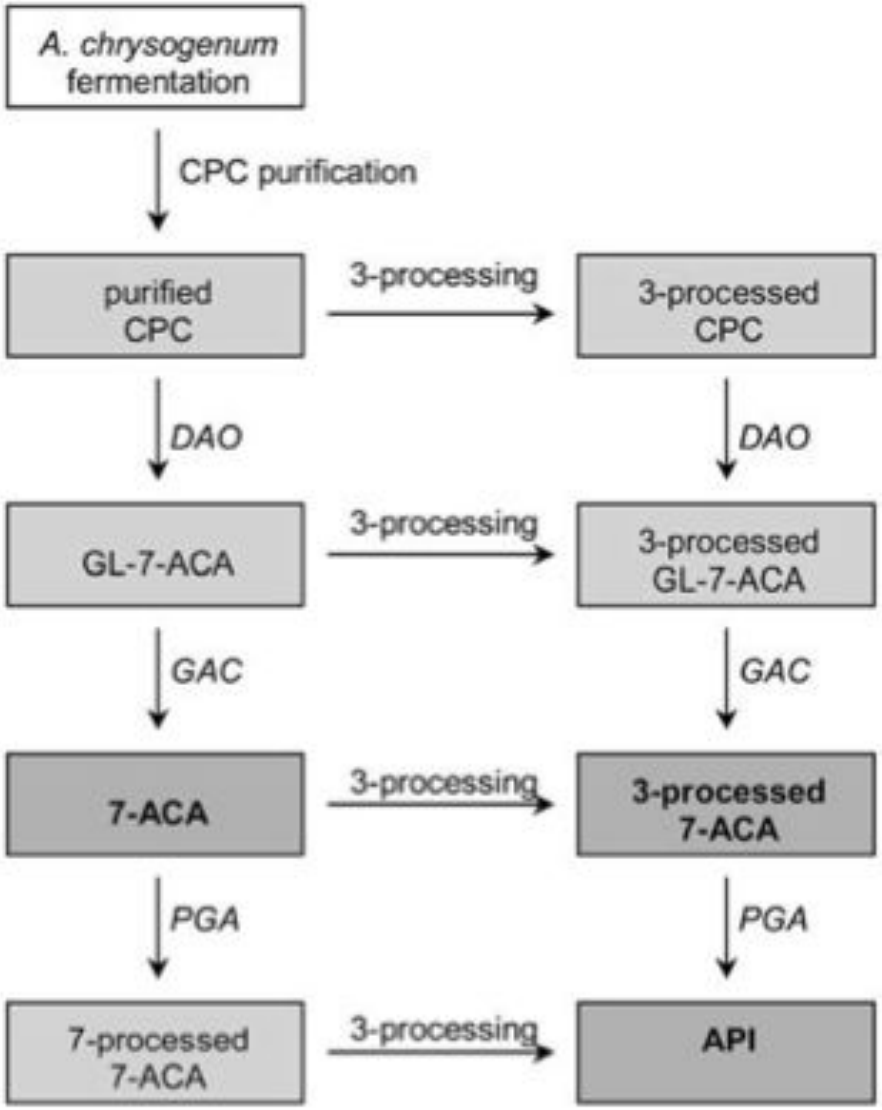
↓

Large scale HIC columns for removal of proteins, peptides

↓

1. Scavenger cloumn: operated at pH5.5-6
2. Adsorber resin: Higher capacity. pH based separation of CPC from DAC and DAOC
3. Anion exchange column: CPC binds along with other anionic pigments and small molecules. Changing ionic strength ensures separation.

Synthetic routes from CPC to 7-ACA and 7,3 derivatives



Enzymatic conversion of CPC to 7-ACA