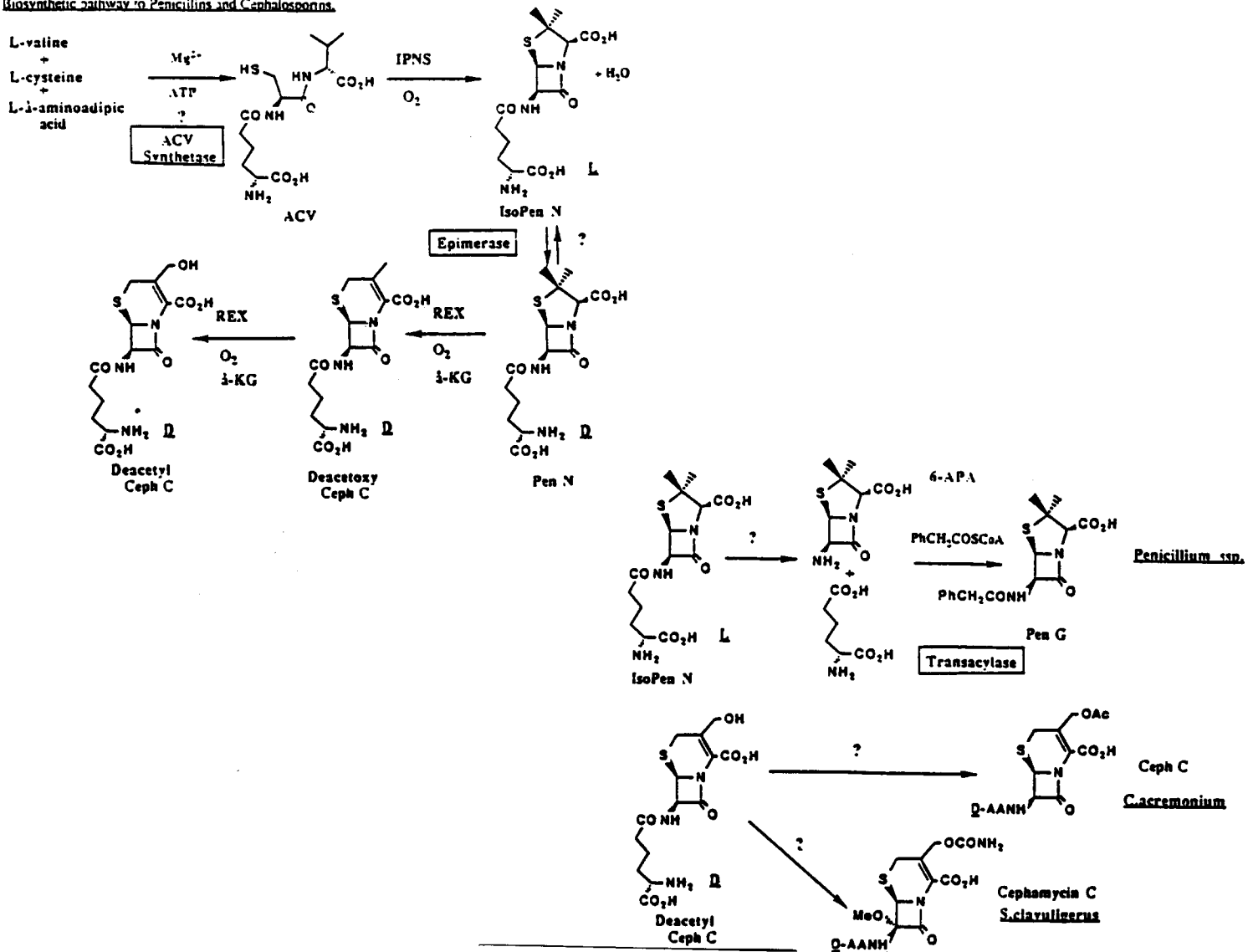


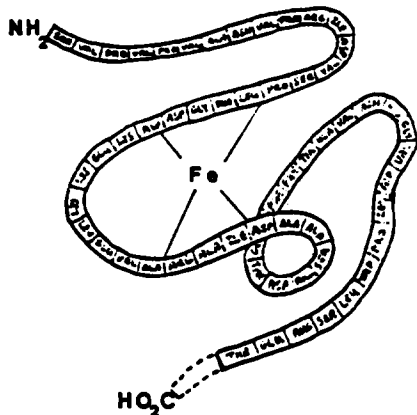
β -Lactam Antibiotics of Microbial Origin

[illegible]

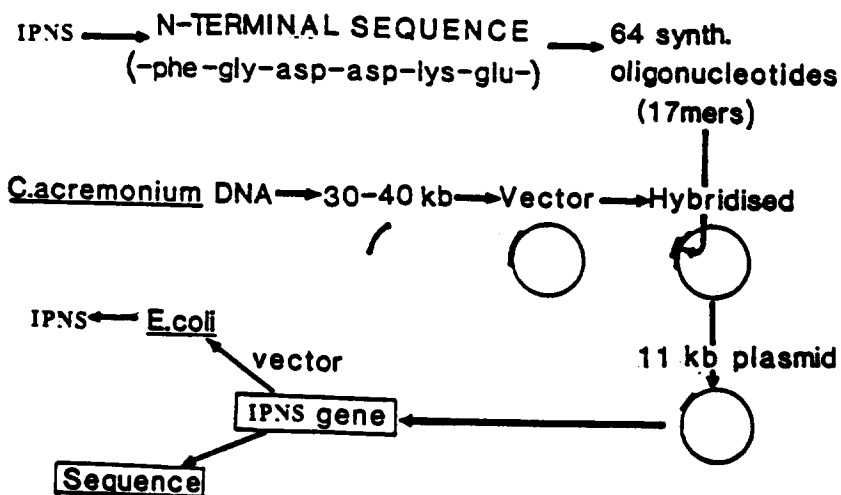
Biosynthetic pathway to Penicillins and Cephalosporins.



PROPERTIES OF ISOPENICILLIN N SYNTHASE IPNS



SINGLE POLYPEPTIDE CHAIN
 MW 38000.336 amino acids
 Km 0.20mM
 pI 4.8
 2 Cys, Fe
 λ_{max} 280nm only
 Inactivated < pH 6



T.D. Ingolia & S.W. Queener

DNA and AMINOACID SEQUENCE of IPNS

CEA	CEA	CEA	CAA	ACC	CTC	ACC	ATG	GCT	TCC	GTT	CCA	GTT	CCA	GTG	GCC	670
							NET	GLY	SEN	VAL	PRO	VAL	PRO	VAL	ALA	680
30																690
AAC	CTC	CCC	CGA	ATC	GAT	CTC	TCC	CCC	CTA	TTC	GCC	GAT	GAC	AAG	GAG	700
ASH	VAL	PRO	ARG	ILE	ASP	VAL	SEN	PRO	LEU	PHE	GLY	ASP	ASP	LYS	GLU	710
10																720
AAG	AAG	CTC	GAG	GTA	GCT	CGC	GCC	ATC	GAC	GCC	GCA	TGC	CGC	GAC	ACA	730
LTS	LTS	LEU	GLN	VAL	ALA	ARG	ALA	ILE	ASP	ALA	ALA	SEN	ARG	ASP	THR	740
																750
GCC	TTC	TTT	TAC	GCG	GTG	AAC	CAC	GCT	GTG	GAC	CTG	CCG	TGG	CTC	TCC	760
40																770
CGC	GAG	ACG	AAC	AAA	TTC	CAC	ATG	ACC	ATC	ACG	GAC	GAG	GAG	AAG	TGG	780
ANG	GLU	THR	ASN	LTS	PHE	NIS	NET	SEN	ILE	THR	ASP	GLU	GLU	LYS	TRP	790
20																800
GAG	CTC	GCC	ATC	CGG	GCC	TAC	AAC	AAG	GAG	CAC	GAG	TCC	CAG	ATC	CGC	810
CAG	LEU	ALA	ILE	ARG	ALA	TYR	ASN	LTS	GLN	NIS	GLU	NIS	GLN	ARG	200	820
70																830
CCG	TAC	CTG	CCG	ATC	CGC	ATC	CGC	ATC	CGC	ATC	CGC	ATC	CGC	ATC	CGC	840
80																850
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90																870
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100																890
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150																990
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170																1030
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180																1050
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560																1810
CCG	TAC	CTG	CCG	ATC	CGC											

IPNS Sequence for Penicillin Cephalosporin

PEN MAST--PKANUPKIDUSPLFGONHEEKMKUARRIDAASRDTGFFYAUNHGUDUKALSNKTR
CEPH G UPU U R DK K LE A A LPW RE

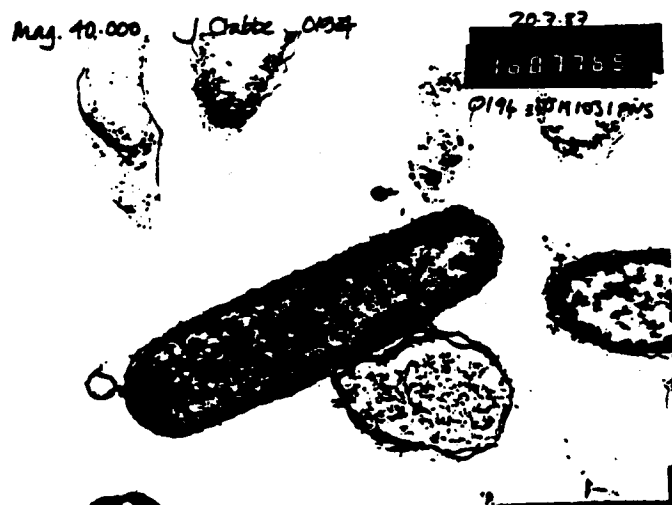
PEN EFMFSITDEEKVDLAINRYNKENQDQIRAGYYLSIPEKKAVESFCYLNPHFKPDNPLIQSK
CEPH K M Q ES P O S S R KEP

PEN TPTHEVNVMPDEKKHNPGRFEPAEQYIYNDVFLSSALLRGYALALGKEEDFFSRHFKKEDAL
CEPH M A A K V A AD TA SAADTT

PEN SSVVLIRYPYLNPIPPAAIKTAEDGKLSFEVHEDUSLITULYQSDVANLQVENPQGILDI
CEPH A D Y EP AD Q KT WQ

PEN EADDNAYLVNCGSYMANITNMYYPAPINRYKVMYNEERQSLPPFVNLGFNDTVQPWOPSKE-
CEPH Q TGF I DD A WE I ATAK

PEN DGKTDQRP----ISYGDYLQNGLYSLINKNGQT3
CEPH AK AAKDKPA E G AG 1



Large Scale Production of Recombinant IPNS

E. coli. JM103 containing plasmid pIT337.

Grown in 25 L fermenter in medium containing kanamycin, producing 300-400 g (w.w.) of cells.

Cells harvested by tangential flow filtration, and lysed by lysozyme/DNase I incubation.

PURIFICATION

STEP	TOTAL PROTEIN (mg)	TOTAL ACTIVITY (i.u.)	SP. ACT. (i.u./mg)	PURIFICATION (fold)
1. LYSIS				
4 x 50 g cells, supernatant after protamine sulphate precipitation	12,500	2,500	0.2	
2. BIOPROCESS				
ion-exchange on Q Fast Flow	1,000	2,000	2.0	10

Samples of material after Bioprocess ion-exchange can be further purified to homogeneity using FPLC Mono Q (16/10) ion-exchange.

TWO FORMS of IPNS

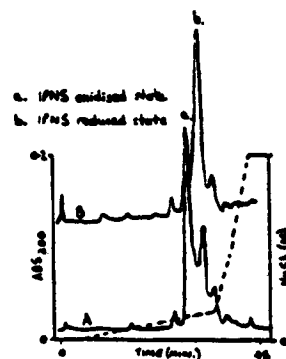


Fig. 1. FPLC of IPNS: (a) before treatment with 10 mM dithiothreitol and (b) after treatment with 10 mM dithiothreitol. (—) Absorbance at 280 nm, (---) UVCT gradient. For details see text.

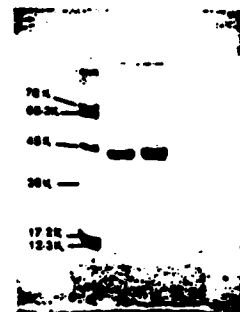
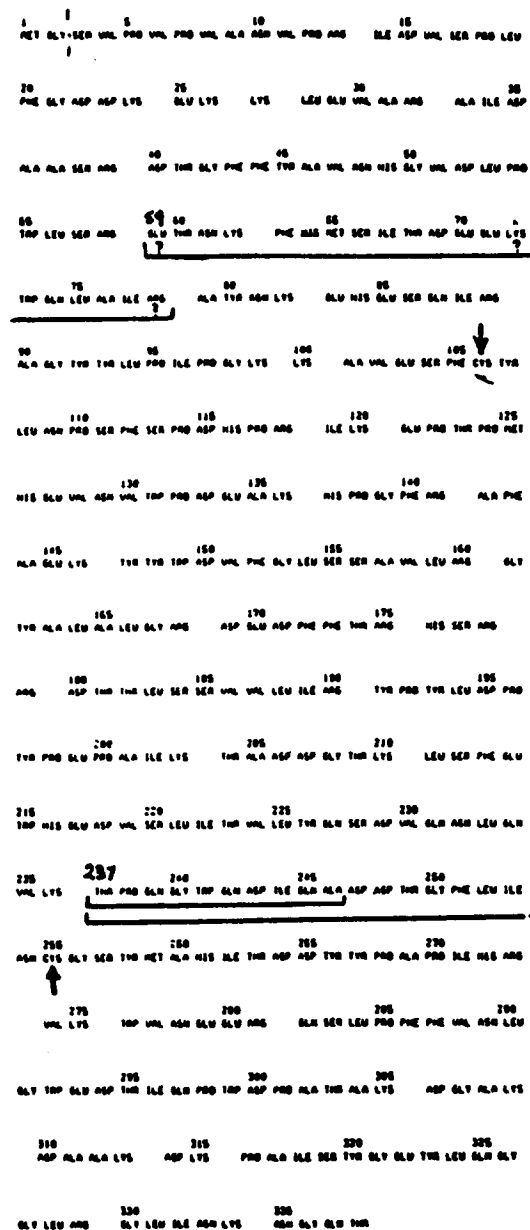
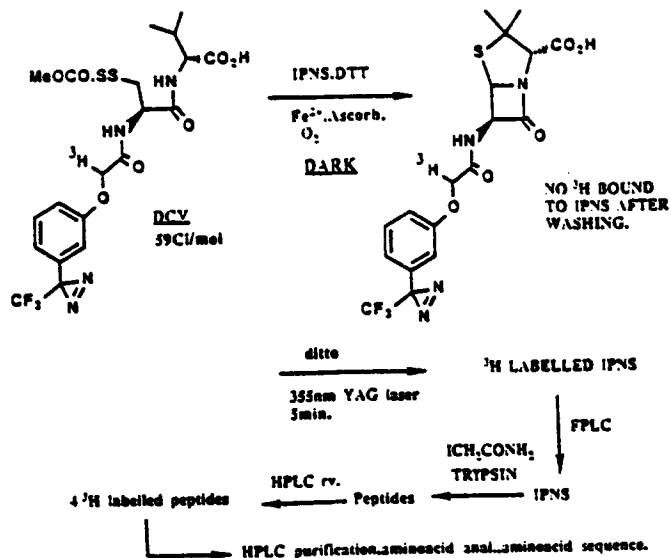
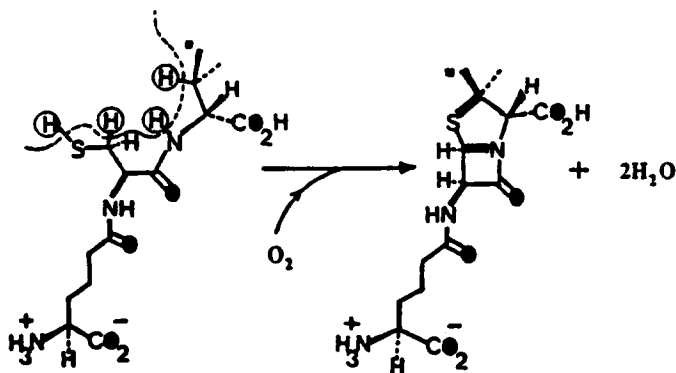
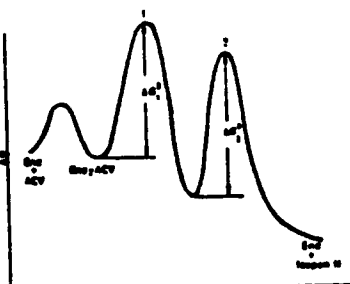
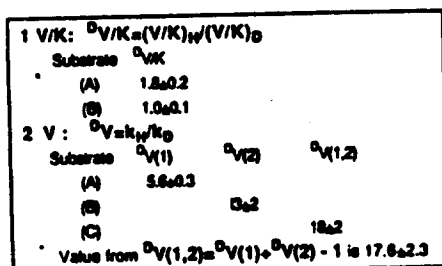
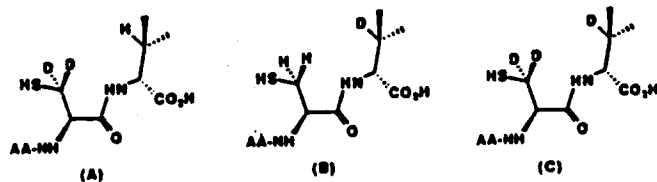


Fig. 2. SDS-PAGE of IPNS: 100 molecular weight markers, 10 oxidized form and 10 reduced form. The oxidized form was obtained by FPLC of the reduced form which had been left at 4°C overnight.

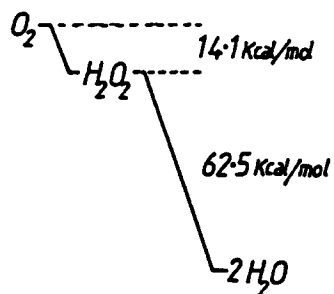
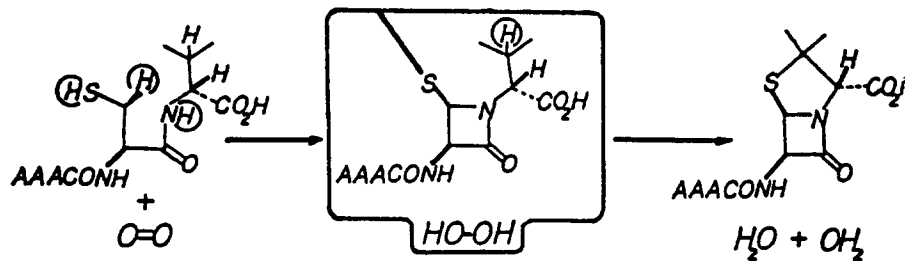
Photoaffinity Labelling of IPNS (rec.)

**STOICHEOMETRY-STEREOCHEMISTRY**

KINETIC ISOTOPE EFFECTS in IPNS



ENZYME-BOUND INTERMEDIATE



Interception of Enzyme-Bound Intermediate

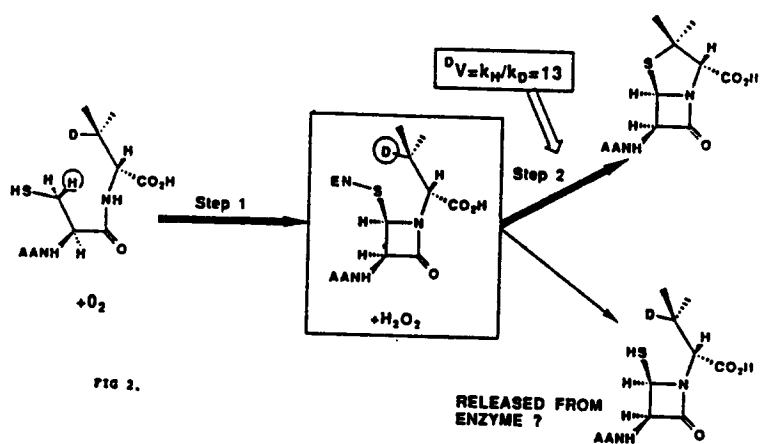
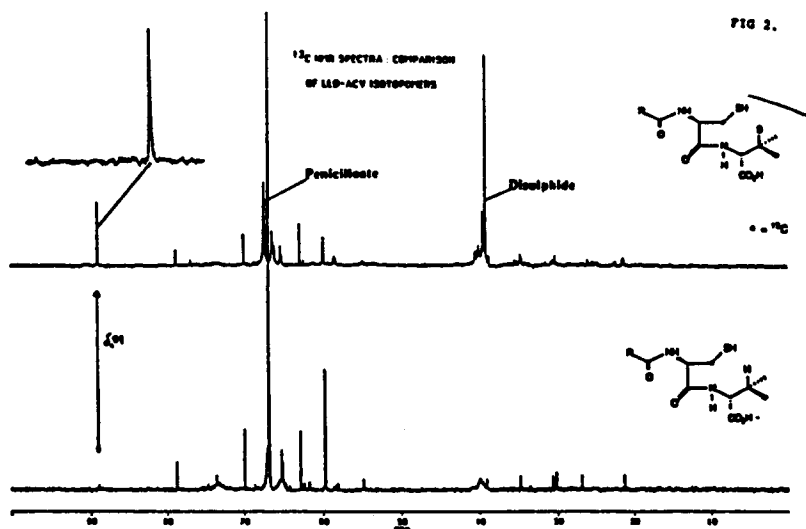
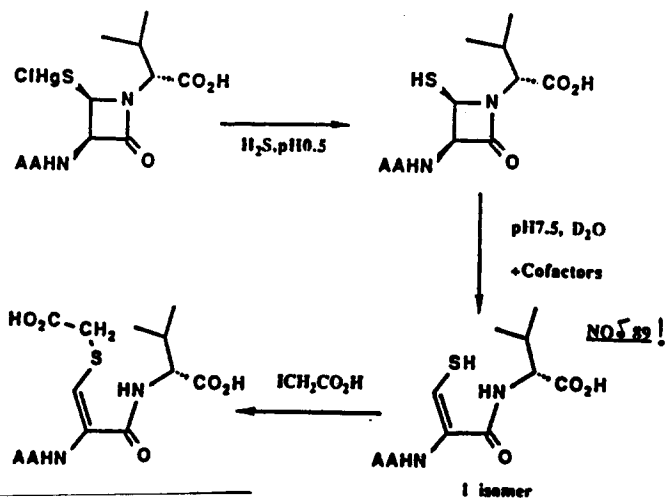


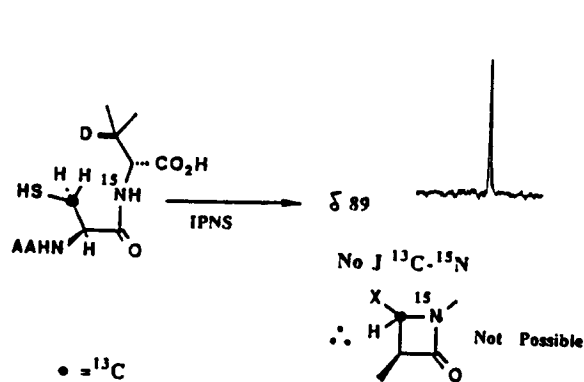
FIG. 2.



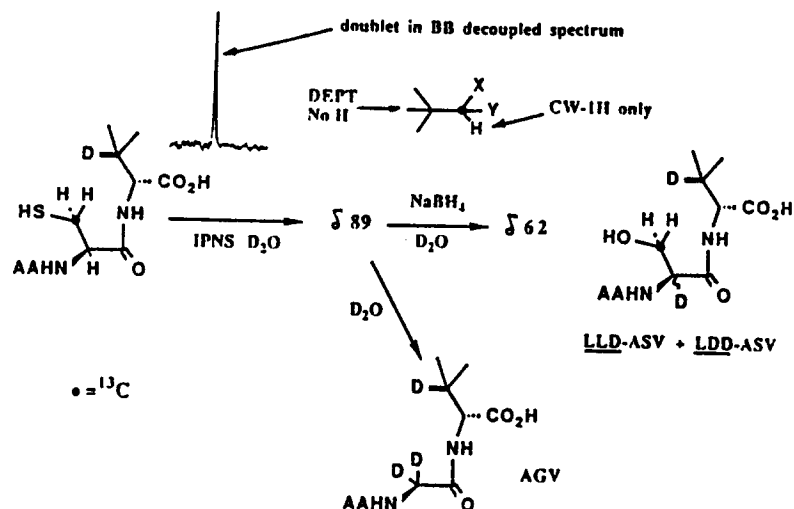
Fate of Monocyclic Mercaptazetidines under Incubation Conditions



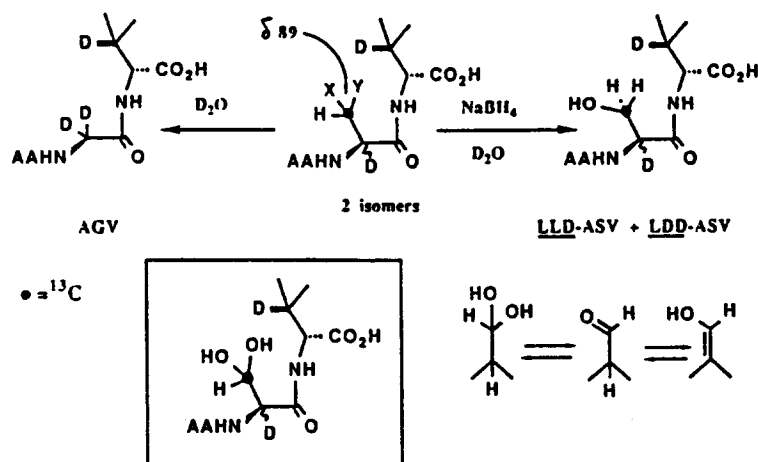
Structure of unstable δ 89 product



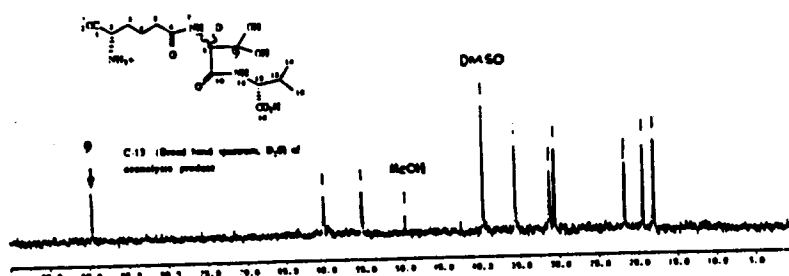
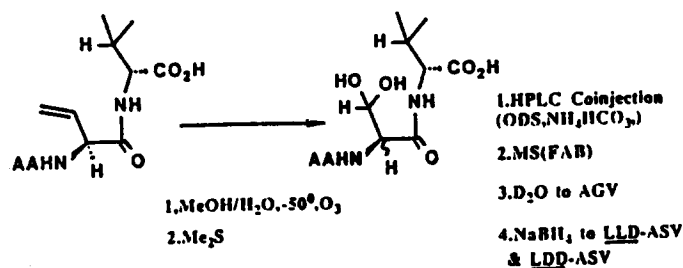
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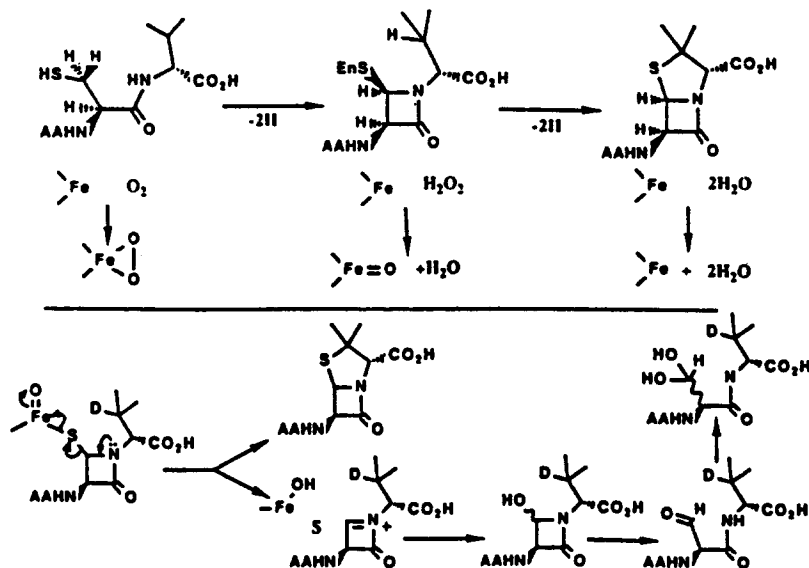
Structure of unstable δ 89 product



Synthesis of δ 89 Product



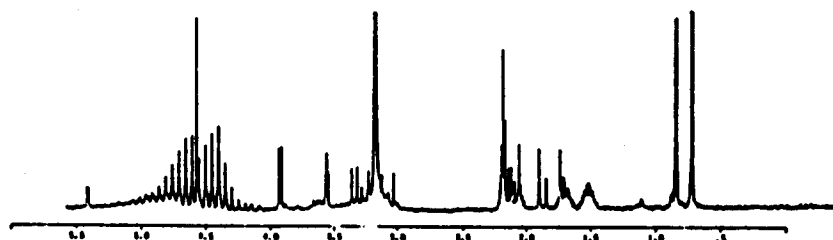
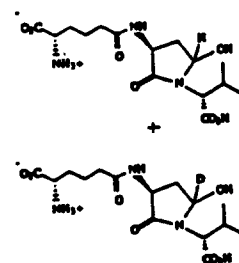
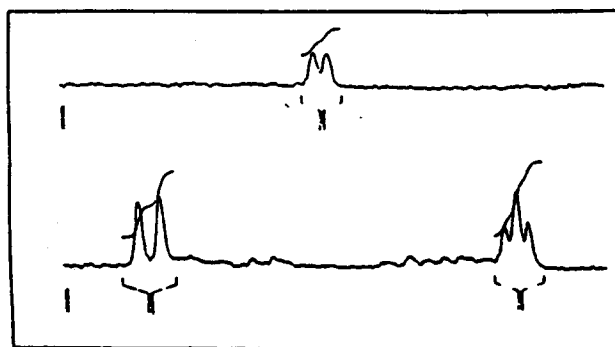
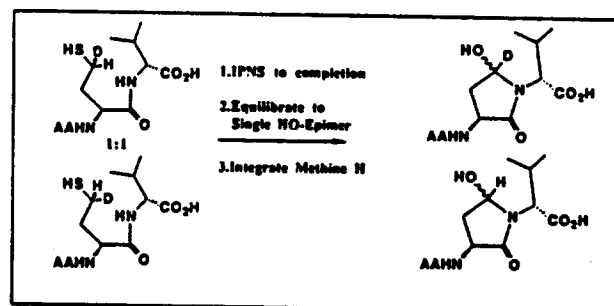
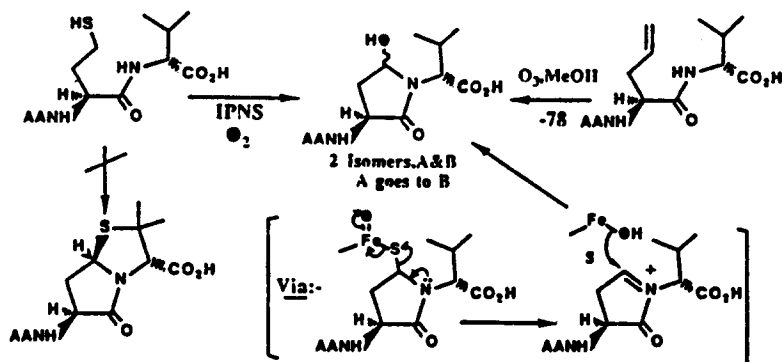
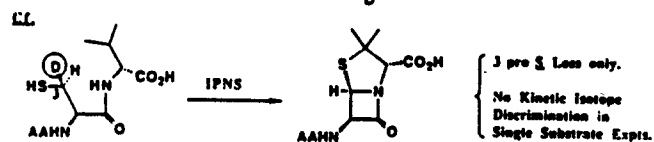
Nature of Intermediate



Stabilisation of Acyliminium Ion

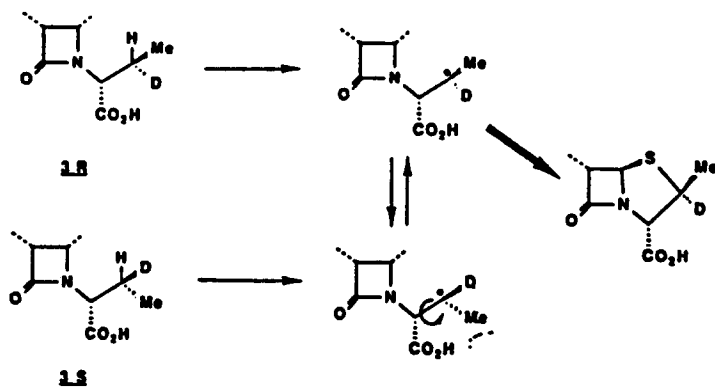
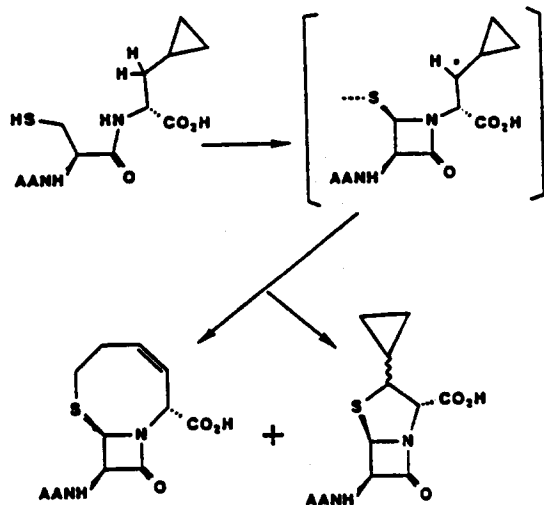
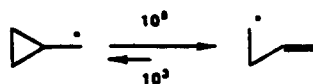
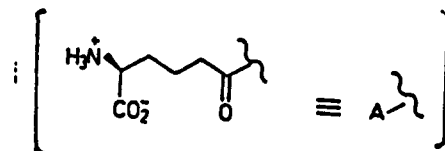
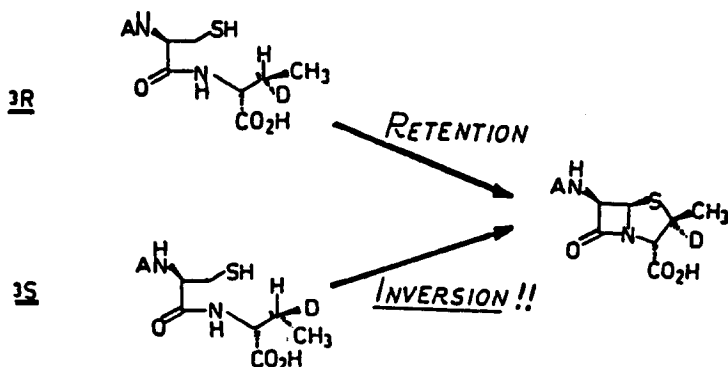
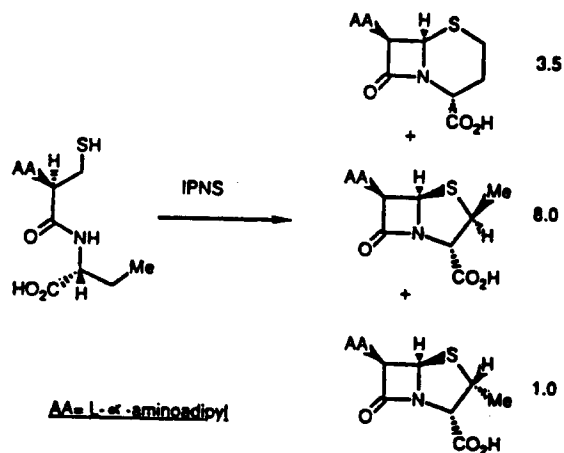
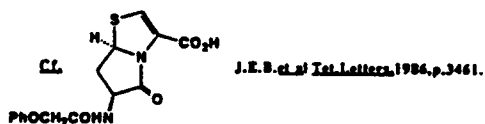
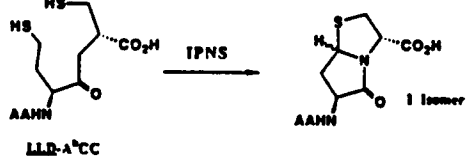
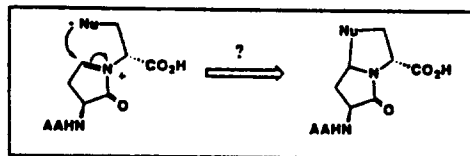


STEREOCHEMISTRY OF LACTAM FORMATION



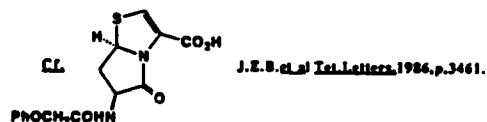
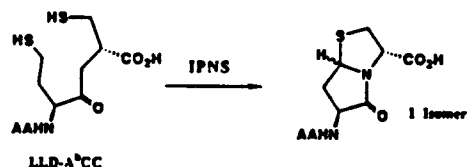
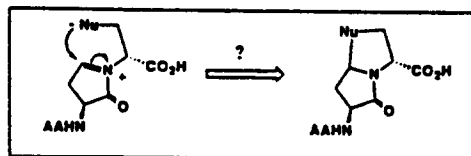
INTERNAL TRAPPING OF ACYLIMMINIUM ION

Formation of [3.3.8] Systems

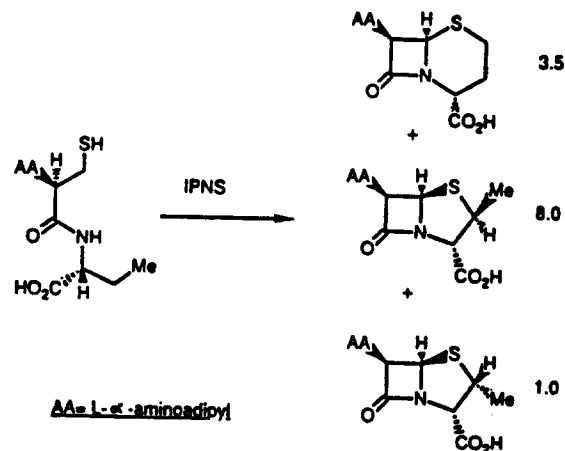


INTERNAL TRAPPING OF ACYLIMMINIUM ION

Formation of [3.3.0] Systems

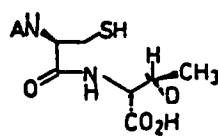


J.E.B. et al. *Tet. Letters*, 1984, p.3461.



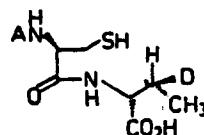
AA = L-α-aminoadipyl

3R

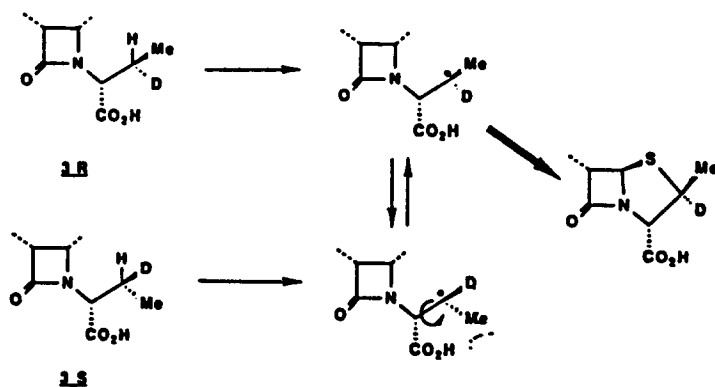
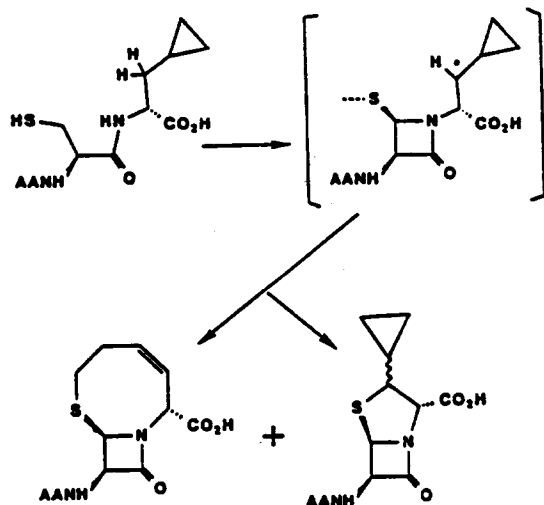
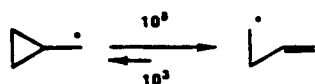
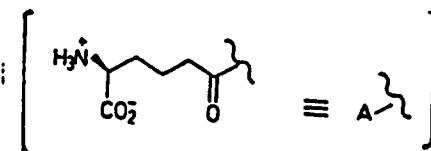
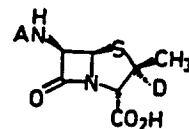


RETENTION

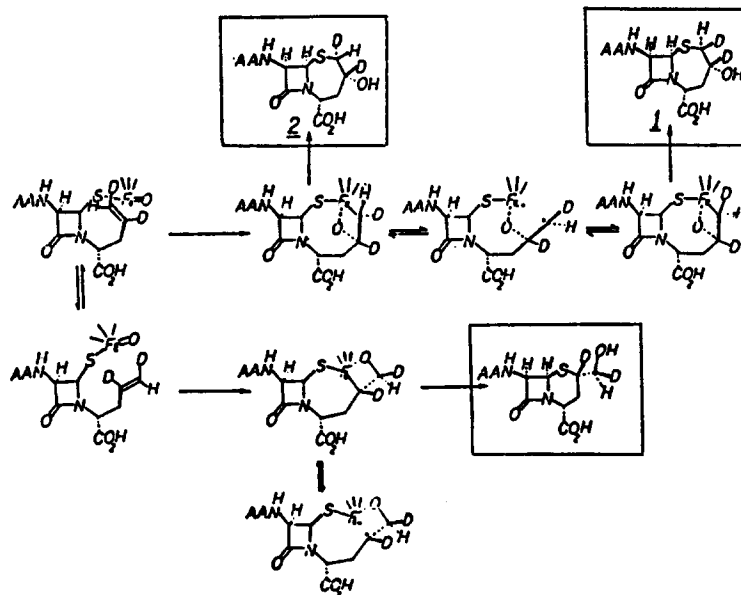
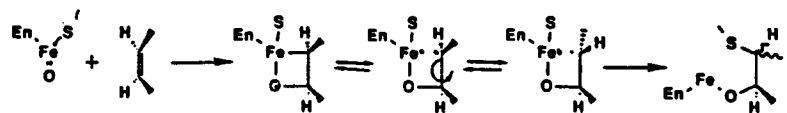
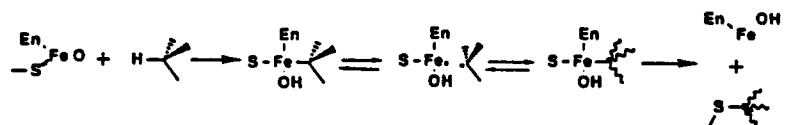
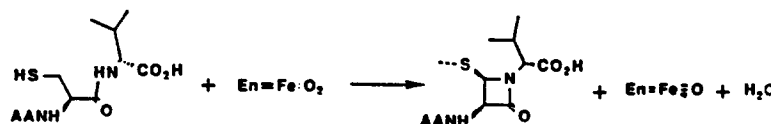
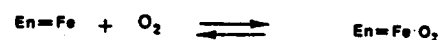
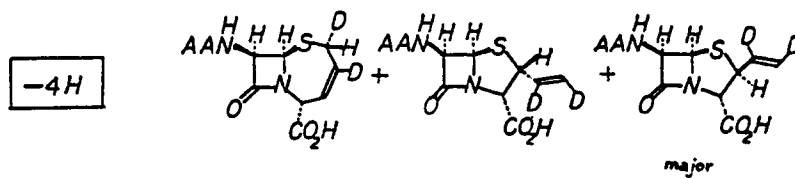
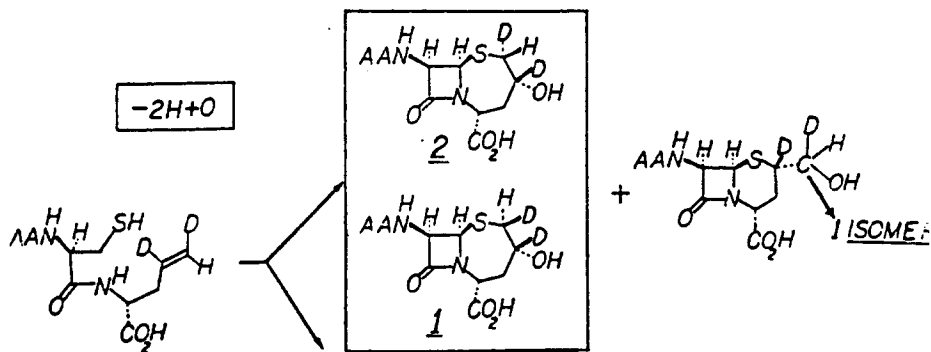
3S



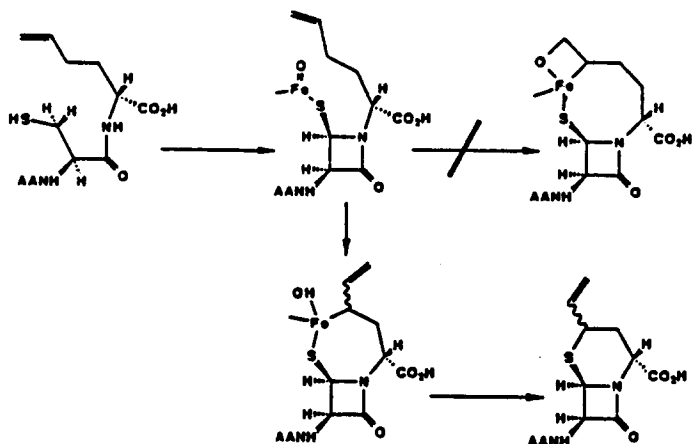
INVERSION !!



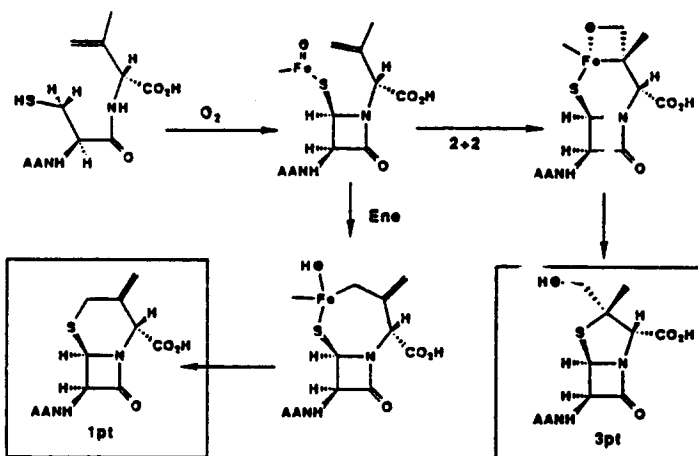
DEHYDROGENATION VS. OXYGEN TRANSFER



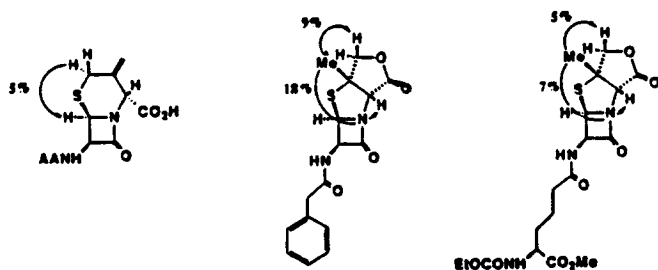
Fe BINDING SITE FIXED RELATIVE TO ACV 1



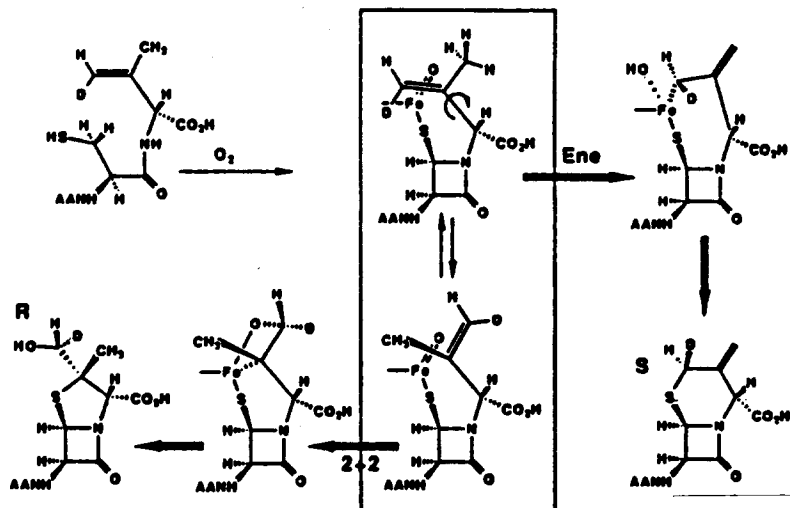
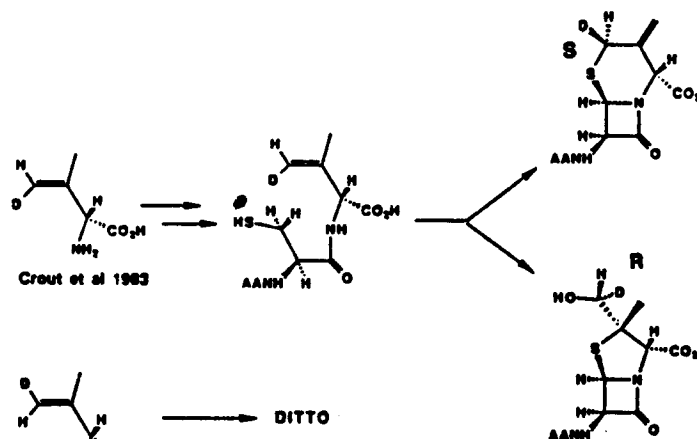
Fe BINDING SITE FIXED RELATIVE TO ACV 2



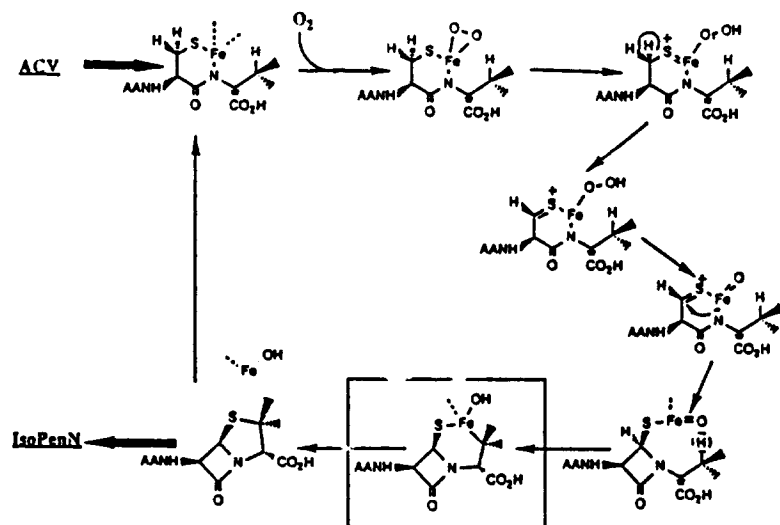
STEREOCHEMISTRY: N.O.s. Enhancements



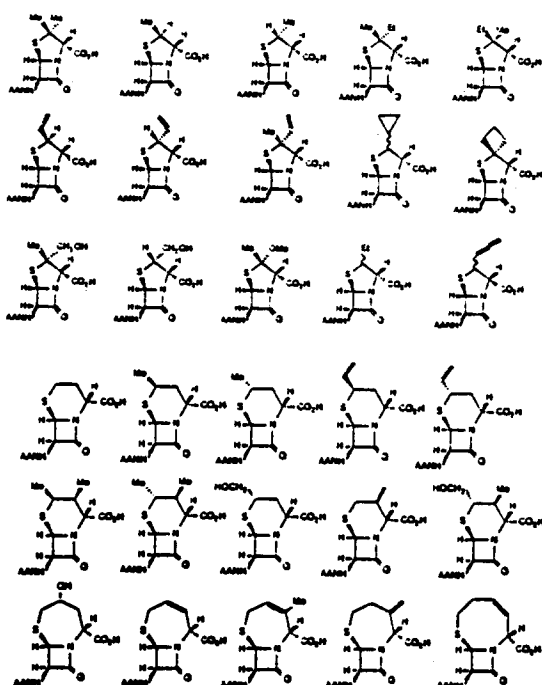
STEREOCHEMISTRY



Proposed Mechanism of IPNS Catalytic Cycle



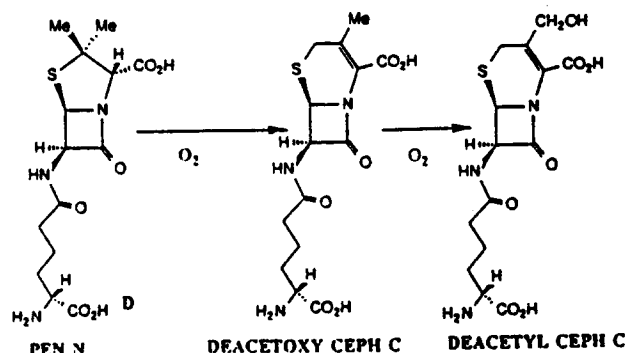
PROPERTIES of RING EXPANSION-HYDROXYLASE (REX)



MW ca 40,000

COSUBSTRATES 1. α -KETOGLOUTARATE
2. DIOXYGEN

COFACTOR Fe^{2+}



BIFUNCTIONAL ENZYME

RING EXPANSION-HYDROXYLASE (REX)

C. acremonium C.O. 728 ———— homogenous protein

peptide fragments sequenced

N-terminus blocked

gene probes

c DNA

PREDICTED AMINOACID SEQUENCE
332 aminoacids

HYPOTHETICAL ACTIVE SITE REGION IN IPNS and REX

REX — GLY-LYS-TYR-SER-ASP-TYR-SER-THR-CYS-TYR
IPNS — GLY-LYS-LYS-ALA-VAL-GLU-SER-PHE-CYS-TYR



-90 -70 -50

TTCGTTCTCACTGGCATCTTCTGCATCTCTAAATTCTCTCTTGAGAACCTTTCTCCACCG

-30 -10 10

TACTCCTCTCAAGTTCATCGCTCAAACCACGACATCAACTGCACTTCCAGGTCCCGCT
MetThrSerLeuValProval

30 50 70

TTTCGTTCTCAAGCACTTCAAGACCGCGAAGGCTCTCACCGAGCTCCGCCAGGCCCTCAGCC
PheArgLeuAspAspLeuLysSerGlyIleValLeuThrGluLeuAlaGluAlaValThr

90 110 130

ACCAAGGCTTCTTCTACTTTCACCGACAGCGCGCTCGTCTGCACGACCAACCAACCTCCGGG
ThrLysGlyTllePheTyrlauThrGluLysSerGlyLeuValAspAspAspHisThrSerAla

150 170 190

CCTGACAGCTTCGTTGACTTTTTCAAGAACGGAAGCTCAGGAGGAGACAAGGCCCTCGAGC
ArgGluThrTrpValAspPhePheLysAsnGlySerGluGluGluLysArgAlaValThr

210 230 250

CTCGCCAGCTTAACACCCCGCCCGCTCTCTCTCCCTCGAGTCGGAGACGACCCCGCTC
LeuAlaAspArgAsnAlaArgArgGlyPheSerAlaLeuGluThrGluSerThrAlaVal

270 290 310

GTCACCGACACGGCAACTATCTCGCACTACTGCACTCTACTCTACCGCATCGCGCGC
ValThrGluThrGlyLysTyrrSerAspTyrSerThrCysTyrSerMetGlyIleGlyGly

330 350 370

AACCTGTTCCGSAACCGCGGCTTCGAGGACCTCTGCAAGCACTACTTCGACCTCATCTAC
AsnLeuPheProAsnArgGlyPheGluAspValTrpGlnAspTyrPheAspArgMetTyr

390 410 430

CGCCGACCCCAAGGATGTCGCGCGCGCGCTTCTCAACTCTGTGGCGCGCGCTCGCGCGG
GlyAlaIleLysAspValAlaArgAlaValLeuAsnSerValGlyAlaProLeuAlaGly

450 470 490

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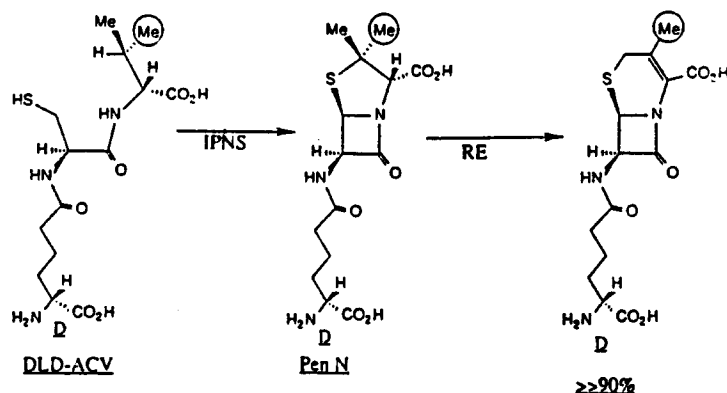
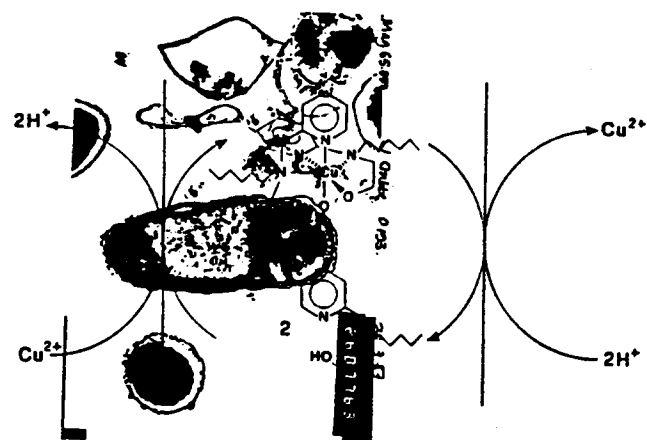
510 530 550

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ValProGluAspArgValAlaGluGluGluProLeuAspMetGlyProHisTyrAspLeu

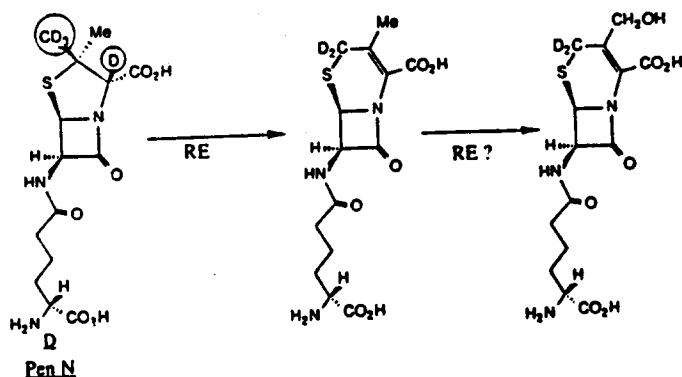
570 590 610

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 SerThrIleThrLeuValHisGlnThrAlaCysAlaAsnGlyPheValSerLeuGlnCys
 630 660 670
 CAGGTGGACGGAGAAATTCGTGCACCTCTCCGACGCTCCCGCGCCCATGTGTGGCTCTCTCG
 GluValAspGlyGluPheValAspLeuProThrLeuProGlyAlaAsnValValPheCys
 690 710 730
 GCGCGCGCTGCCACCGCTGGCCACGCGCGCGCAAGCTCAAGCGCGCCCAAGCGCCCGGTCAAG
 GlyAlaValGlyThrLeuAlaThrGlyGlyGlyLysValIleYalaProLysHisArgValIys
 750 770 790
 TCTCCCGCGCGCACAGCGCGCTCGCCAGCGCGACGCGCGAGCTCGAGCGCTCTCTCTCTCGCG
 SerProGlyArgAspGlnArgValGlyGlySerSerArgThrSerSerValPhePheLeuArg
 810 830 850
 CGCAAGCGCGACTTCAGCTTCAACGTCACGCGACGTCGAGCGAGTGGGGTTTCAACGTCCCG
 ProLysProAspPheSerPheAsnValGlnGlnSerThrSerValTrpGlyPheAsnValArg
 870 890 910
 ATCCGCTCGGAGCGCACGACTTTCAGCGAGTGGCTTCGCGCGAACTATGTCACACATCGCG
 IleProGlyIleArgThrThrPheArgGluTrpLeuGlyGlyAsnTyrValAsnMetArg
 930 950 970
 AGGCATAAGCGCGCGCGCACGCGCGCGCTTCTCCCGCGCGCTCGCCCTCTCTCTACCGCA
 ArgAspLysProAlaAlaGluAlaAlaValProAlaAlaAlaProValSerThrAla
 990 1010 1030
 GCTCTATAGCGACTTAGCGAACCCTGGATCGAGTAATAAATCTACCGCGAGTTTAAAGA
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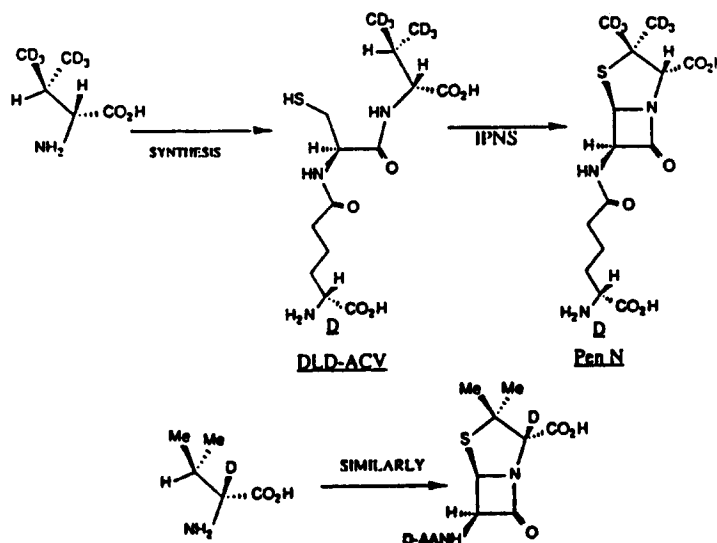
STEREOCHEMISTRY of RING EXPANSION

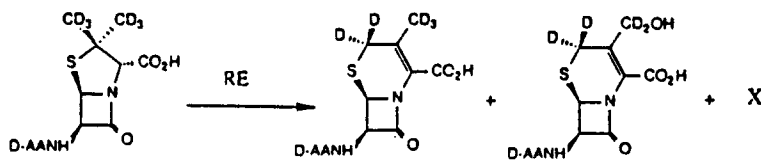


ISOTOPE EXPERIMENTS



PREPARATION OF DEUTERATED PENNS

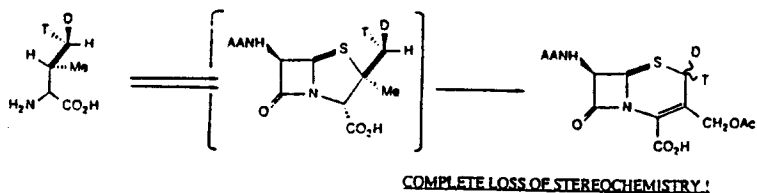




		D ₃	D ₄	D ₅		D ₄	D ₅
%Conversion	10	2	1	0		—	—
	40	3	3	1		—	—
	100	—	—	—		0	1

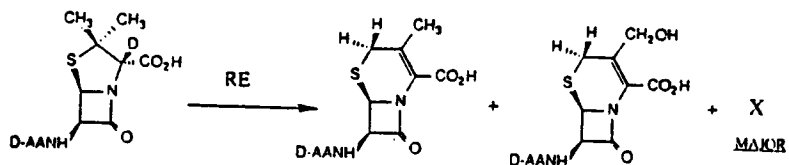
CEPHIS : X = 80 : 1

INTACT CELL EXPERIMENTS (C.acremonium)



C.A.TOWNSEND 1985

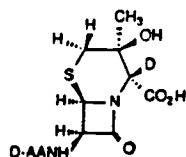
D.H.G.CROUT and E.P.ABRAHAM 1984



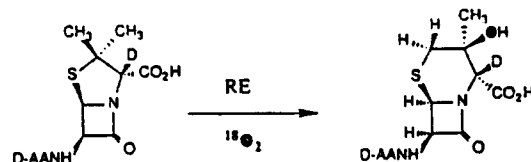
ORIGIN of HYDROXYL GROUP

STRUCTURE of X:

CEPHIS : X = 50 : 50

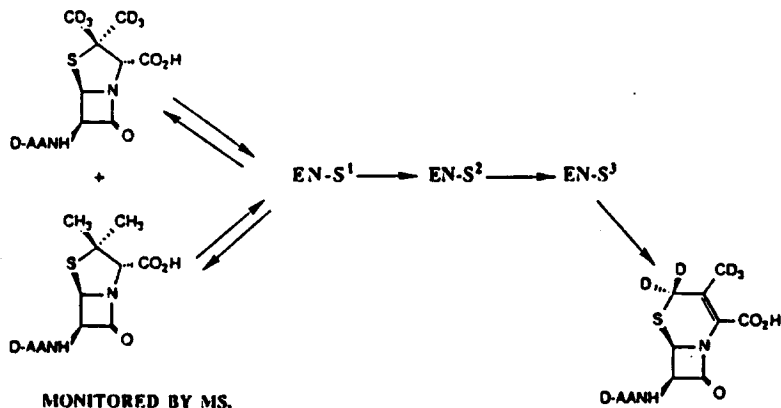


Identical to authentic sample

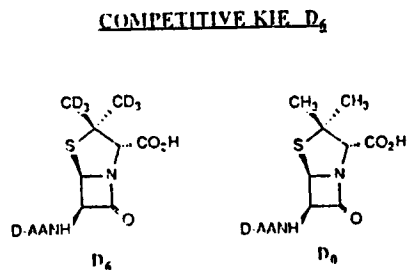


MS Analysis

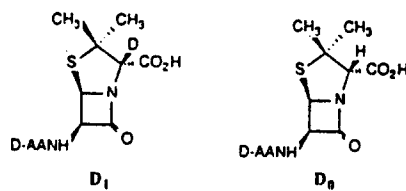
COMPETITIVE ISOTOPE EFFECT



COMPETITIVE KIE D_1

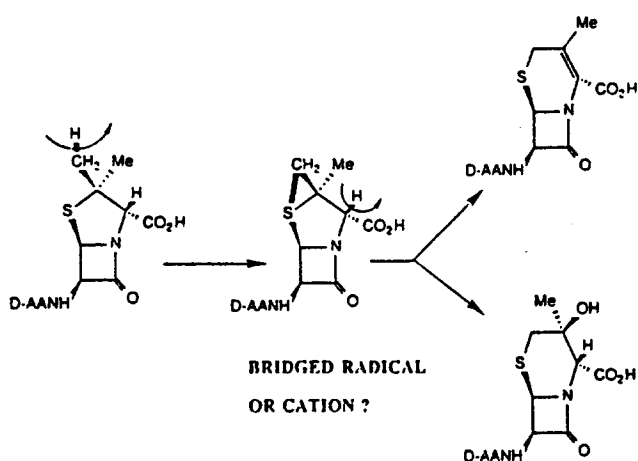


% CONVERSION	$D_4 : D_6$
0	1 : 0.94
30	1 : 0.50

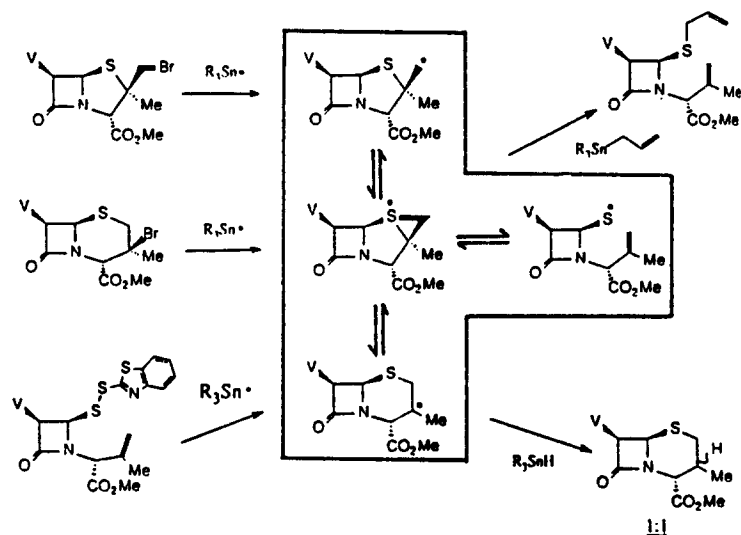


% CONVERSION	$D_1 : D_6$
0	1 : 0.95
30	1 : 0.95
65	1 : 0.93

ORDER OF HYDROGEN LOSS

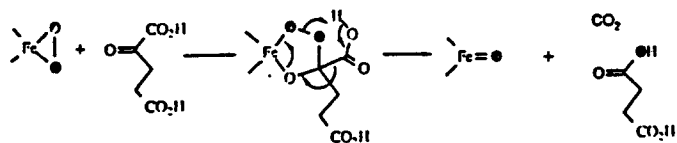


A SET OF EQUILIBRATING RADICALS

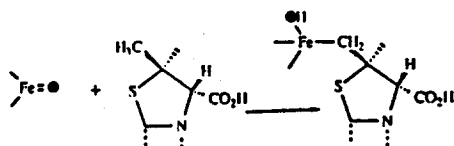


MECHANISM PROPOSED FOR RING EXPANSION

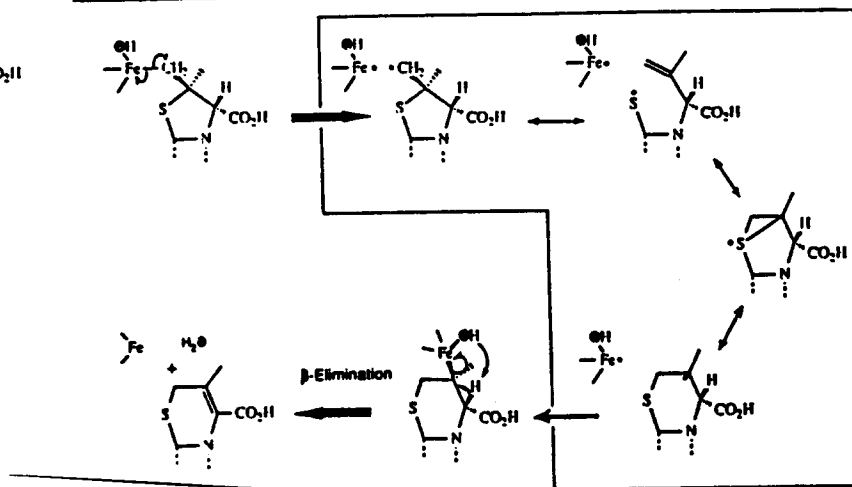
1. Iron-Oxo Formation



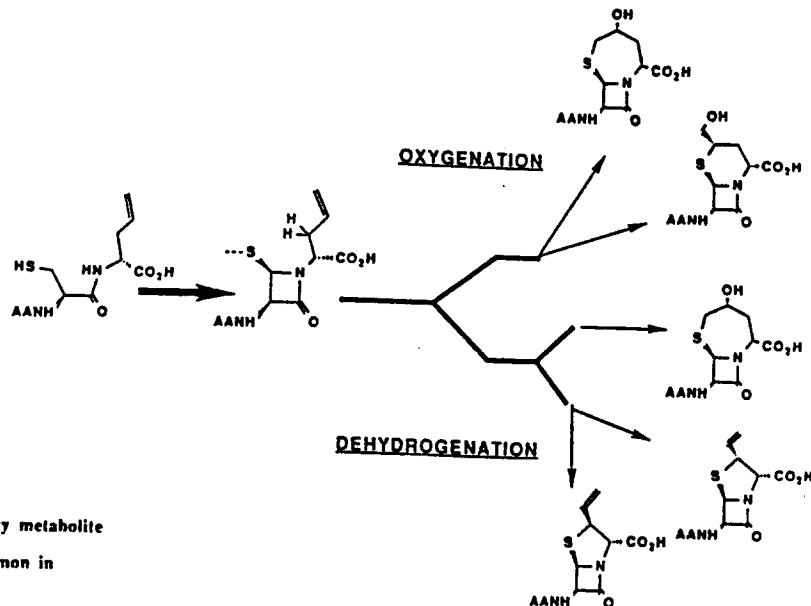
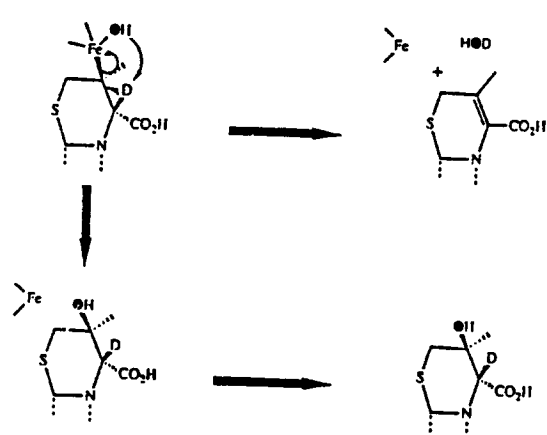
2. Insertion to form Iron-Carbon bond



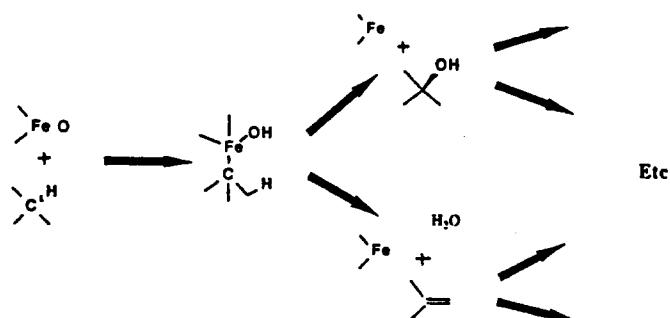
3. Homolysis and Rearrangement



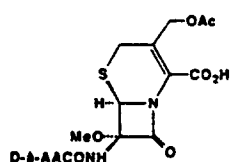
Radical Effect on Rearrangement



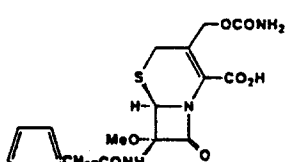
Can the presence of highly reactive iron-oxo species in secondary metabolite oxidative enzymes be a source of the structural multiplicity common in families of natural products ?



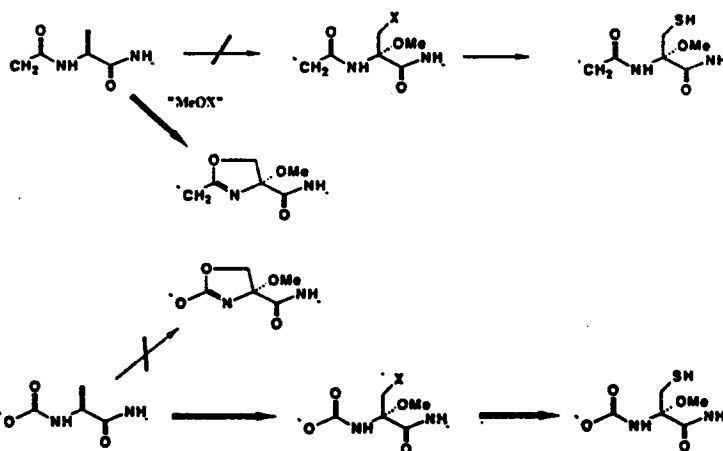
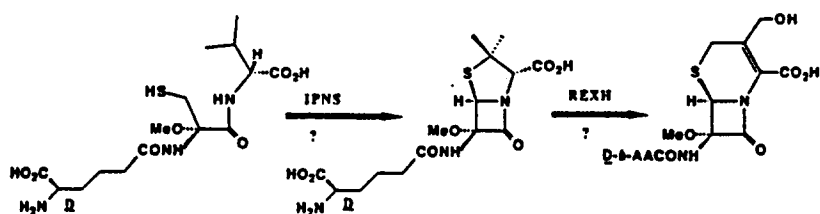
ENZYMATIC SYNTHESIS of CEPHAMYCINS 2



CEPHAMYCINS
Streptomyces sp
Nagarajan et al 1971



CEFOXITIN



METHOXYL SUBSTITUTION IN VALINE MOIETY.2

