β-LACTAMS
AND THEIR USES IN HETEROCYCLIC SYNTHSIS

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Abbreviations for Substituents and Commonly Used Reagents:

(a) Substituents:

Ac	─COCH3	(Acetyl)
Ar	Aryl	
All	─CH_2─CH=CH_2	(Allyl)
Bn	─$CH_2C_6H_5$	(Benzyl)
Boc	─OCO^{t}Bu	(*t*-Butyloxycarbonyl)
nBu	─$(CH_2)_3CH_3$	(*n*-Butyl)
*i*Bu	─$CH_2CH(CH_3)_2$	(*iso*-Butyl)
s-Bu	─$CH(CH_3)CH_2CH_3$	(*sec*-Butyl)
t-Bu	─$C(CH_3)_3$	(*tert*-Butyl)
Et	─CH_2CH_3	(Ethyl)
Me	─CH_3	(Methyl)
Ms	─SO_2Me	(Methylsulfonyl)
PMP	*p*- $CH_3OC_6H_4$	(*p*-Methoxyphenyl)
PNB	*p*-$NO_2C_6H_4$ CH_2	(*p*-Nitrobenzyl)
Ph	─C_6H_5	(Phenyl)
Phth	─$N(CO)_2C_6H_4$	(Phthalimido)
Pr	─$CH_2CH_2CH_3$	(*n*-Propyl)
*i*Pr	─$CH(CH_3)_2$	(*iso*-Propyl)
TBDPS	─Si^{t}BuPh_2	(*t*-Butyldiphenylsilyl)
TBS	─$SiBu_3$	(Tributylsilyl)
Tf	─SO_2CF_3	(Trifluoromethylsulfonyl)
TIPS	─Si^iPr_3	(Triisopropylsilyl)
TMS	─$SiMe_3$	(Trimethylsilyl)
Ts	─$SO_2C_6H_4CH_3$	(*p*-Tluenesulphonyl)
TPS	─$Si(C_6H_5)_3$	(Triphenylsilyl)
TSE	*p*-$CH_3C_6H_4SO_2CH_2CH_2$─	(*p*-Tosylethyl)

(b) Reagents:

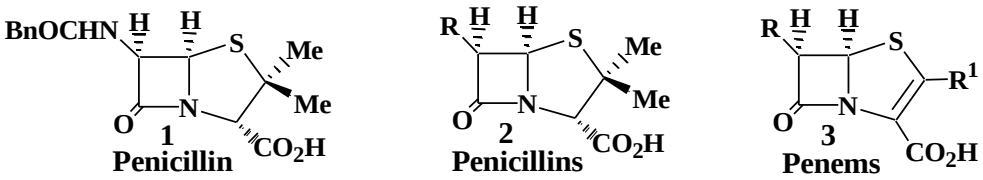
AIBN	Azoisobutyronitrile
CAN	Cerium(IV)ammoniumnitrate
CSA	Camphorsulfonic acid
CSI	Chlorosulfonylisocyanate
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBN	1,5-Diazabicyclo[4.3.0]non-ene
DBU	1,8-Diazabi[4.3.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DIAD	Diisopropylazodicarboxylate
DIBALH	Diisobutylaluminium hydride
DMAD	Dimethylacetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMPU	N,N´-Dimethylpropylineurea
IBX	2-Iodoxybenzoic acid
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
mCPBA	*m*-Chloroperbenzoic acid
NCS	N-Chlorosuccinimde
NMM	N-Methylmorpholine
TBDMSCL	*tert*-Butyldimethylsilylchloride
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy radical
THF	Tetrahydrofuran
TMSOTf	Trimethylsilyltrifluoromethylsulfonyloxy
TMST	2-(Trimethylsilyl)thiazole
TMSTf	Trimethylsilyltrifluoromethylsulfonyl
TsOH	*p*-Toluenesulfonic acid

CONTENTS

1. INTRODUCTION:

Alexander Fleming discovered penicillin **1** in **1928**, and since then a lot of work in the β-lactam area has been done, and a heavy stream of publications has been pumped into the literature. This tremendous enthusiasm about the β-lactam chemistry is mainly due to:

(i) For several decades, the penicillins **2** and related antibiotics have been widely used for the control and treatment of bacterial infections. In the recent years, countless numbers of penicillin derivatives and a wide variety of new β-lactam ring systems including penems **3** have been prepared and tested.



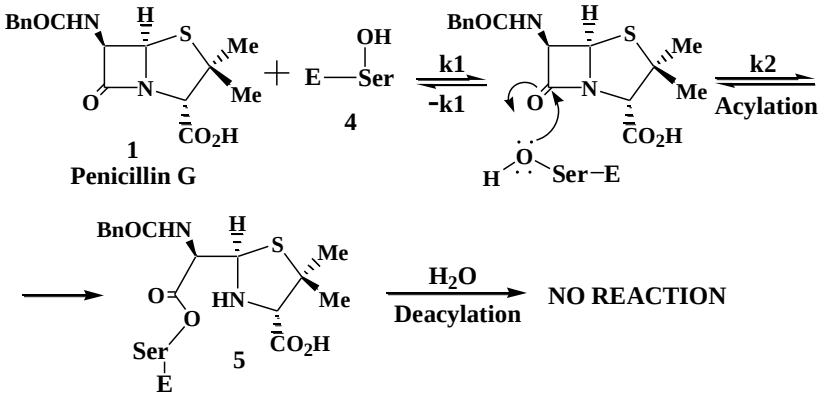
(ii) The growing challenge to synthetic chemists comes from the increasing resistance of bacterial strains to certain types of antibiotics. Thus, over the years, bacteria developed β-lactamase enzymes that confer resistance to penicillin. The nucleophile active site serine hydroxyl group of the β-lactamses that adds to penicillin results in breaking down the β-lactam ring and producing an acyl enzyme, which is easily hydrolysed to regenerate the β-lactamase enzyme together with the degraded antibiotic, which is no longer active against their target transpeptidase enzymes.[1]

(iii) Recently, the β-lactam skeleton has been recognized as a potent tool for the synthesis of a wide range of non-lactamic compounds including natural products and non-classical complex molecules, which their synthesis resembles a real challenge to organic chemists.

2. THE β-LACTAM ANTIBIOTICS (BACKGROUND):

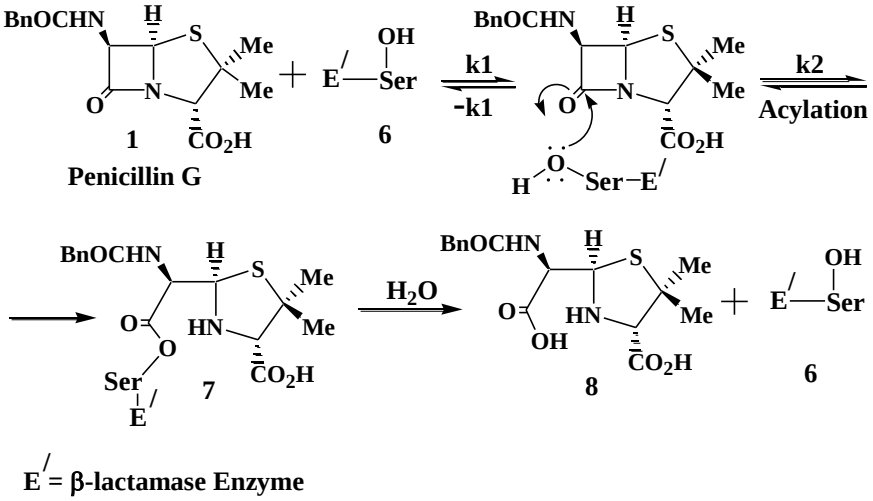
Since penicillin was first being discovered in **1928** and the β-lactam antibiotics continue to represent a very important class in the chemotherapy, and the synthesis of the monobactams has become the main target for many organic chemists global wide.[2,3]

Penicillins and other related antimicrobial agents which have been effectively used for fighting various bacterial infections over the years, have in common a β-lactam ring fused to a five- or six-membered hetero ring to form a rigid bicyclic molecule with v-shape conformation.[1] It is believed that the β-lactam antibiotics mimic the structures of the C-terminal D-alany-D-alanine residues of the peptide chain of uncross-linked peptidoglycan. They inhibit the transpeptidase enzyme, which is involved in the last step of the biosynthesis of the bacteria cell-wall formation by irreversible acylation of its active site serine forming an acyl-enzyme intermediate, as shown in Scheme 1. Consequently the transpeptidase enzyme cannot catalyse bacterial cell-wall biosynthesis, resulting in cell death.



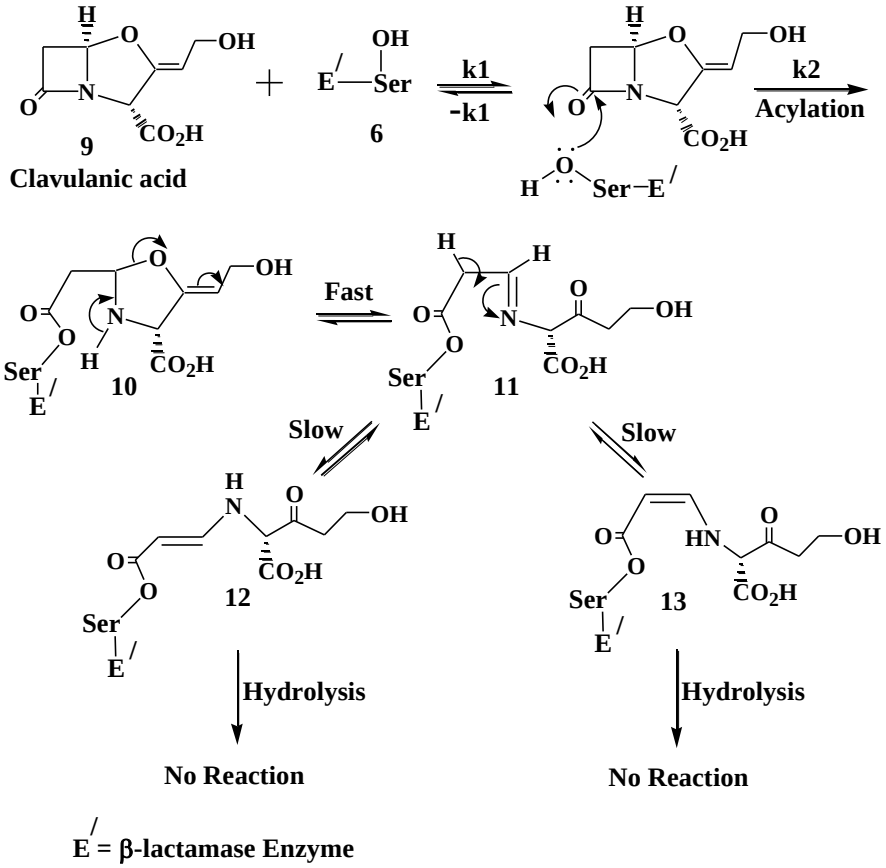
Scheme 1

However, bacteria have developed an effective self-defense mechanism against some antibiotics, e.g. penicillin G, by producing β-lactamase enzymes which also have an active site serine hydroxyl group. The active site serine hydroxyl group in the new developed β-lactamases, similarly attacks the carbonyl carbon of the β-lactam to form an acyl-enzyme intermediate, which is easily hydrolysed to regenerate the β-lactamase enzyme together with the degraded antibiotic, Sheme 2. By this means the β-lactam antibiotics become of no use before reaching their target transpeptidase enzymes.[4]



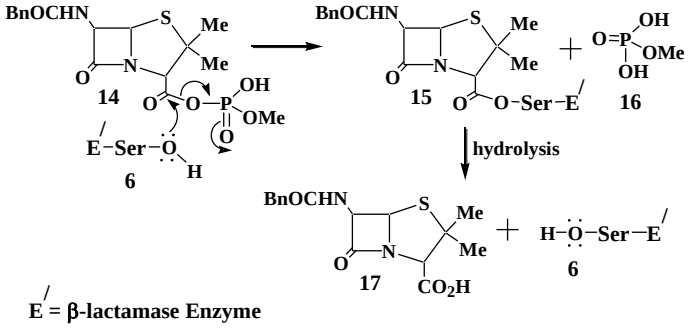
Scheme 2

Some other antibiotics e.g. clavulanic acid (Clav) inactive the β-lactamase enzymes and to some lesser extent the transpeptidase, the proposed mechanism is depicted in Scheme 3. In this case the active site serine hydroxyl group attacks the carbonyl carbon of the β-lactam ring producing the expected acyl-enzyme intermediate, which subsequently undergoes rearrangement to form an enamine which cannot be hydrolysed.



Scheme 3

However, Kluger has reported that the acyl phosphate monoester of the carboxyl of benzyl penicillin irreversibly inactivates RTEM β-lactamase, presumably through the reaction of the enzyme active site nucleophile, Scheme 4.[5,6]

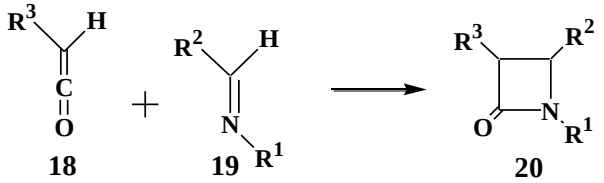


Scheme 4

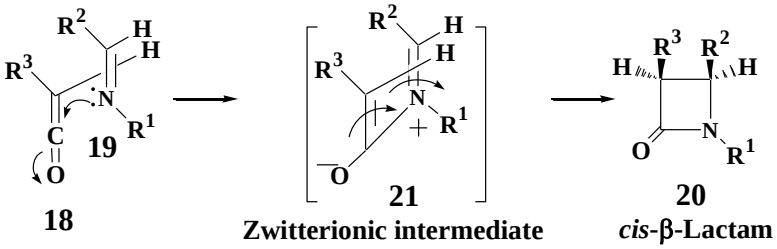
3. THE SYNTHESIS OF β-LACTAMS

3.1 Staudinger Reaction:

The classical Staudinger [2+2] cycloaddition reaction still resembles the back bone for the synthesis of the β-lactam nucleus, Scheme 5. In the recent years, the Staudinger reaction mechanism has been commonly accepted as a stepwise in nature, instead of a concerted (although asynchronous) [2+2] cycloaddition. During the first step the nuclephilic iminic nitrogen attacks the sp-hybridized carbon atom of the ketene **18** from the face opposite the large R^3 group to form a zwitterionic intermediate **21**, which subsequently transformed into the final product through a conrotatory electrocyclization process, Scheme 6.

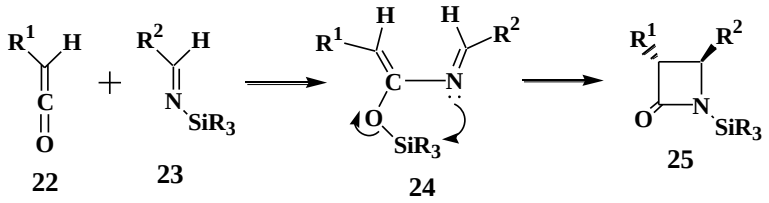


Scheme 5



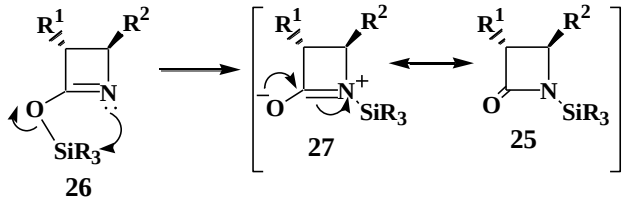
Scheme 6

The decisive reports concerning the stepwise mechanism came from Pannunzio laboratories, which have evidenced the stepwise nature of the Staudinger reaction.[7-10] Thus the isolation of the O-silylated intermediat **24** of the reaction between the ketenes **22** and N-silylimines **23** has revealed the naked fact about such reaction mechanism, Scheme 7.



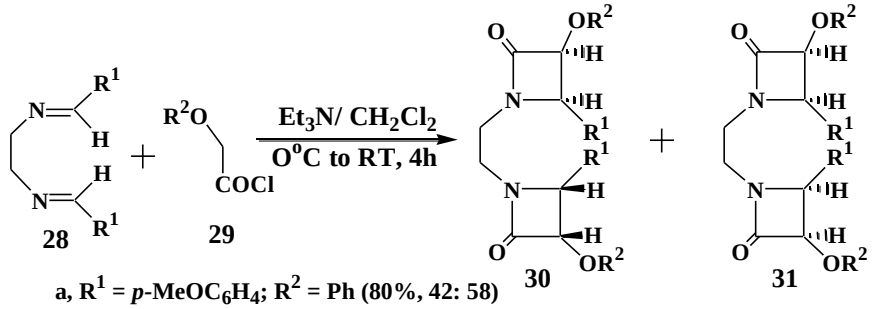
Scheme 7

It was reported that the formation of the N-silylated cycloadducts **25** is occured *via* a nucleophilic attack of the nitrogen on the silyl group with the oxygen atom acting as a leaving group, Scheme 8.



Scheme 8

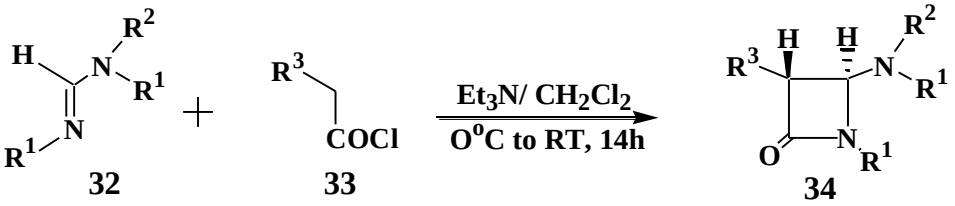
The reaction between the acid chlorides and imines generally provides the *cis*-β-lactams as the sole product or as the major isomer. Thus, Bhawal *et al.*[11] has reported that the reaction of N,N´-bis(p-anisylmetheylene) ethane diamine **28** with the acid chloride **29** in the presence of Et_3N in CH_2Cl_2 gave isomeric mixtures of the *cis*-bis-β-lactams **30** and **31** in excellent yields (75-86%), Scheme 9.



a, R^1 = *p*-$MeOC_6H_4$; R^2 = Ph (80%, 42: 58)
b, R^1 = *p*-$MeOC_6H_4$; R^2 = Bn (86%, 55: 45)
c, R^1 = *p*-$MeOC_6H_4$; R^2 = Ac (75%, 51: 49)

Scheme 9

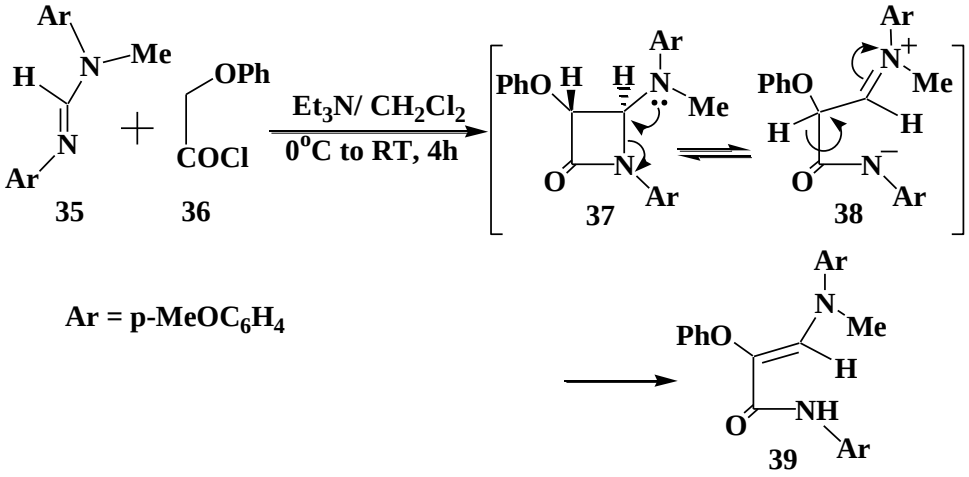
However, in another study for the same authors showed that the reaction of the amidines **32** with the acid chlorides **33** in the presence of Et_3N in dichloromethane (typical Staudinger Conditions) afforded the *trans* β-lactams **34** as the only products in high yields ranging from 72 to 89%, Scheme 10. On the other hand, the N,N′-di-(*p*-anisyl)-N′-methylamidine **35** under similar conditions gave the acyclic enaminoamide **39** in 62% yield, probably *via* the firstly formed *trans*-β-lactam 37, Scheme 11.[12]



32 **33** **34**

a, R^1 = Ph; R^2 = H; R^3 = PhO (77%)
b, R^1 = Ph; R^2 = H; R^3 = PhthN (79%)
c, R^1 = Ph; R^2 = PhCO; R^3 = PhO (72%)
d, R^1 = Ph; R^2 = *p*-$MeC_6H_4SO_2$; R^3 = PhthN (82%)
e, R^1 = *p*-$MeOC_6H_4$; R^2 = *p*-$MeC_6H_4SO_2$; R^3 = PhthN (89%)

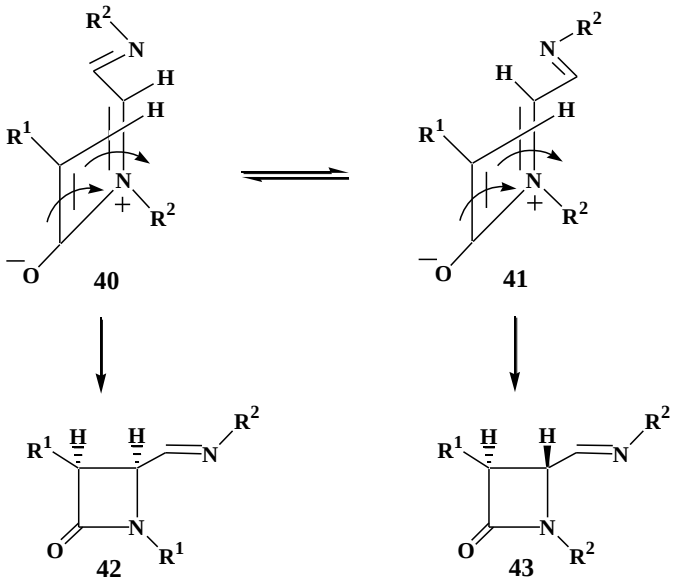
Scheme 10



35 **36** **37** **38** **39**

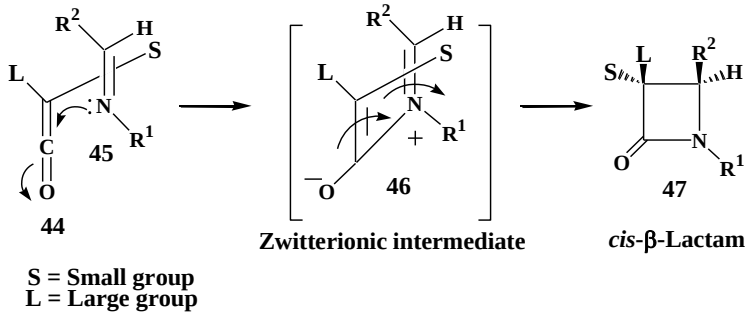
Scheme 11

The unpredictability of the stereochemical outcome of any particular system in the classical Staudinger ketene-imine cycloaddition is mainly due to: (i) the stepwise nature of the cycloaddition process, and (ii) the possibility for isomerization of the initially formed zwitterionic intermediate prior to ring closure. However, Alcaide has excluded such isomerization (**40**↔**41**) according to the high *cis*-stereoselectivity observed in their extensive work.[13]



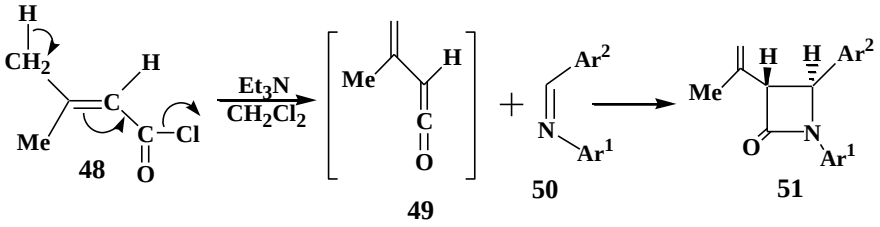
Scheme 12

The stereoselectivity of a vast majority of the ketene-imine cycloaddition reactions has been rationalized on the basis of steric effects alone, as the reaction occurs by the nucleophilic attack of the imine **45** from the less hindered side of the ketene **44**, with the plane of the imine is being perpendicular to that of the ketene, followed by conrotatory ring closure, Scheme 13.



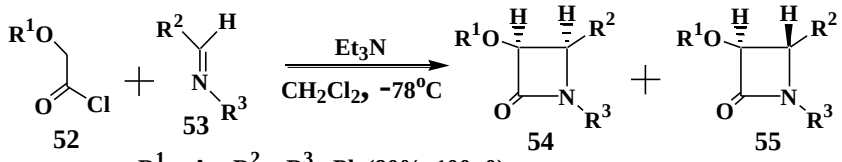
Scheme 13

Meegan and his group[14,15] have showed how the steric factors affect the [2+2] cycloaddition process, as the 3-methyl-2-crotonyl chloride **48** reacted with the sterically hindering imine **50** to give the 3-vinyl-β-lactams **51** as the only sole cycloadducts, Scheme 14.



Scheme 14

Banick and Becker[16] have reported that the N-substitution in the used imines has affected the stereochemical outcome of the [2+2] cycloaddition process. Thus, the acid chlorides ($R^1O{-}CH_2{-}COCl$) **52**, reacted with the imines **53** in the presence of Et_3N in dichloromethane at –78°C to give exclusively the *cis* or *trans* β-lactams depending on the bulkiness of the N-substituents, Scheme 15.

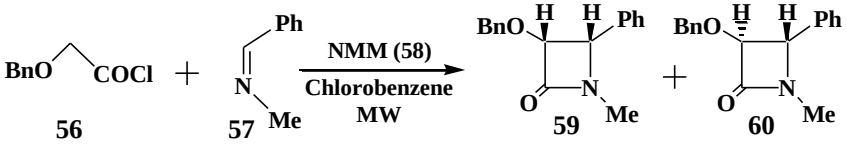


52 **53** **54** **55**

a, R^1 = Ac; R^2 = R^3= Ph (80%, 100: 0)
b, R^1 =R^2 = R^3= Ph (90%, 100: 0)
c, R^1 = Ac; R^2 = Ph; R^3= *p*-$MeOC_6H_4$ (80%, 100: 0)
d, R^1 = R^2 = Ph; R^3= *p*-$MeOC_6H_4$ (80%, 100: 0)
e, R^1 = Ac; R^2 = Ph; R^3= 1-naphthyl (60%, 0: 100)
f, R^1 = R^2 = Ph; R^3= 1-naphthyl (47%, 0: 100)
g, R^1 = phthalimido; R^2 = Ph; R^3= 1-naphthyl (48%, 0: 100)
h, R^1 = Ac; R^2 = Ph; R^3= 1-anthracenyl (60%, 0: 100)
i, R^1 = R^2 = Ph; R^3= 1-anthracenyl (65%, 0: 100)

Scheme 15

The microwave chemistry has recently attracted considerable attention due to: (i) fast heating goes directly into the reacting molecules, (ii) environment friendly chemistry (no much solvent is needed) and (iii) the reactions nearly take no time (a few minutes).[17] Bose *et al.*[18] have used such technique in the β-lactam synthesis by irradiating a mixture of the acid chloride **56** and imine **57** in the presence of N-methylmorpholine **58** in preheated chlorobenzene (69-96°C) in a domestic microwave oven for short time (1-5min) afforded an isomeric mixtures of *cis/trans* β-lactams **59** and **60** in ratios ranging form 84:16 to 55:45, Scheme 16. This example showed that both the temperature and irradiation time are effective parameters in the stereochemical outcome in the synthesis of the β-lactams. The microwave chemistry, yet again added more doubts on the stereochemical outcome of the [2+2] cycloaddition reaction.



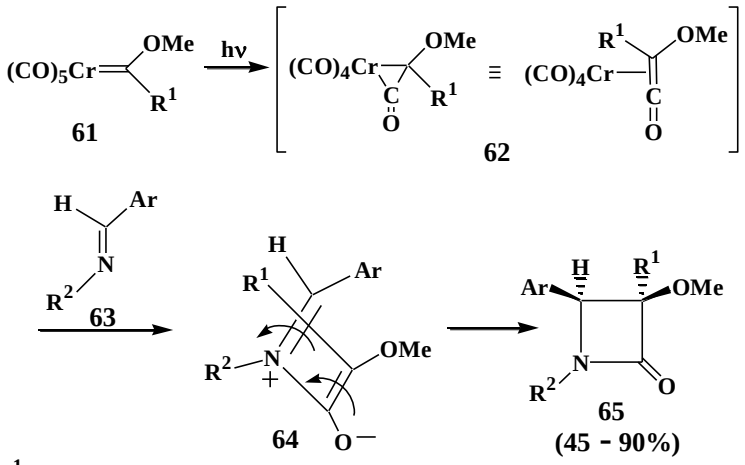
56 **57** **59** **60**

NMM = N-methylmorpholine
MW = microwave

69°C, 1 min.(84: 16)
75°C, 2 min.(80: 20)
94°C, 4 min.(55: 45)
96°C, 5 min.(55: 45)

Scheme 16

However, Hegedus showed that the stereochemistery observed in the photochemical (visible light) reaction of (methoxy)(alkyl)-carbene complexes **61** with simple imines **63**, was exactly opposite to that predicted by the steric factors, i.e. the nucleophilic attack occurred from the more hindered side, Scheme 17.[19]



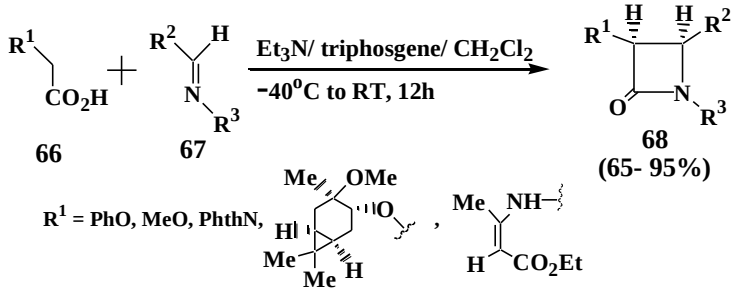
R^1 = Me, Ph

R^2 = Me, Ph, *p*-$MeOC_6H_4$, Bn, $CH_2PO(OEt)_2$, CH_2=CH

Ar = Ph, PhCH=CH

Scheme 17

As mentioned above the ketene was generated *in situ* by treating the acid chlorides by a base, e.g. triethylamine. However, there are some other different methods by which the ketene is also generated *in situ*, and then cycloadds to imines in the normal fashion. Thus, Bhawal *et al.*,[20] reported a novel method for the synthesis of the β-lactam by treating a mixture of the carboxylic acids **66** and imines **67** with triphosgen in the presence of Et_3N in dry CH_2Cl_2 (-40°C to RT, 12h) to obtain acceptable to almost quantitative yields of the *cis*-β-lactams **68**, Scheme 18.



R^1 = PhO, MeO, PhthN,

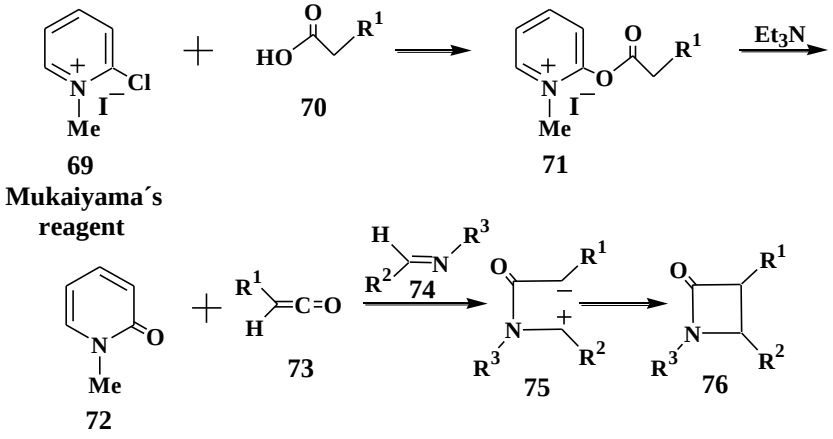
R^2 = Ph, *p*-$MeOC_6H_4$, PhCH=CH

R^3 = Ph, *p*-$MeOC_6H_4$

Scheme 18

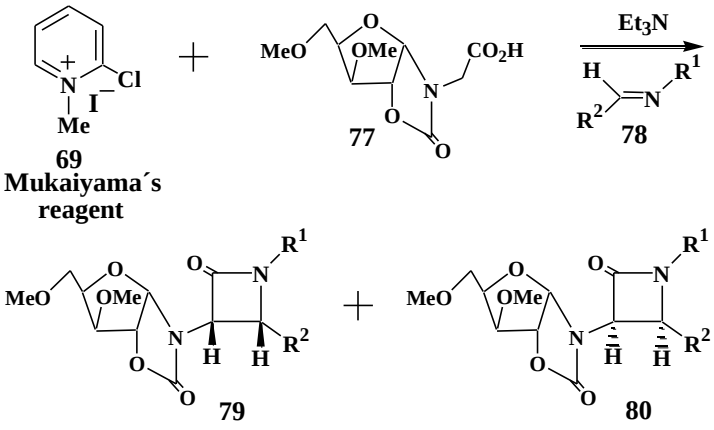
Koll[21] and others[22] have reported that the reaction of Mukaiyuma's reagent **69** (2-chloro-1-methylpyridinium iodide) and carboxylic acids **70**

in the presence of Et_3N generated the ketenes **73**, which reacted *in situ* with imines **74** to form the desired β-lactams **76** *via* the zwitter ion **75**, Scheme 19.



Scheme 19

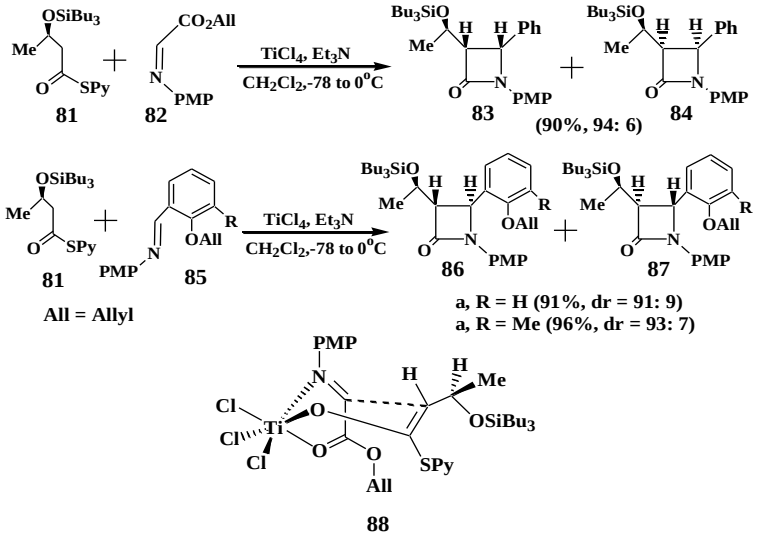
However, Koll showed in Scheme 20 that subsequent addition of triethylamine and the imine **78** to a suspension of the acid **77** and Mukaiyama's reagent **69** in dichloromethane at 0°C afforded moderate to fairly good yields (38-71%) with excellent distereoselectivity (>99:1) of the *cis* β-lactams as the sole products.



a, R^1 = Bn; R^2 = Ph (67%, > 99: 1)
b, R^1 = *p*-$MeOC_6H_4$; R^2 = Ph (69%, > 99: 1)
c, R^1 = Bn; R^2 = PhCH=CH (71%, > 99: 1)
d, R^1 = *p*-$MeOC_6H_4$; R^2 = PhCH=CH (38%, > 99: 1)

Scheme 20

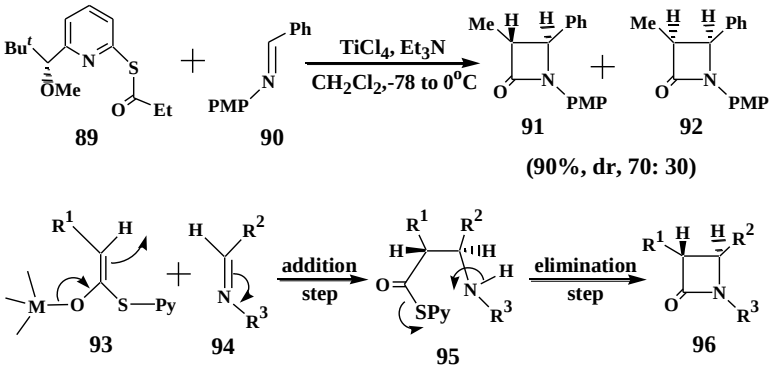
Titanium-mediated condensation of the chiral (*R*)-S-(2-pyridyl) thioester **81** (which is capable of enolization and easy to undergo addition/elimination) with imine **82** afforded a 94:6 mixture of the tow *cis* products, Scheme 21.[23]



Scheme 21

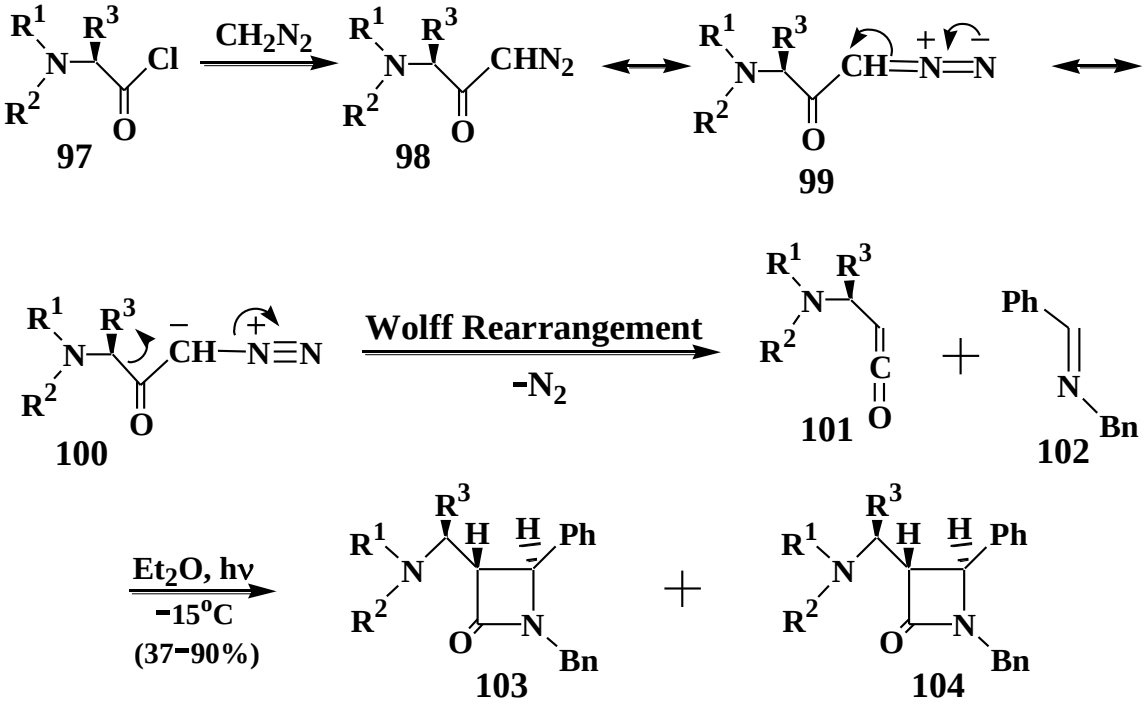
The major product 3,4-*cis*-3,3′-anti β-lactam is obtained through the transtion state **88**, in which the enolate attacks the chelated imine, placing the small hydrogen substituent in the more crowded position to minimize steric repulsion. On the other hand, the same (*R*)-thioester **81** reacted similarly with the more sterically demanding imines 4a,b to give the opposite stereochemistry as mixture of two *trans* isomers in excellent yields (91%, dr 91:9 and 96%, dr 93:7), respectively with the 3,4-*trans*-3,3′-anti isomer is the major product, in each case, Scheme 21. Yet again, the bulkiness of the substitutent at the C-terminus of the imine has affected the stereochemical outcome to a great extent and resulted in the opposite stereochemistry.

On the other hand, imine **90** reacted with (*R*)-S-(2-pyridyl) thioester derivative **89** under the same conditions to give 90% of an isomeric mixture of *trans/cis* β-lactams **91** and **92** in a 70:30 ratio, respectively and the products were in the racemic form. This very poor stereoselectivity is likely to be due to the remote distance between the chiral center on the (*R*)-thioester and the newly obtained ones on the β-lactam nucleus, Scheme 22.



Scheme 22

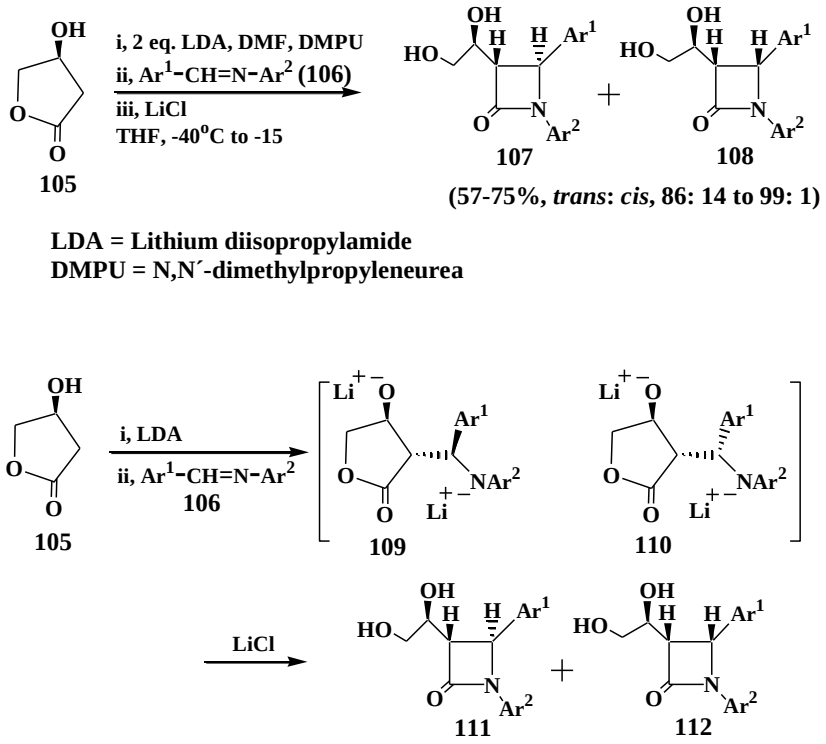
Podlech and Linder[24] have reported that ketenes **101** obtained *via* Wolff rearrangement of diazoketones **98** reacted with imine **102** to afford a stereoselective synthesis of the *trans* aminolkyl-substituted β-lactams **103** and **104** in (37-90%) yields, Scheme 23. They reported that the stereoselectivity was highly effected by the bulkiness of the parent amino acid side chain .i.e. when (R^3 = Me) the ratio was (67:33), but when (R^3 = *t*-Bu) the ratio was (93:7), however in the case of (R^1 = R^2 = Phthalimido) and (R^3 = Me) the ratio was (17:83).



a, R^1 = BnOCO; R^2 = H; R^3 = Me (67: 33)
b, R^1 = BnOCO; R^2 = H; R^3 = ^{t}Bu (93: 7)
c, R^1 = R^2 = Phth; R^3 = Me (17: 83)

Scheme 23

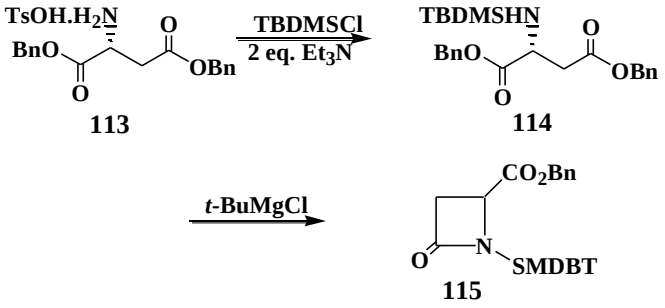
Wu *et al.*[25] reported that successive treatment of (*S*)-3-hydroxy-γ-lactone **105** with 2 equivalents of LDA, DMF/DMPU, followed by the addition of the imine **106** to the resulting mixture and finally addition of LiCl, afforded the *trans/cis* β-lactams **107** and **108**, respectively in reasonable to good yields (57-75%) with high diastereoselectivity ranges from 86:14 to 99:1 (*trans:cis*), Scheme 24. The reaction goes through the metalo intermediates **109** and **110** to give the *trans* and *cis* β-lactams, respectively.



Scheme 24

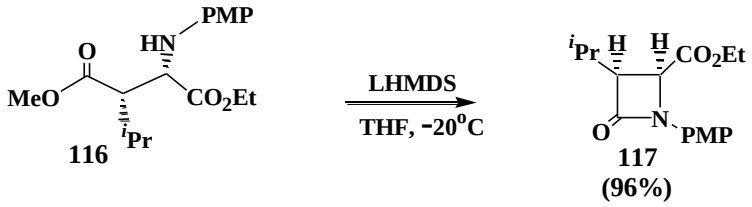
3.2 DIFFERENT METHODS FOR THE SYNTHESIS OF β-LACTAMS:

McCarthy[26] reported a direct cyclization of the β-amino esters under basic conditions by treating the N-*p*-toluene-sulphonic acid salt dibenzyl-D-aspartate **113** with TBDMSCl (*tert*-butyldimethylsilylchloride) and *t*-BuMgCl in the presence of 2 equivalents of Et_3N to produce the corresponding β-lactam **115**, Scheme 25.



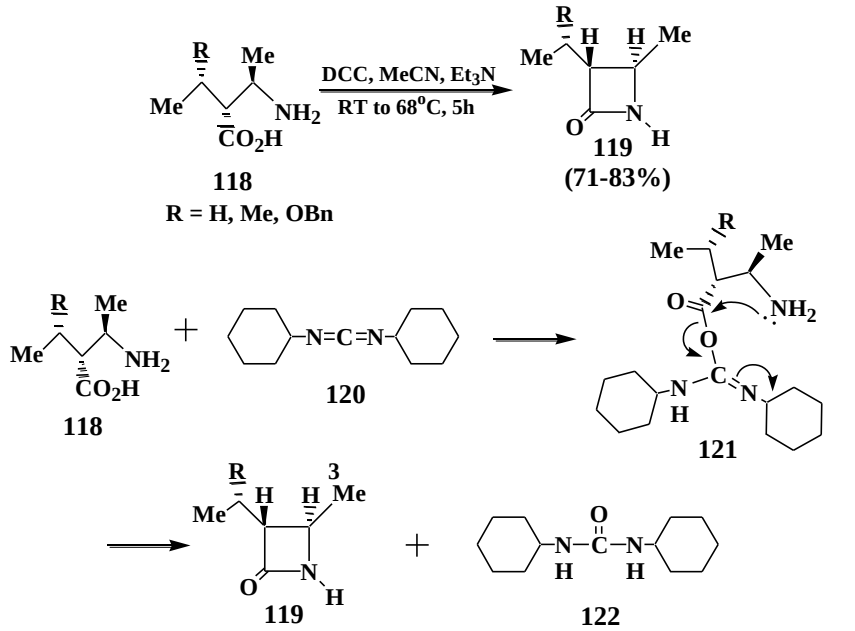
Scheme 25

It was recently reported that the amino diester **116** under basic conditions in THF at ─20°C afforded the *cis* β-lactam **117** in 96% yield with enantiomeric excess 93%, Scheme 26.[27]

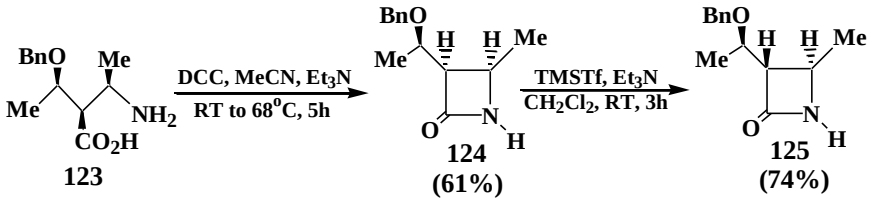


Scheme 26

Jacobi *et al.*[28] reported that the sequential treatment of the enantiopure β-amino acids **118** with Et_3N and the dicyclohexylcarbodimide (DCC) **120** yielded an enantiomeric mixture of *trans*-β-lactams **119** in 71-83% yields, Scheme 27. However, the other diastereomer **123** under the same condition conditions afforded the *cis*-β-lactam, which on the treatment with trimethyl triflоromethanesulfonate yielded the *cis*-β-lactams **124**, Scheme 28.



Scheme 27

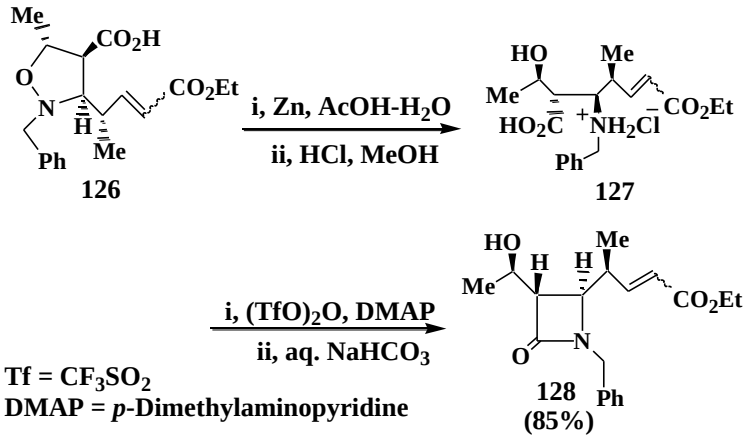


DCC = dicyclohexylcarbodiimide
TMSTf = trimethylsilyltrifluoromethylsolfonyl

Scheme 28

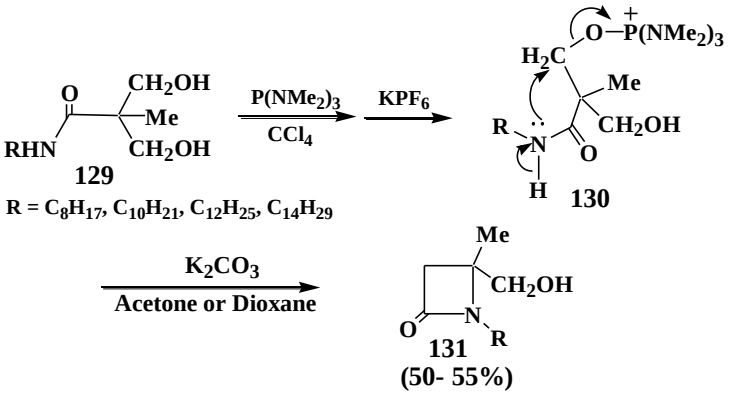
Kang and Lee[29] reported a novel method, thus, heating the isoxazolidine **126** in aqueous acetic acid at 70°C in the presence of zinc followed by methanolic HCl afforded the β-amino acid hydrochloride **127**. Cyclization

of **127** by the effect of trifloroacetic anhyderide in the presence of *p*-dimethylaminopyridine (DMAP) and then hydrolysis with aqueous $NaHCO_3$ yielded 85% of the corresponding *trans* β-lactam **128**, Scheme 29.



Scheme 29

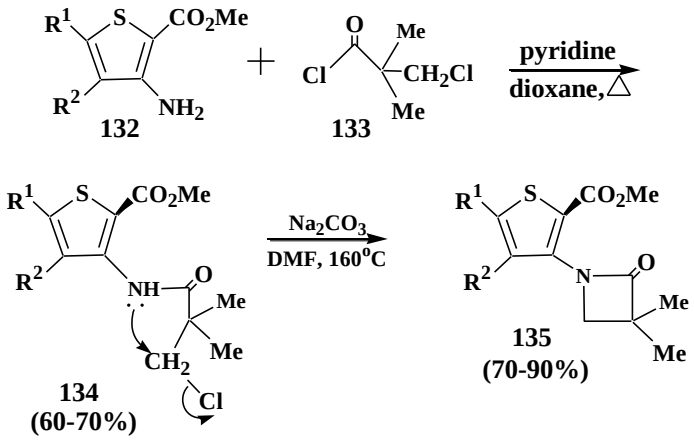
In the mid ninties of the last century, Selve[30] reported that the fatty amide derivatives of 2,3-dihydroxymethyl propanoic acid on the reaction with $P(NMe_2)_3$-CCl_4 couple and then KPF_6 afforded the alkoxy tris(dimethylamine) phosphonium salt, which underwent cyclization by treatment with anhydrous K_2CO_3 either in acetone or dioxane, to give moderate yields (50-55%), Scheme 30.



Scheme 30

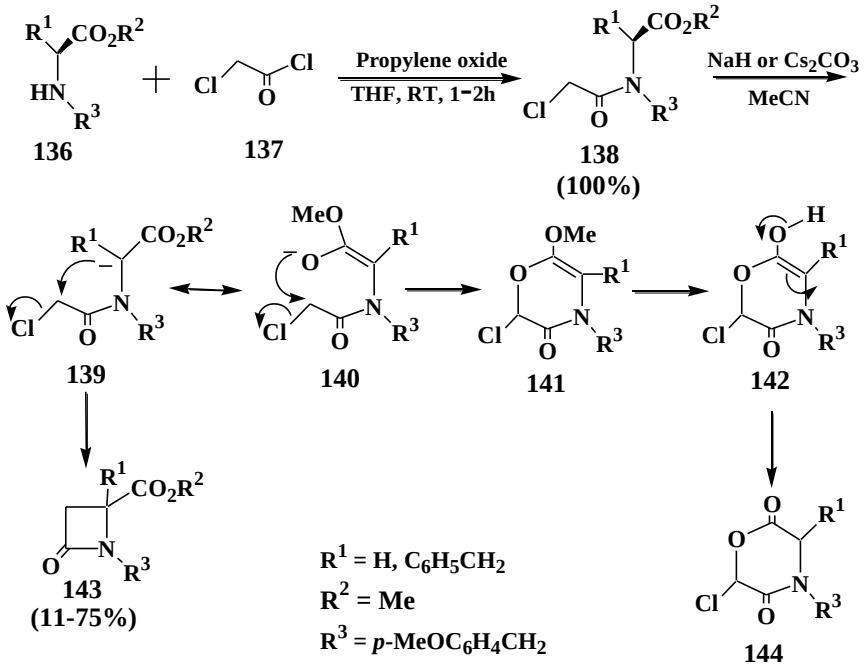
El Kashef and Lancelot[31] have reported an appreciable short cut synthesis of the 4-unsubstituted β-lactam **135** *via* the N1-C4 bond formation. Thus, treating the 3-aminothiophene-2-carboxylates **132** with pivaloyl chloride **133** in dioxane in the presence of pyridine afforded the corresponding N-monosubstituted-3-chloropropionamides **134** in fairly good yields (60-70 %). Heating the obtained chloroamides **134** in DMF at

160°C in the presence of Na_2CO_3 gave rise to the β-lactams **135** in good to excellent yields (70-90%), Scheme 31.



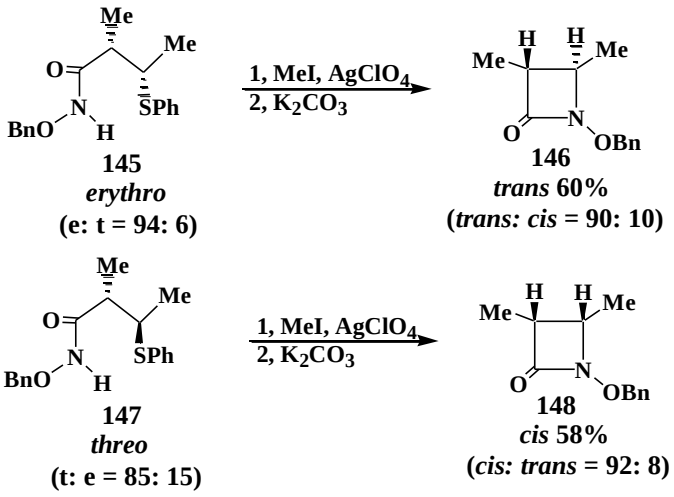
Scheme 31

It was reported that the synthesis of 2-azetidinones **143** by C3-C4 bond formation through the reaction of the N-substituted-α-amino acids **136** with chloroacetyl chloride **137** in the presence propylene oxide as HCl scavenger, followed by a base treatment afforded the 4-alkyl-4-carboxy-2-azetidinones **143** in yields ranging from very modest (11%) to good (75%) yields, Scheme 32.[32] Although, NaH-promoted reaction took place in short time (1 day), but it caused considerable extent of sabonification for the carboxymethyl ester. However, in some cases (R^2 = Me) besides the formed β-lactam main products **143**, the six-membered heterocycles **144** were obtained.



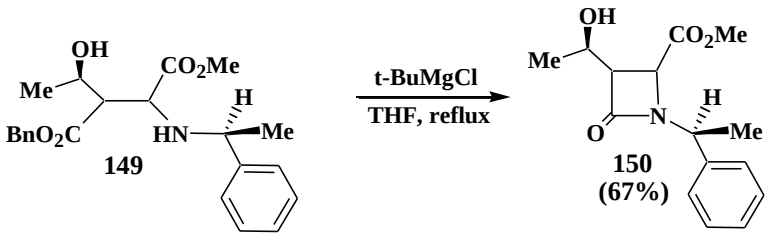
Scheme 32

Naito *et al.*[33] reported that the alkylation reaction of the O-benzyl hydroxamate (unseparable mixture of *erythro/threo* = 94:6) with methyl iodide in the presence of silver perchlorate afforded the corresponding isomeric mixture of the β-lactams **146** (*trans/cis* = 90:10) in a 60% yield, Scheme 33. Analogously the other diastereomeric mixture (*threo/ erythro* = 85:15) gave the opposite stereomeric mixture of β-lactams **148** (*cis/trans* = 92:8) in a 58% yield.



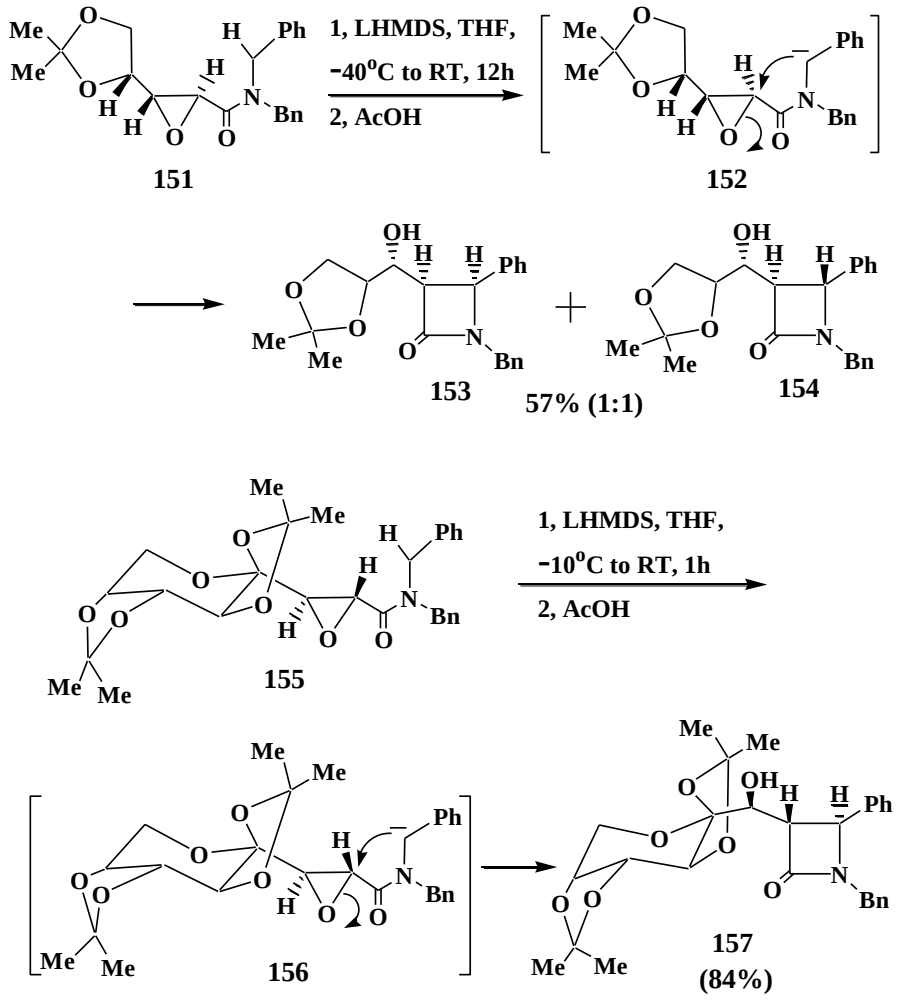
Scheme 33

Paquette *et al.*,[34] showed that heating the β-amino esters **149** with *tert*-butylmagnesium chlorid (*t*-BuMgCl) in THF afforded the corresponding β-lactam **150** in a 67% yield, Scheme 34.



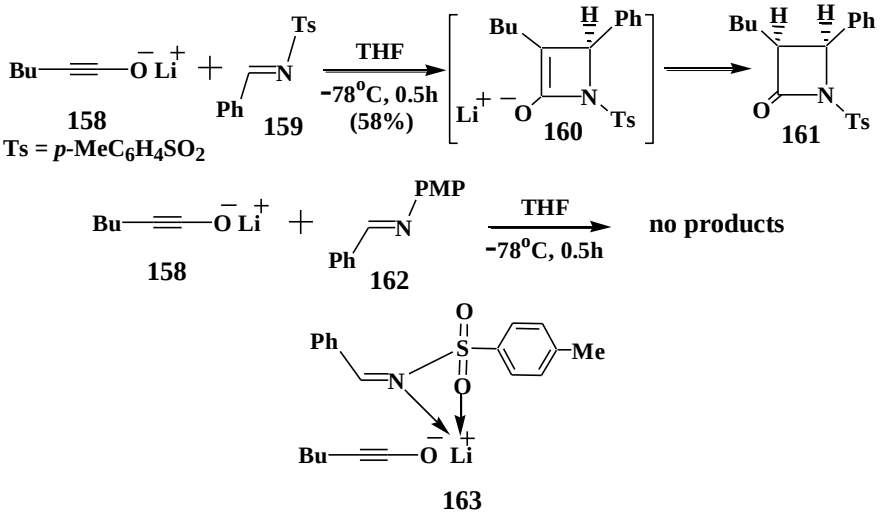
Scheme 34

Izquierdo et al.[35] have reported that α,β-epoxyamide **151** reacted with lithium hexamethyldisilazide (LHMDS) in THF at low temperature (−40˚C) gave an isomeric mixture of the *cis* and trans β-lactam **152** and **153** in a 1:1 ratio in a 57% total yield, whereas the α,β-epoxyamide **155** (having a larger sugar moiety) reacted similarly with (LHMDS) to give only the trans β-lactams **157** in 84% yield, Scheme 35. It is believed that the steric clash between the larger sugar moietie at C3 and the phenyl group at C4 during the interamolecular cyclization step is responsible for the high sterioselectivity in the latter case .

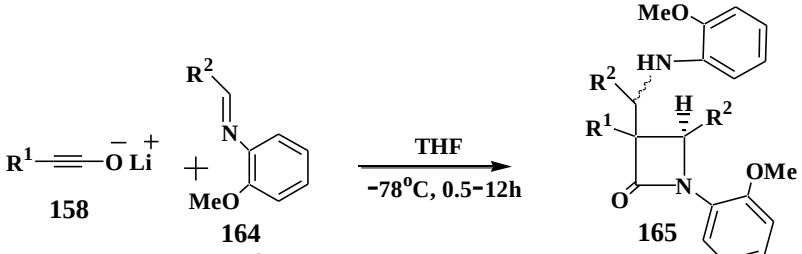


Scheme 35

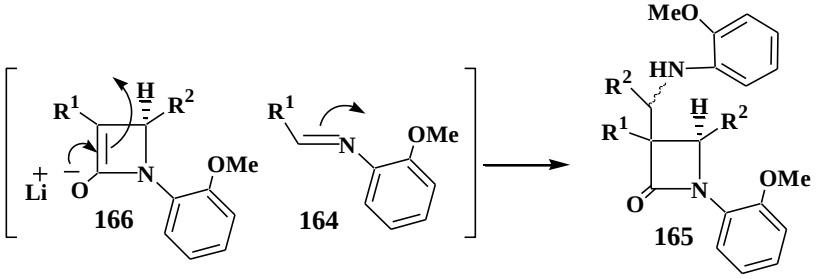
Shindo and co-workers[36] reported that the ynolate (Bu–≡–O^-Li^+) **158** racted with the imine **159** in THF at –78°C to give one single isomer the *cis*-β-lactam **161** in a 58% yield, however under the same conditions imine **162** gave no reaction products, Scheme 36. Acordingly, they suggested a complex **163** through which the reaction takes place, in the proposed complex both the imino nitrogen and the sulfonyl group chelate to the lithium centre of the lithium ynolate. On the other hand, the ynolate **164** (R^1 = Bu) reacted with the imines **165** to afford 74-79% yields of the *cis*-β-lactams as single diastereomers, whereas **164** (R^1 = Me) gave much better yields (88-97%) of unseparable diasteriomers in a ratio ranging from 1:1 to 3:1, Scheme 37. The N-2-methoxyphenyl group, apperently increased the nucleophilicity of the lactam enolate and gave rise to the C-3-disubstituted β-lactams.



Scheme 36

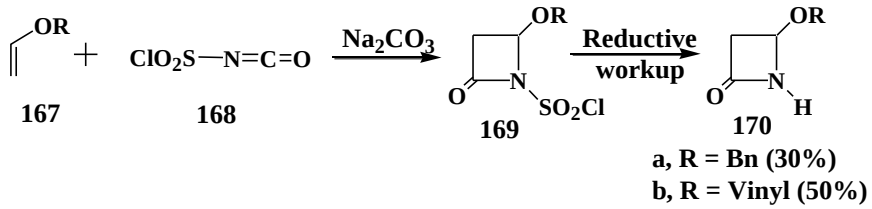


a, R^1 = Me; R^2 = Ph (96%, 1: 1)
b, R^1 = Me; R^2 = 1-naphthyl (88%, 2: 1)
c, R^1 = Me; R^2 = 2-naphthyl (93%, 3: 1)
d, R^1 = Me; R^2 = *p*-$MeOC_6H_4$ (97%, 3: 1)
e, R^1 = Bu; R^2 = Ph (79%, single diastereomer)
f, R^1 = Bu; R^2 = 1-naphthyl (78%, single diastereomer)
g, R^1 = Bu; R^2 = 2-naphthyl (74%, single diastereomer)



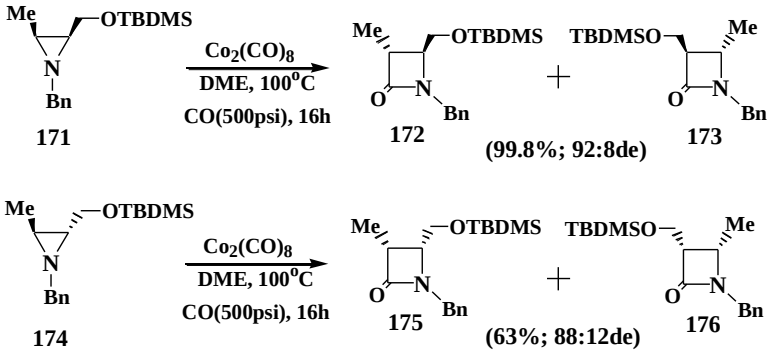
Scheme 37

It was reported that benzyl vinyl and divinyl ethers **167a,b** on the reaction with chlorosulphonyl isocyanate **168** followed by reductive work up with sodium bis(2-methoxyethoxy)aluminium hydride afforded the corresponding β-lactams **170a** and **170b** in 30 and 50% yields, respectively, Scheme 38. The importance of such work is that using cheap reagents afforded very useful β-lactams.[37]

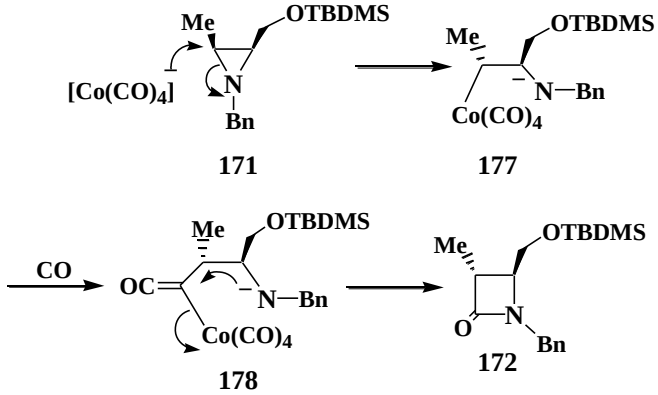


Scheme 38

An elegant report came from Alper's laboratories showing that the treatment of the *cis*-1-benzyl-2-((*tert*-butyldimethylsilyloxy)methyl)-3-methylaziridine **171** with carbon monoxide (CO) under pressure (500 psi) in the presence of catalytic amount of dicobaltoctacarbonyl [$Co_2(CO)_8$] in 1,2-dimethoxyethane (DME) afforded almost quantitative yield (99.8%) of a regeoisomeric mixture of the *trans*-β-lactams **172** and **173** in a 92:8 ratio, respectively. On the other hand, the *trans*-1-benzyl-2-((*tert*-butyldimethylsilyloxy)methyl)-3-methylaziridine **174** reacted in the same way to give the *cis*-β-lactams **175** and **176** in a lower yield with poorer regeoselectivity (63%, 88:12), Scheme 39.[38] It is believed that the aziridine **171** underwent a nucleophilic ring opening by the in *situ*-generated tetracarbonylcobaltate anion [Co(CO4)]$^-$, with the attack at the C3 ring carbon atom, Scheme 40.

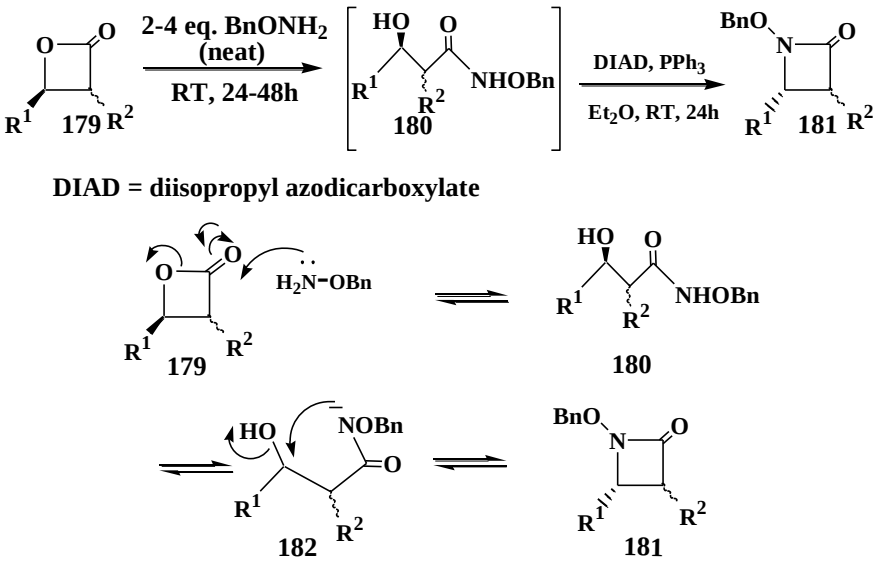


Scheme 39



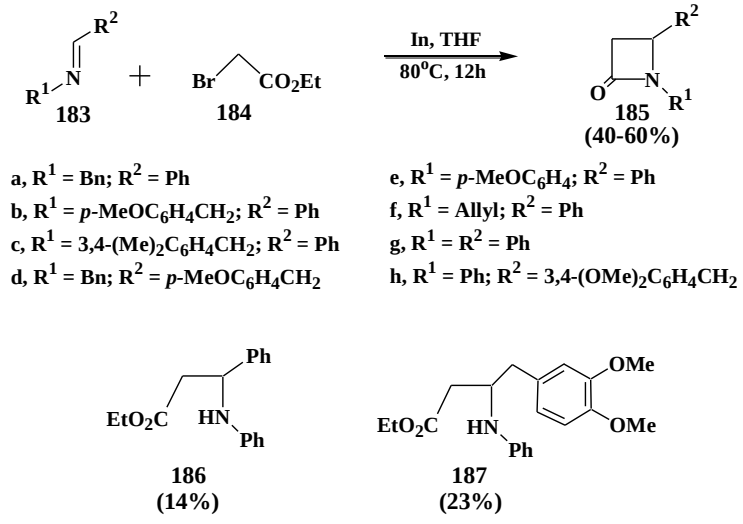
Scheme 40

Yang and Romo,[39] have reported that treatment of β-lactons **179** with 2-4 fold excess of $BnONH_2$ at room temperature followed by the addition of DIAD/PPh_3 in Et_2O at room temperature gave the corresponding β-lactams **181** in reasonable to excellent yields (45-87%) with poor stereoselectivity (~2:1, *trans:cis*), Scheme 41.



Scheme 41

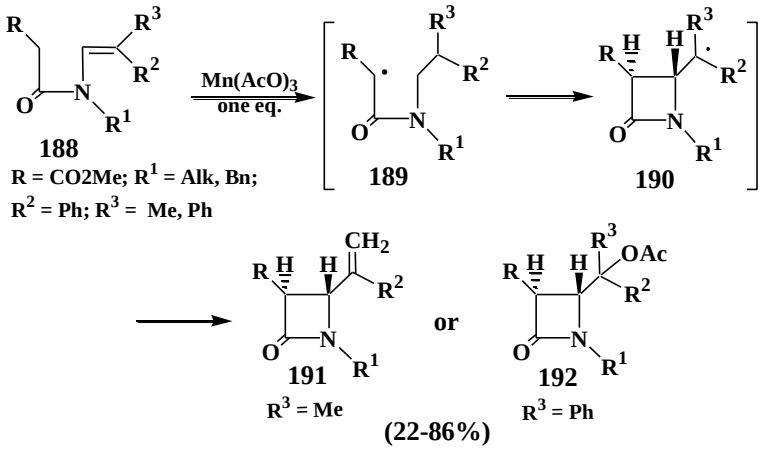
Banik *et al.*[40] reported that imines **183** reacted with ethyl bromoacetate **184** in THF at 80°C in the presence of indium afforded the corresponding β-lactams **185** in reasonable yields (40-60%), Scheme 42. However imines 183g,h under similar conditions gave only 28% and 30% yields of the β-lactams **185g,h** together with the β-amino esters **186** and **187** in 14% and 23 % yields, respectively.



Scheme 42

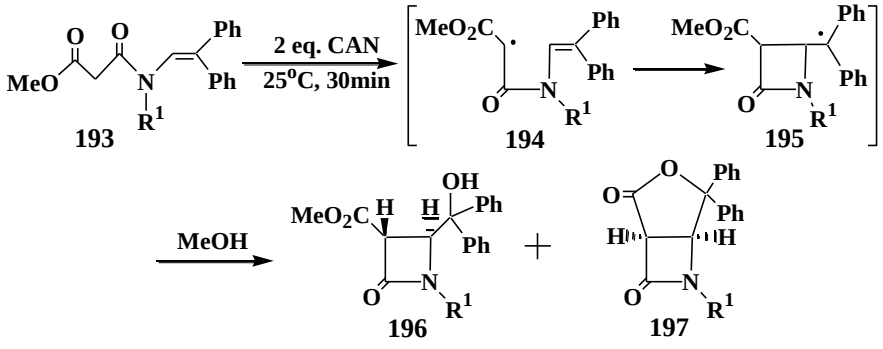
3.3 THE RADICAL SYNTHESIS OF THE β-LACTAMS:

D'Annibale and Trogolo[41-43] reported an effective method for the synthesis of β-lactams **191** and **192** in yields ranging from 22 to 86% through the 4-*exo*-*trig* oxidative radical cyclization, Scheme 43.



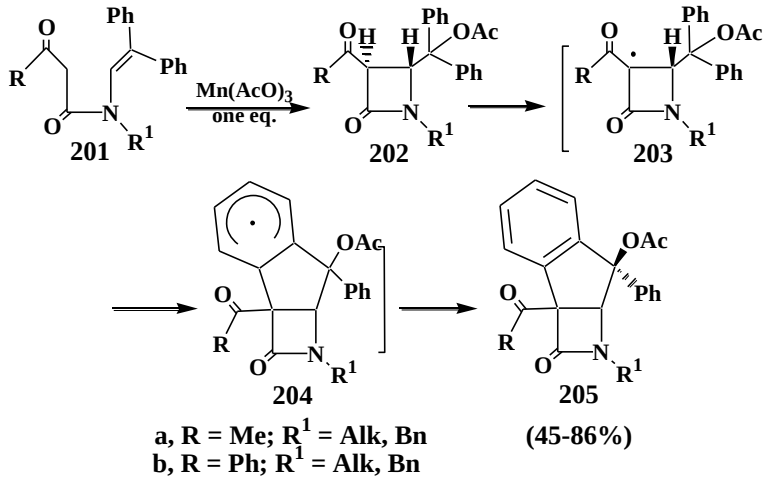
Scheme 43

D'Annibale *et al.*[44] have reported the first example of the radical oxidation of amides by using cerium ammonium nitrate (CAN), thus the treatment of the enamides **193** and **198** with CAN generates α-carbamoyl radicals **194** which undergo 4-*exo*-*trig* cyclization followed by methanol quenching to provide the corresponding functionalized β-lactams, Scheme 44.



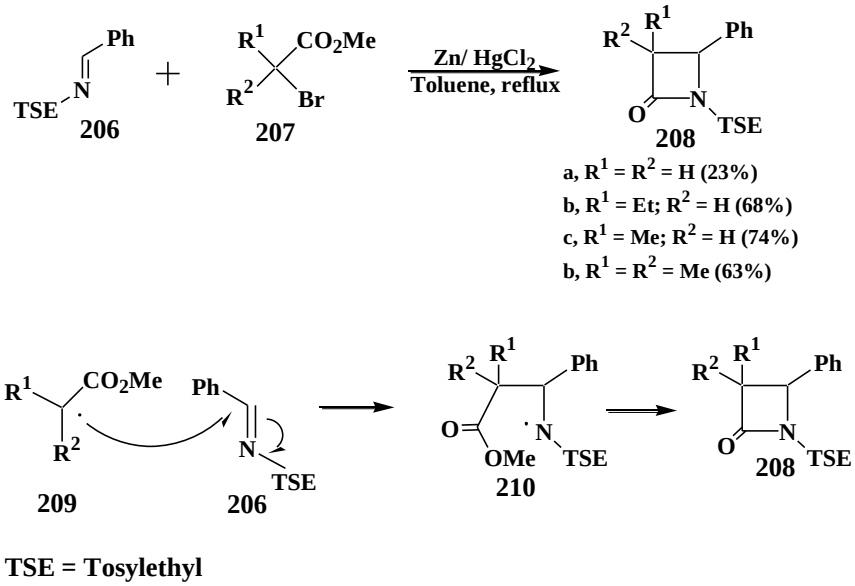
Scheme 44

They have also repored that treating the enamide **201** with two equivalents of the Mn(III) salt gave the tricyclic-fused hydroindene-azetidinone (benzocarbapenams) **205** in reasonable to excellent yields (45-86%), Sceme 45. [45]



Scheme 45

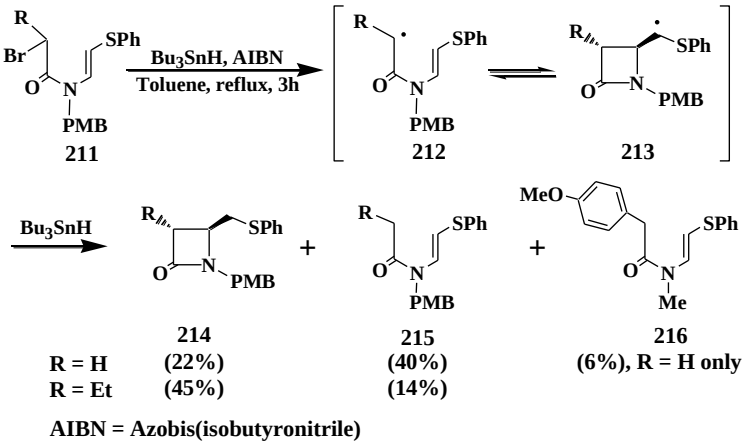
Weinreb[46] has repoted that refluxing a mixture of β-tosylethylimine **206** and α-bromoacetic acids **207** in toluene in the presence of $Zn/HgCl_2$ afforded the corresponding β-lactams **208** in modest to good yields (23-74%), as isomeric mixtures of *trans/cis* β-lactams in a 1.3:1 ratio respectively, Scheme 46.



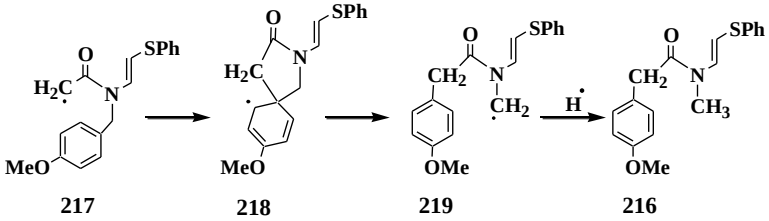
Scheme 46

Ishibashi *et al.*[47] have reported that bromoaetamide **211** and **212** underwent a radical 4-*exo*-*trig* cyclzation to give the the *trans*-βlactam **214** together with reductive products **215** and rearrangment product **216** in 22,

40 and 6% yields, respectively only in the case of (R = H), Scheme 47. The rearanged enamide was obtained *via* an intramolecular *ipso* attack of the radical **217** to give the spiro radical **218**, followed by ring opening with retroaromatization to give the radical **219** which finally reduced by Bu_3SnH to give **216**, Scheme 48.



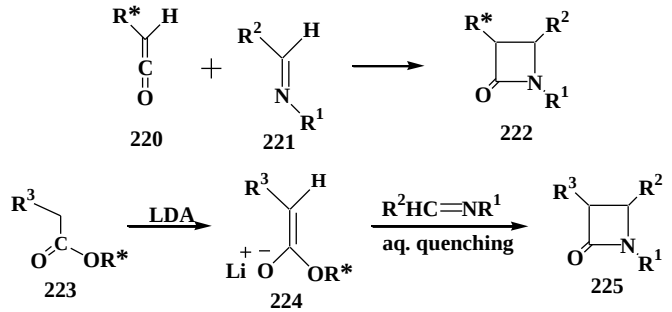
Scheme 47



Scheme 48

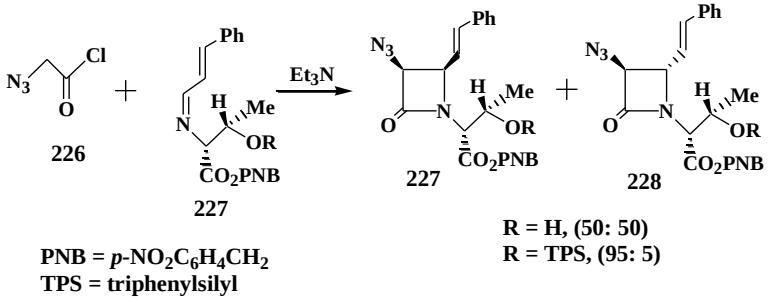
3.4 THE CHIRAL SYNTHESIS OF THE β-LACTAMS:

There are two distingueshed routes for the asymmetric synthesis of the β-lactams: (i) the Staudinger asymmetric ketene-imine [2+2] cycloaddition, and (ii) the chiral ester enolate-imine cyclocondensation, Scheme 49. This forms the foundation for the asymmetric synthesis of both lactamic and non-lactamic building blocks that are not easily prepared by conventional synthetic methods.



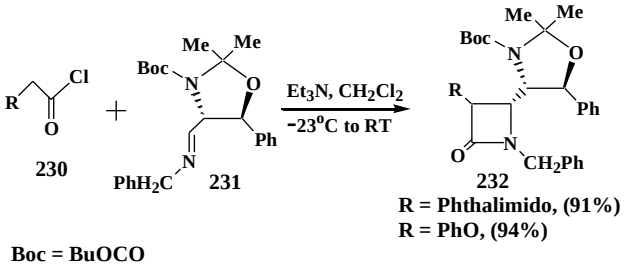
Scheme 49

Bose's group,[48] reported that using O-TPS-(*R*,*R*)-Threonine PNB (TPS = triphenylsilyl; PNB = *p*-nitrobenzyl) ester as a chiral auxiliary attached to the N-terminus of the imine **227**, the 3-azedo-β-lactam **228** (R = TPS) was obtained in a 90% de, Scheme 50. However, they showed that the presence of a free β-hydroxyl group on the chiral auxiliary resulted in no selectivity.



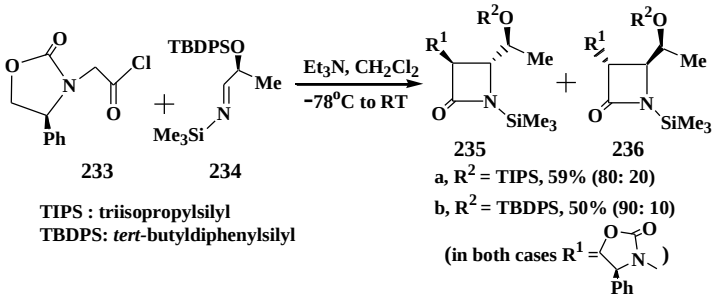
Scheme 50

When a chiral auxillary is attached to the C-terminus of an imine such as **231**, the diastereoselectivity has been changed dramatically and the predominant isomers **232** are isolated in excellent yields, Scheme 51.[49]



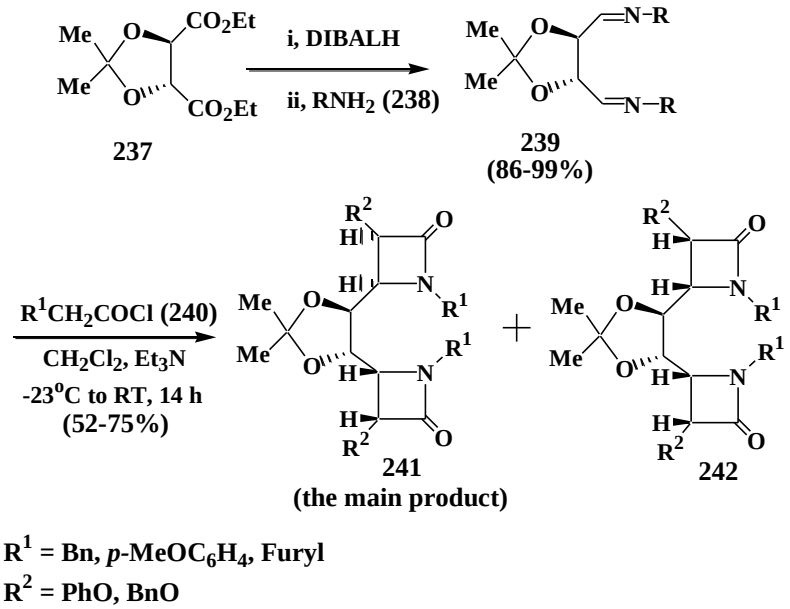
Scheme 51

However, appreciable double induction is observed by using the chiral auxiliaries at both the ketene precursor **233** and the C-terminus of the imine **234**, the stereochemistry of the resulting β-lactams **235** and **236** was switched to completely *trans* with a reasonable diastereomeric excess (80:20 to 90:10), Scheme 52.[50]



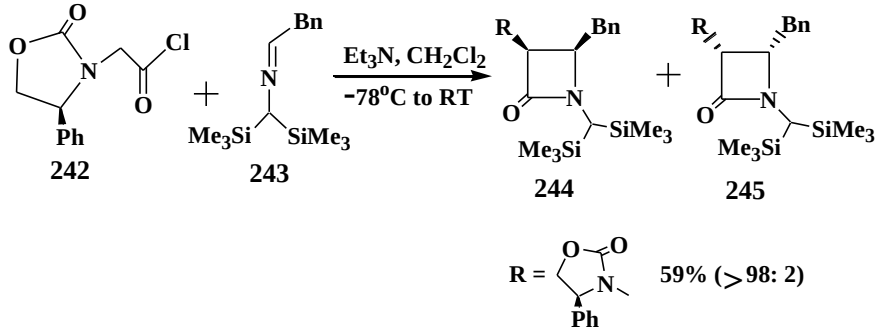
Scheme 52

Bhawal *et al.*[51] have reported that the reduction of (4*R*,5*R*)-(-)-diethyl 2,3-O-isopropylidene-L-tartarate **237** with diisobutylaluminium hydride (DIBALH), followed by treatment with amines **238** gave 86-99 yields of the di-imines **239**, which bear the chiral auxiliary at both C-termini of the bis-imine. The obtained di-imnes **239** reacted with the acid chlorides **240** under the standard Staudinger reaction conditions to afford the homochiral β-lactams **241** (the main product) in reasonable to good yields (52-75%), Scheme 53.



Scheme 53

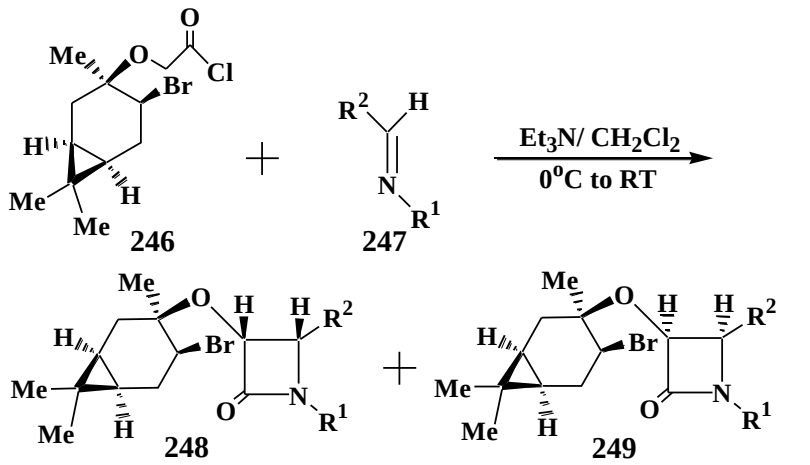
Palomo's group[52] in their extensive studies, showed that (*S*)-oxazalidinone-3-ylactyl chloride **243** reacted with the N-bis (trimethylsilyl)methylaldimine **244** in the presence of triethylamine to give **245** in a 55% yield with >96 de, Scheme 54.



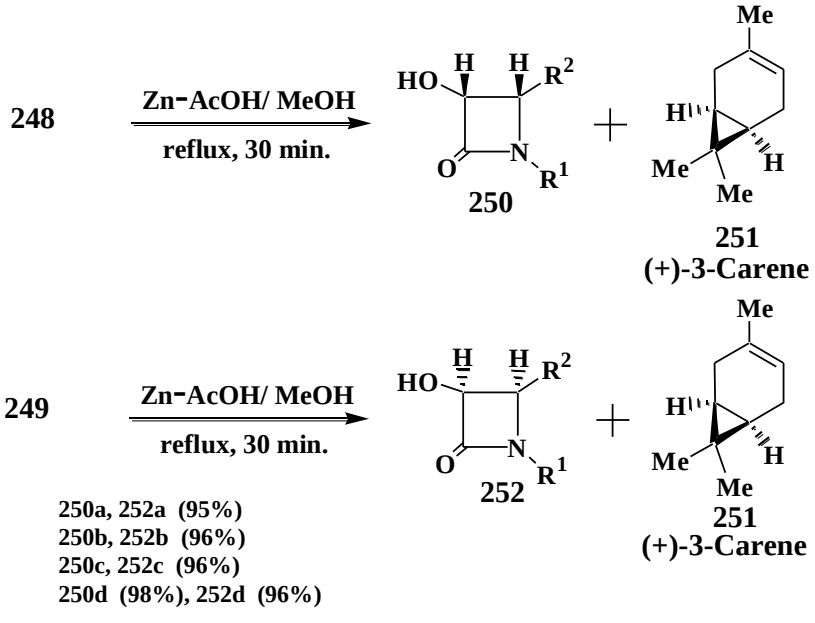
Scheme 54

On the other hand, Bhawal *et al.*,[53] quite recently in their extensive studies showed the effect of the chiral auxiliary when it is attached to the ketene carbon in the reaction between (1′*S*,3′*R*,4′*R*,6′*R*)-2-(4′-bromo-

3′,7′,7′-trimethylbicyclo [4.1.0]hept-3′-yloxy)acetyl chloride **246** with the imines **247** in the presence of Et_3N in CH_2Cl_2 afforded separable diasteriomeric mixture of the *cis* β-lactam **248** and **249** in acceptable yields (60-70%), which on zinc-induced removal of the chiral auxilary gave nearly quantitative yields (95-98%) of the enantiomerically pure 3-hydroxy-cis-β-lactams **250** and **251**, Scheme 55.



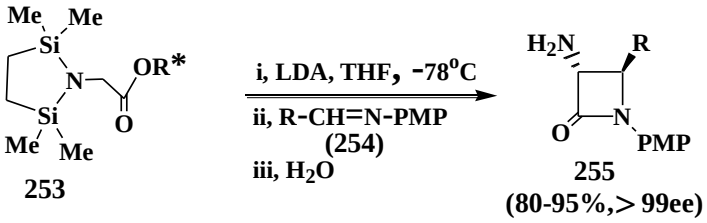
a, R^1 = *p*-$MeOC_6H_4$; R^2 = Ph (70%, 60: 40)
b, R^1 = R^2 = Ph (65%, 58: 42)
c, R^1 = R^2 = *p*-$MeOC_6H_4$ (70%, 64: 36)
d, R^1 = *p*-$MeOC_6H_4$; R^2 = PhCH=CH (60%, 60: 40)



250a, 252a (95%)
250b, 252b (96%)
250c, 252c (96%)
250d (98%), 252d (96%)

Scheme 55

The chiral ester enolate-imine cyclocondensation provides another efficient route to asymmetric synthesis of 3-amino and 3-hydroxy-β-lactams, Schemes 56 and 57. [54,55]

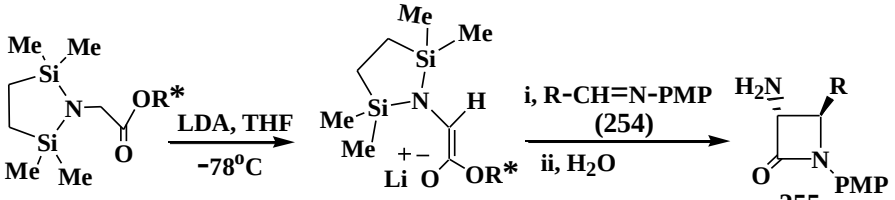


LDA = Lithium diisopropylamide

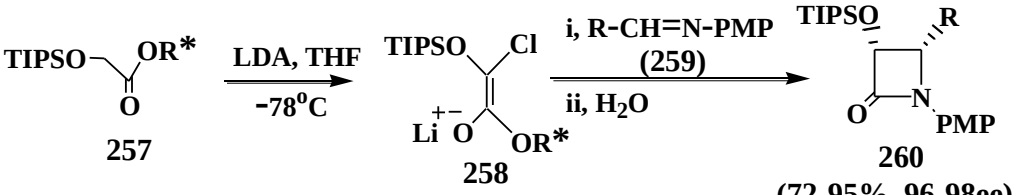
R* = (-)-menthyl, (+)- or (-)-*trans*-2-phenylcyclohexyl

R = Ph, *p*-FC_6H_4, *p*-$CF_3C_6H_4$, *p*-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$

PMP = *p*-$MeoC_6H_4$



Scheme 56



LDA = Lithium diisopropylamide

R*= (+)-*trans*-2-phenylcyclohexyl

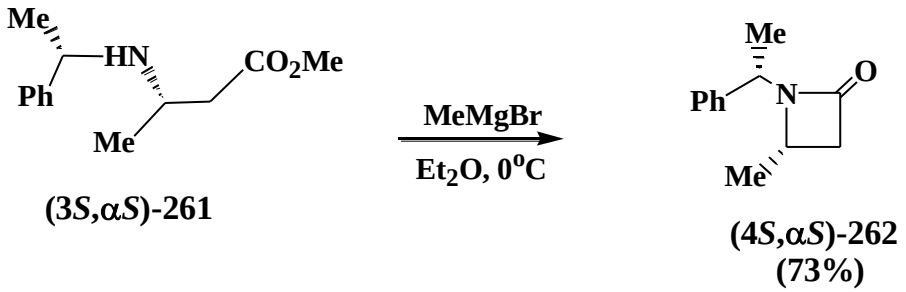
R = Aryl, Alkenyl, Alkyl

PMP = *p*-$MeoC_6H_4$

TIPS : triisopropylsilyl

Scheme 57

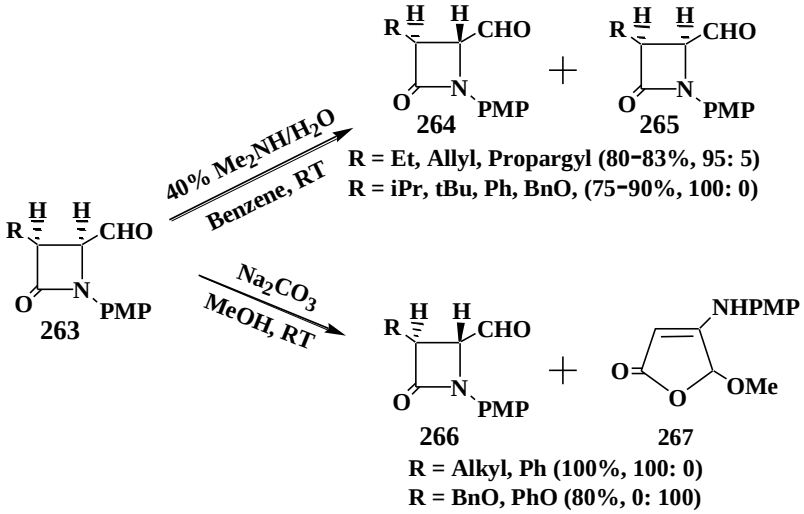
It was reported that the (3*S*,α*S*)-β-amino ester **261** on the treatment with methylmagnesium bromide in diethyl ether at 0°C followed by quenching with a pH7 buffer gave rise to the enantiomerically pure (3*S*,α*S*)-1-(α-methylbenzyl)-4-methylazetidine-2-one **262** in 73% yield, Scheme 58.[56]



Scheme 58

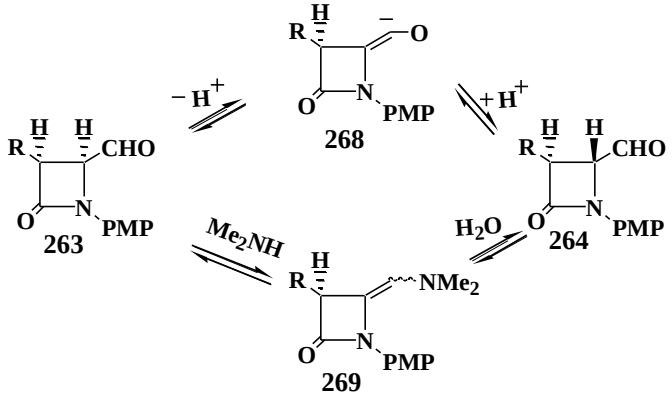
3.5 *cis/trans* β-LACTAM ISOMERIZATION:

Alcaide´s group[57,58] reported that the treatment of the cis-β-lactams **263** with dimethylamine afforded excellent yields (75-90%) of the corresponding *trans*-β-lactams **264**, Scheme 59. The bulkiness of the substituents at C3 controlled the reaction phathway, thus the *cis*-β-lactams **263** (R□□□□□□□□ = Et, allyl and propargyl) resulted in isomeric mixtures of *trans/cis* in a 95:5 ratio, whilst **265** (R□□□□□□□□ = *i*-Pr , *t*-Bu, Ph and BnO) gave the trans isomers only in 100% conversion. However, the Na_2CO_3/MeOH system seemed to be a very effective tool in the isomerisation process with some limitation. Thus, the β-lactams having benzyloxy or phenoxy groups at C3 under the Na_2CO_3/MeOH conditions rearranged to give the enaminone **267** in 80% yield as the only product.

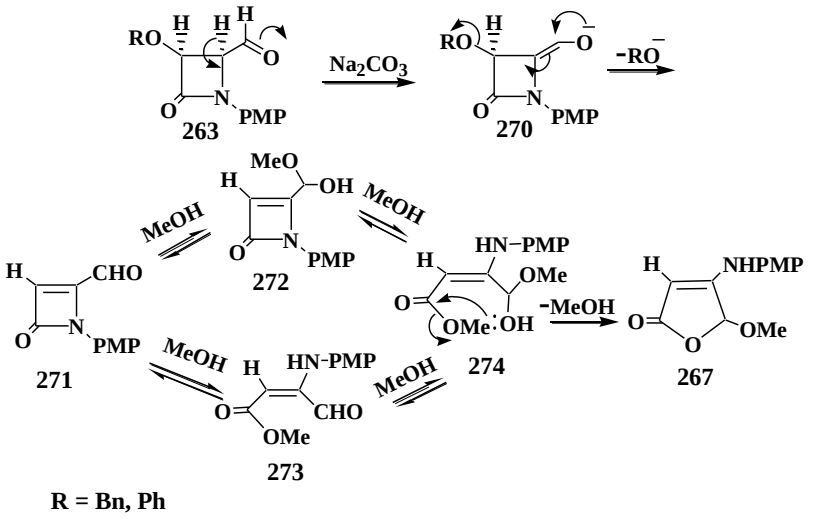


Scheme 59

They reported a mechanism for the Me_2NH mediated isomerization involves two pathways, Scheme 60. However, the sodium carbonate rearrangement mechanism is represented in Scheme 61.

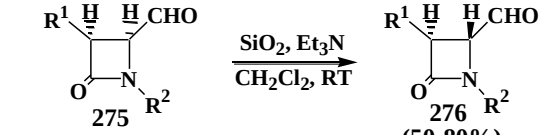


Scheme 60

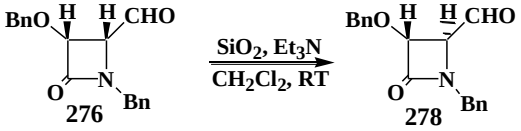


Scheme 61

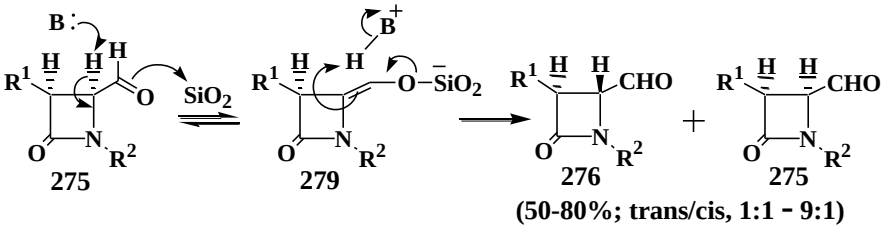
A convenient cheap and general procedure was reported for the *cis/trans* β-lactams isomerization, thus the racemic *cis*-β-lactams **275** were transformed into the racemic *trans*-β-lactams **276** in acceptable to good yields (50-80%) by the effect of SiO_2 in the presence of triethylamine, Scheme 62.[59] The enantiopure *cis*-β-lactam **(+)-277** analogously, under the same conditions, gave the enantiomerically pure *trans*-isomer **(+)-278** in 55% yield. It is believed that the isomerisation process occurs *via* the enol formation mechanism, Scheme 63. In the transient enol intermediate **279** the stereochemistry at C4 is lost, and the enol intermediate **279** can then revert back to the more stable trans isomer **276**.



R^1 = Et, ^{i}Pr, ^{t}Bu,Ph, MeO, BnO, PhO, malimidyl, phthalimidyl
R^2 = *p*-$MeOC_6H_4$, Bn

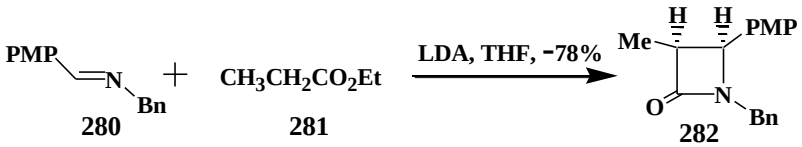


Scheme 62



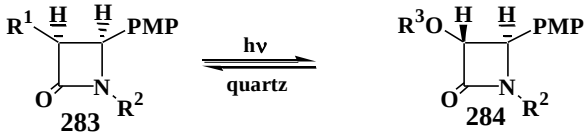
Scheme 63

Sierra *et al.*[60] have reported that the addition of N-benzyl-*p*-methoxyphenylimine **280** to a THF solution of ethylpropionate in LDA at –78°C, followed by acid quenching afforded exclusively the *cis*-β-lactam **282** in 40% yield, Scheme 64.

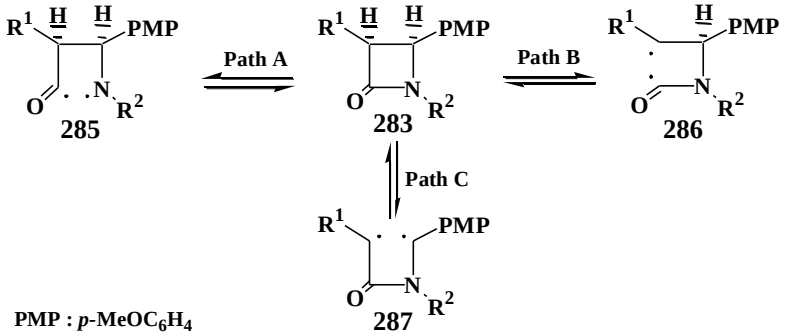


LDA = Lithium diisopropylamide,
PMP = *p*-$MeOC_6H_4$

Scheme 64



PMP = *p*-$MeOC_6H_4$
R^1 = OPh; R^2 = Me, (cis: trans, 1: 1), 0.5h
R^1 = OPh; R^2 = Bn, (cis: trans, 1: 1), 0.75h
R^1 = OPh; R^2 = Allyl, (cis: trans, 6: 1), 2.5h
R^1 = Me; R^2 = Bn, no isomerization
R^1 = Me; R^2 = Ph, no isomerization



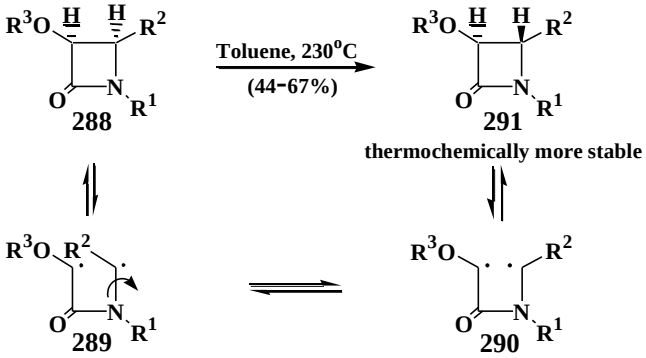
PMP : *p*-$MeOC_6H_4$
Path A is effective when R^2 = Ph
Path B is ruled out as it results in decarbonylation
Path C is more favoured as the resulting diradicals are highly stable

Scheme 65

They have also showed that the irradiation of an oxygen free acetonitrile solutions of the *cis*-βlactam **282** at room temperature in quartz tube with a 125w medium pressure mercury lamp resulted in an isomeric mixture of *cis/trans* β-lactams in ratios ranging from 1:1 to 9:1, it is believed that isomerization occurs thrugh the highly stable diradicle **287** obtained *via* path C, Scheme 65. However, the replacement of the alkoxy group at C3 by a methyl group, totally inhibits the isomerization process.

Alcaide's group[61] in their extensive studies reported that the heating of *cis*-4-aryl-β-lactams **288** in toluene in sealed tubes at 230°C afforded the *trans*-4-aryl-β-lactams **291** in (44 to 67%) yields, after a homolytic C3-C4

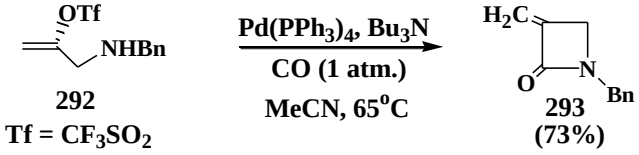
bond cleavage, the obtained diradical intermediate **289** would give the other diradical intermediate **290** after the bond rotation, Scheme 66.



Scheme 66

3.6 SYNTHESIS OF UNSARURATED β-LACTAMS:

Crisp and Meyer[62] reported that the amino vinyl triflate **292** under one atmospheric pressure of carbon monoxide in the presence of tributylamine and a palladium catalyst in acetonitrile at 65°C gave the corresponding 1-benzyl-3-methylazetidin-2-one **293** in 73% yield, Scheme 67.



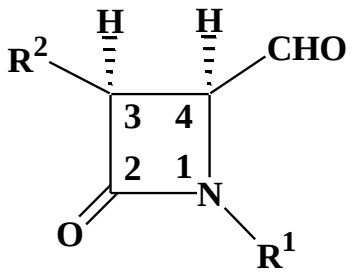
Scheme 67

4. β-LACTAMS AS VERSATILE BUILDING BLOCKS IN HETEROYCLIC SYNTHESIS:

The β-lactam skeleton has attracted significant interest among synthetic and medicinal chemists over the years, mainly because it is the core structure of natural and synthetic β-lactam antibiotics.[63,64] Although, that interest has a set back due to the β-lactamase enzymes resistance, synthetic chemists are still working hard on the β-lactam to obtain some interesting non-lactamic building blocks for the construction of some conformationally restricted heterocyclic compounds .[65-67]

4.1 THE 1,3-DIPOLAR CYCLOADDITION REACTIONS:

It is well documented that the 1,3-dipolar cycloaddition process is a very convenient route for constructing simple and complex molecules containing a hetero atom. During the last ten years, Alcaide[65,68,69] and others,[70,71] showed that the *cis*-4-formyl-2-azetidinone **294** is recognized as one of the most powerful tools in the synthesis of a wide variety of both lactamic and non-lactamic products.

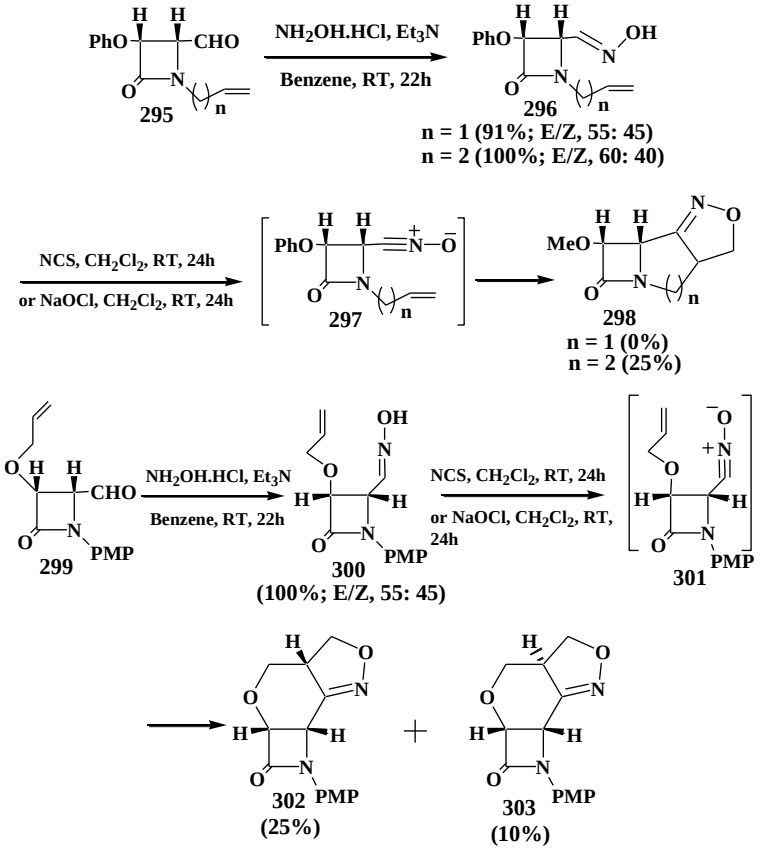


294

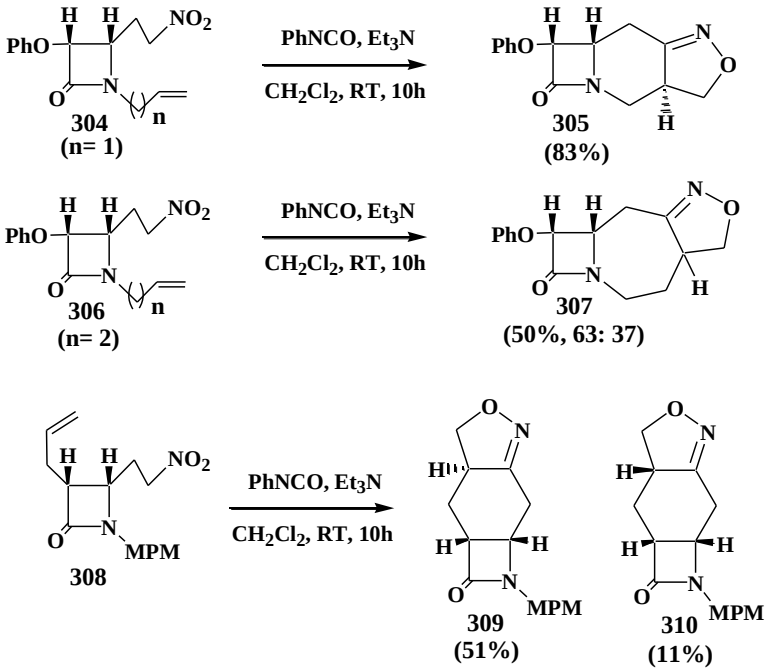
4.1.1 The Nitrile N-Oxides:

Alcaide[65] very recently reported that the *cis*-4-oxoazetidine-2-carbaldehyde **295** reacted smoothly with hydroxylamine to form the oximes **296** in almost quantitative yields (91-100%). The resulting oximes under chlorination with N-chlorosuccinimide or sodium hypochlorite followed by treatment with triethylamine gave the cycloadducts **298** in poor yields (0-25%), *via* the generated *in situ* nitrile N-oxides **297**, Scheme 68. They attributed the very low yield to the difficulty of obtaining the nitrile N-oxides, as the unreacted starting oximes were

recovered. On the other hand, the β-lactams **299** under the same conditions gave the fused tricyclic β-lactams **302** and **303** in 25 and 10 % yields respectively. The same authors reported a different route for obtaining the nitrile N-oxides in high yields, thus the reaction of the nitro derivatives **304** (n = 1) with the phenylisocyanate gave the corresponding tricyclic β-lactams in high yield (83%), in a stereospecific manner as a single isomer, however, **306** (n = 2) and **308** under the same conditions gave lower yields of isomeric mixtures 50% of **307** (63:37) and 62% of **309** and **310** (51:11), Scheme 69.[72]



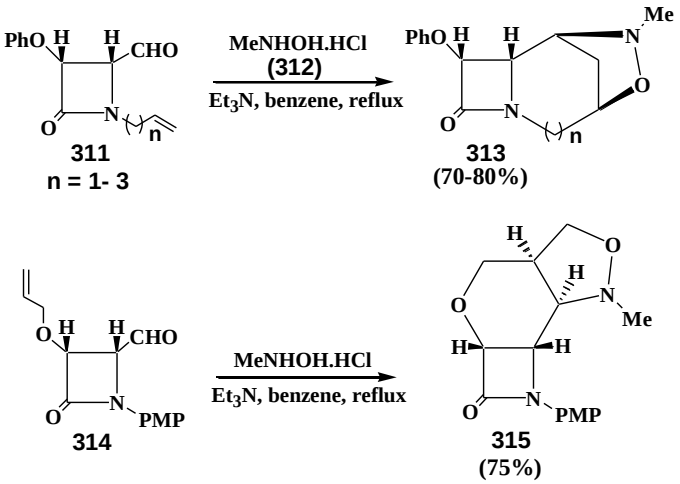
Scheme 68



Scheme 69

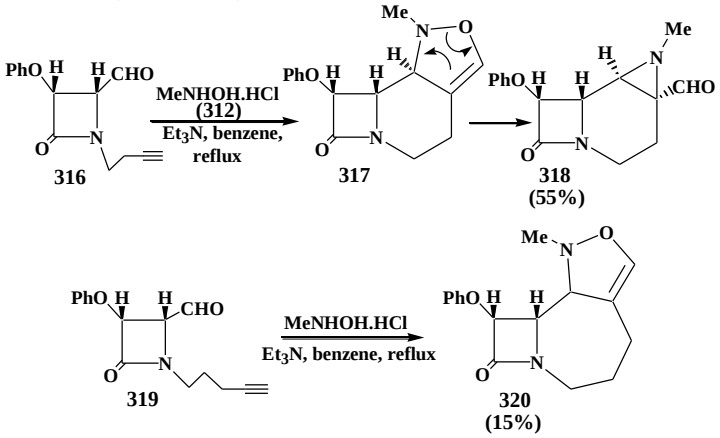
4.1.2 The Nitrones:

It was reported that 2-azetidine-tethered alkenyl aldhydes **311** reacted with N-methylhydroxylamine hydrochloride **312** in benzene in the presence of Et_3N to form the bridged tricyclic β-lactams **313** in good yields (70-80%), on the other hand, the β-lactam aldehyde **314** under the same conditions afforded the fused tricyclic β-lactam **315** in a 75% yield, Scheme 70.[68,73,74] It seemes that regioselectivity of the cycloaddition process is mainly depending on the substituent position. The firstly obtained nitrones cycloadds intramolecularly to the tethered alkenyl group at N1 on the β-lactam ring to form the corresponding cyloadducts. The formation of the bridged tricyclic β-lactams is due to the rigid angular disposition imported by the planer β-lactam group, which would increase the energy of the fused ring transition state and make less competetive with the usually unfavoured bridged ring transition state.



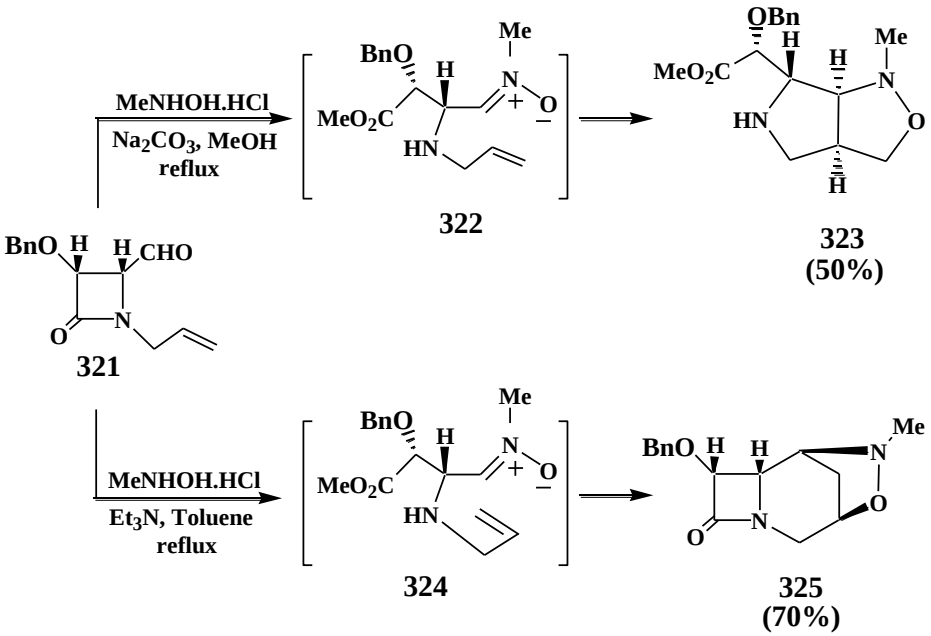
Scheme 70

As shown in Scheme 71, the alkynyl derivative **316** underwent the intramolecular nitrone-alkynyl cycloaddition to afford the aziridine carbaldehyde **318** in a 55% yield, which may arise by a thermal sigmatropic rearrangment through the intermediate **317** (arrows).



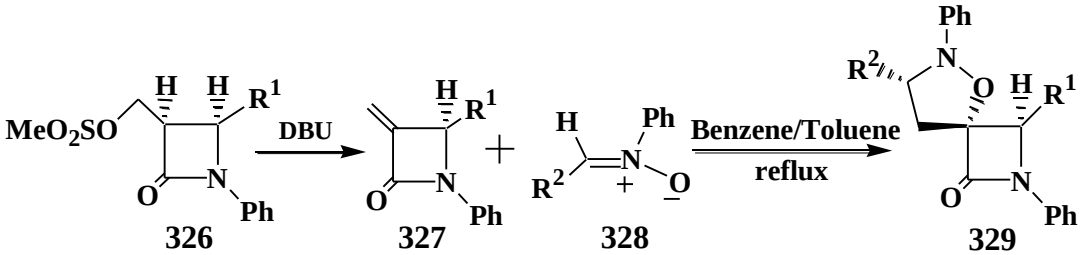
Scheme 71

Alcaide's group[75] reported that the 4-formyl β-lactam **321** reacted with N-methylhydroxylamine hydrochloride **212** in refluxing MeOH in the presence of sodium carbonate to afford the bicyclic derivative **323** *via* the intermediate nitrone **322**, whereas conducting the same reaction under different conditions (using Et_3N as a base in boiling toluene, gave the tricyclic bridged β-lactam **325** *via* the nitrone **324**, Scheme72.



Scheme 72

Basak *et al.*[76] reported that the treatement of the amylates **326** with DBU afforded the alkenyl β-lactam **327** which reacted with the nitrones **328** to give the spiro β-lactams **329** in excellent yields (89-93%) in a regio- and stereospecific manner, Scheme 73. It is believed that the nitrone during the cycloaddition process is approaching the dipolarophile from the opposite face to the C4 substituent on the β-lactam ring.



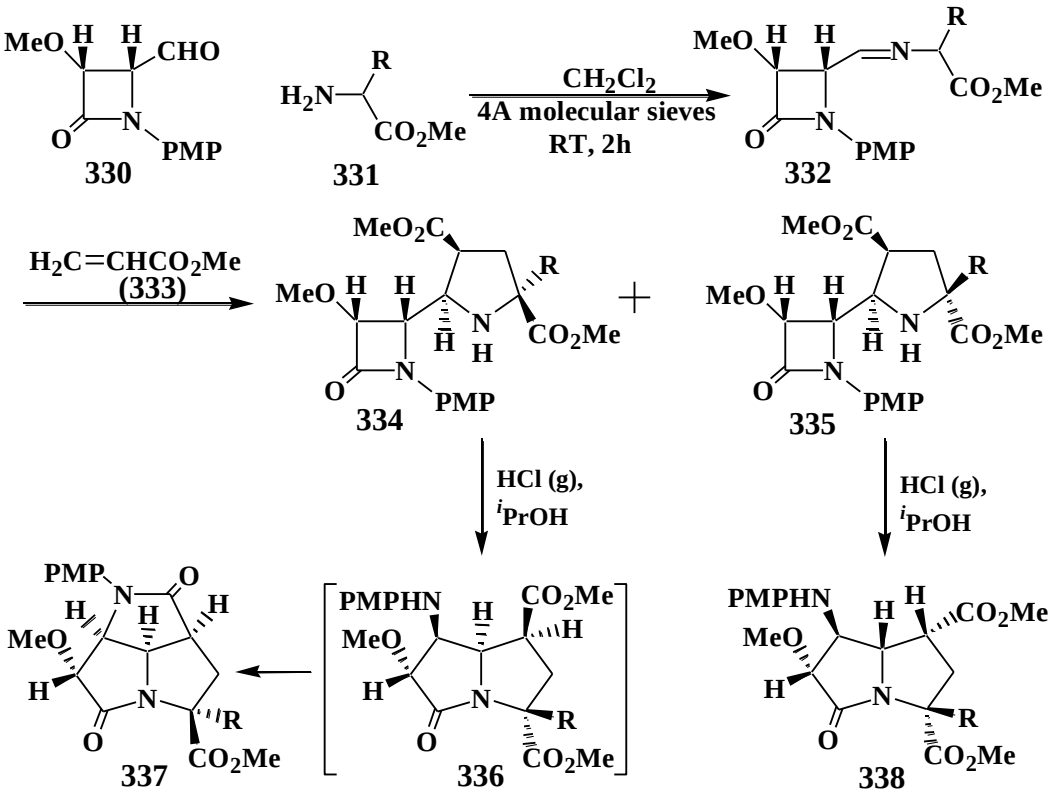
R^1 = Ph, Furyl, Thienyl;
R^2 = Ph, Furyl, p-$MeOC_6H_4$, p-$MeOC_6H_4CH_2$

Scheme 73

4.1.3 The Azomethine Ylides:

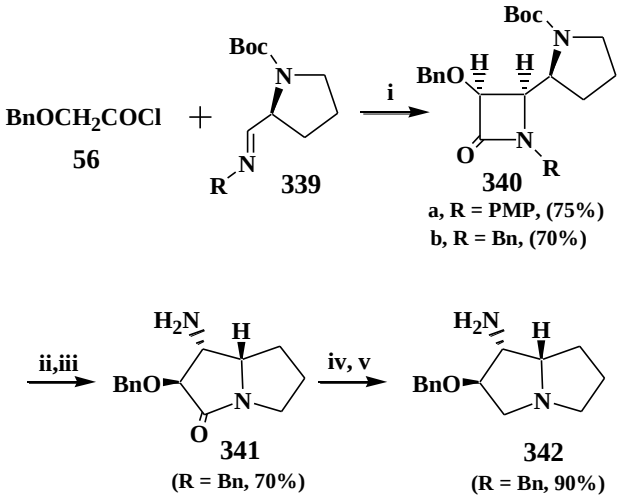
The reaction of the β-lactam **330** with the amino acid esters **331** afforded the aliphatic aldimines **332**, which reacted with methyl acrylate **333** in toluene at room temperature in the presence of AcOAg to afford a chromatography separable

isomeric mixture of the cycloadducts **334** and **335** in reasonable to good diastereoselectivity (30-90% d.e.). The cycloadduct **334** in acidified isopropanol gave the tricyclic pyrrolizidine system **337,** whereas the cycloadduct **335** under the same conditions gave the bicyclic pyrrolizidine alkaloides skeleton **338**, Scheme 74.[69,77] The anti relationship between the ester and amine moieties in **338** prevented the additional cyclization to occur.



Scheme 74

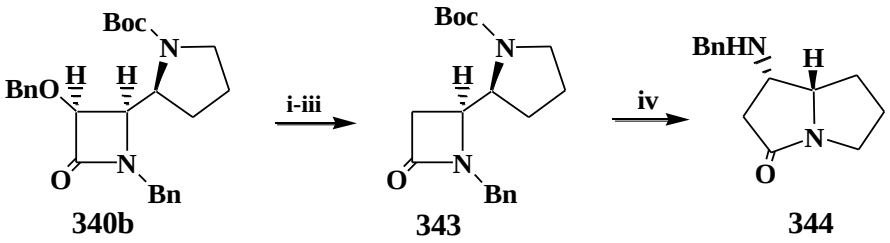
However, Palomo[78] in 1996 reported a novel method for the synthesis of some pyrrolizidine alkaloides skeleton, thus the β-lactam **340** on the N-dearylation by CAN followed by deprotection of the butoxycarbonyl (Boc) group afforded an intermediate which cyclized immediately under the deprotective conditions to give the bicyclic γ-lactam **341**. The γ-lactam **341** was reduced to afford the 4-amino-3-hydroxy-pyrrolizidine alkaloid, Scheme 75.



Reagents and conditions:
i Et_3N, CH_2Cl_2, -78°C, RT, 20-24h; ii $(NH_4)_2Ce(NO_3)_6$, MeCN-CH_2Cl_2-H_2O, 0°C, 15-20min; iii $ClSiMe_3$, MeOH, reflux or CF_3CO_2H, CH_2Cl_2, then12 NHCl, EtOH, reflux; iv $BH_3.SMe_2$, THF, reflux, 2h; v AcONa, MeOH, 5min, then I_2, $CHCl_3$.

Scheme 75

However, the β-lactam **340b** reacted similarly to afford 70% yield of the 4-amino-pyrrolizidine alkaloid **344**, Scheme 76.

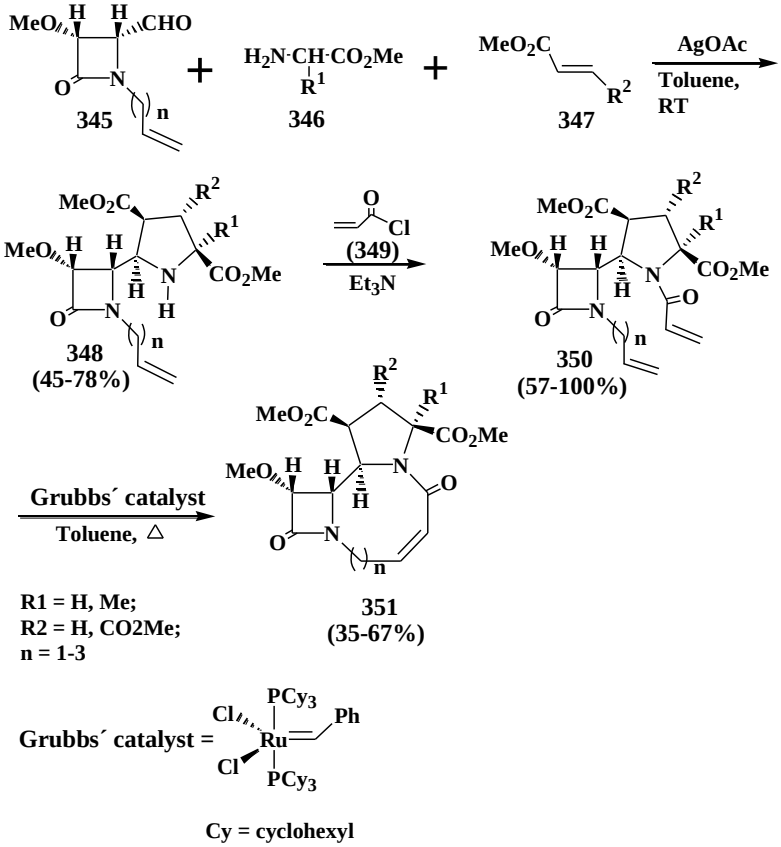


i NH_4HCO_3, Pd-C,Me_2CO, reflux (80%); ii NaH, CS_2, THF-HMPA, MeI, RT, 30min (86%); iii Bu_3SnH, AIBN, Toluene, reflux, 1h (80%); iv 12N HCl, EtOH, reflux, 24h, (70%).

Scheme 76

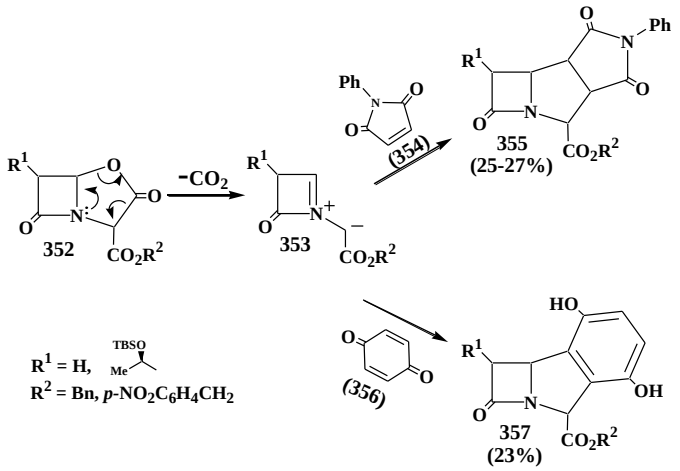
Just at the beginning of the 21st century, it was shown that the combination of [2+2] and [3+2] cycloadditions and ring closing metathesis provided a very useful tool for the asymmetric construction of the tricyclic β-lactams containing fused medium-sized ring and two bridgehead nitrogen atoms. Thus, the 4-formyl-2-azetidinone **345** (obtained from the classical Staudinger reaction) reacted with the α-amino acid esters **346** and dipolarophiles **347** in the presence of AgOAc in toluene at room temperature to give the pyrrolidines **348** in 45-78% yields, N-acylation of the obtained cycloadducts **348** afforded

quantitative yields of the dialkenyl derivatives **350** which serve as the desired candidates for the ring closing metathesis (RCM) process giving finally the tricyclic β-lactams **351** in moderate to acceptable yields (35-67%), Scheme 77.[79]

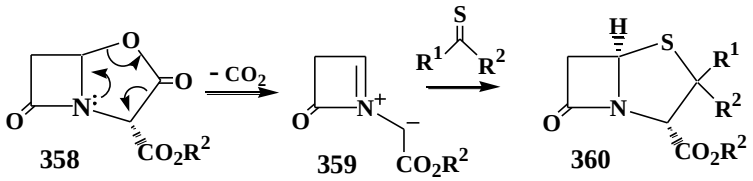


Scheme 77

The synthesis of carbapenems and carbapenams (an important class of the β-lactam antibiotics) which consist a pyrroline moiety fused to a β-lactam nucleus is a real challenge. Gallagher's group[80-82] in their elegant work utilised the 1,3-dipolar cycloaddition methodology as a powerful synthetic tool to provide a one pot synthesis for producing a wide variety of such cyclic β-lactamic products **355**, **357** and **380**, in which the β-lactam ring is fused to a five-membered carbocycle or heterocycle, Schemes 78 and 79, respectively.

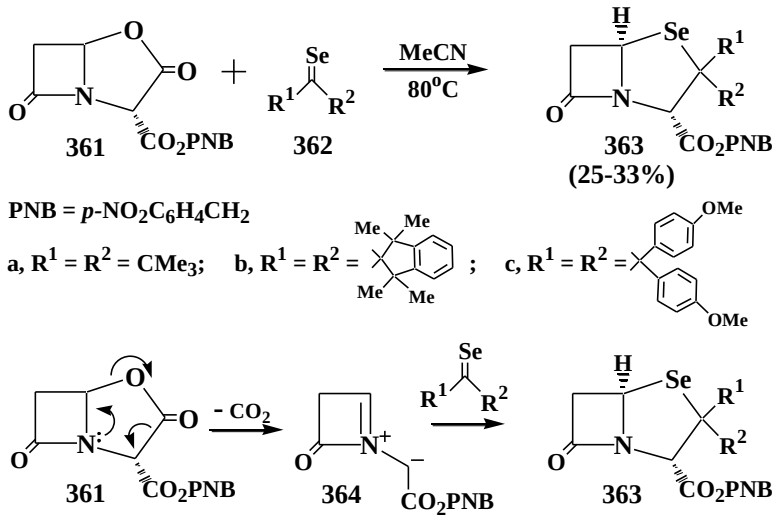


Scheme 78



Scheme 79

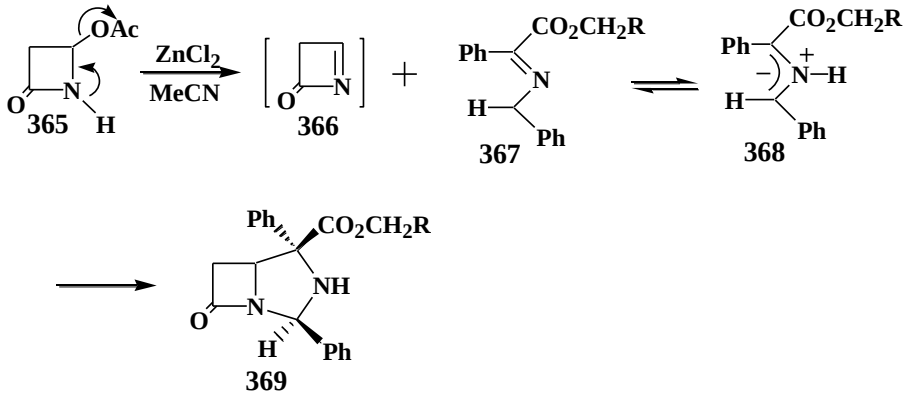
Unlike the penams and penems, very little is known about the synthesis of the corresponding selenium containing bicyclic β-lactams. However, a report came from Gallagher's laboratories[83] showing the possibility of the synthesis of the selenopenams **363**. Thus, the reaction of **361** with selenoketones **262** in boiling acetonitrile afforded modest yields (25-33%) of **362**, Scheme 80.



Scheme 80

Costero and his co-workers[84] showed that the 4-acetoxy-azetidin-2-one **1** reacted with methyl N-

benzylidenephenylglycinate **2** in acetonitrile under Lewis acid catalysis to give the corresponding bicyclic β-lactams **3a,b** in moderate yields (30.3-43.7%), respectively, Scheme 81.

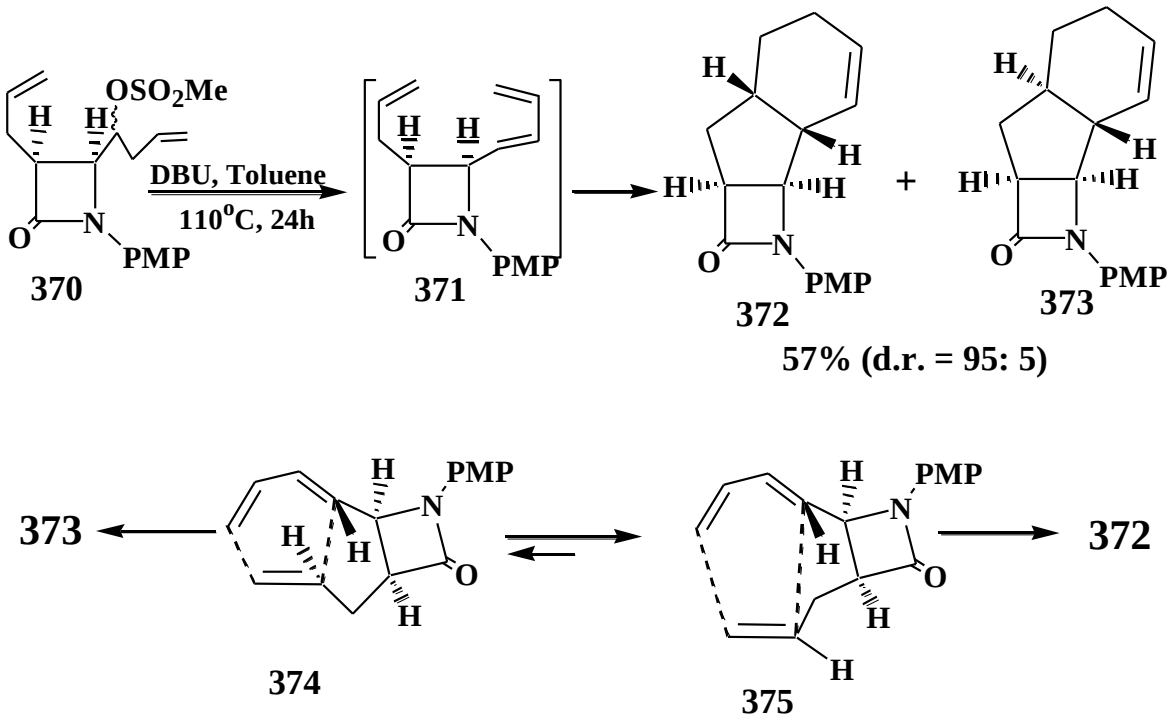


a, R = H (30%)
b, R = polymeric support (Merrifield resin), i- 2-dimethylaminoethanol/DMF, RT 6h;
ii- MeOH, RT, 2 days (44%)

Scheme 81

4.2 Diels-Alder Reactions:

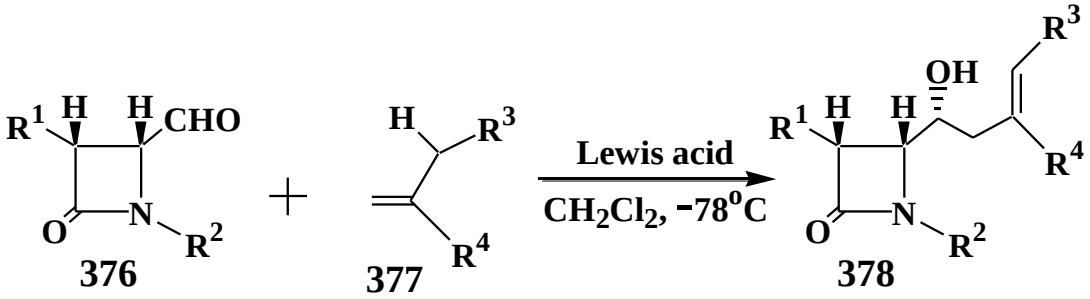
Alcaide *et al.*[85,86] reported that the mesylate derivatives **370** reacted with DBU in boiling toluene to afford the tricyclic β-lactams **372** and **373** in reasonable total yield (57%) with high diasereoselectivity (95:5) *via* a tandem elimination-intramolecular Diels-Alder reaction, Scheme 82. The two transition states **374** and **375** are represented, in which the stereochemical outcome seems to be governed by the C4 stereogenic center in the β-lactam ring.



Scheme 82

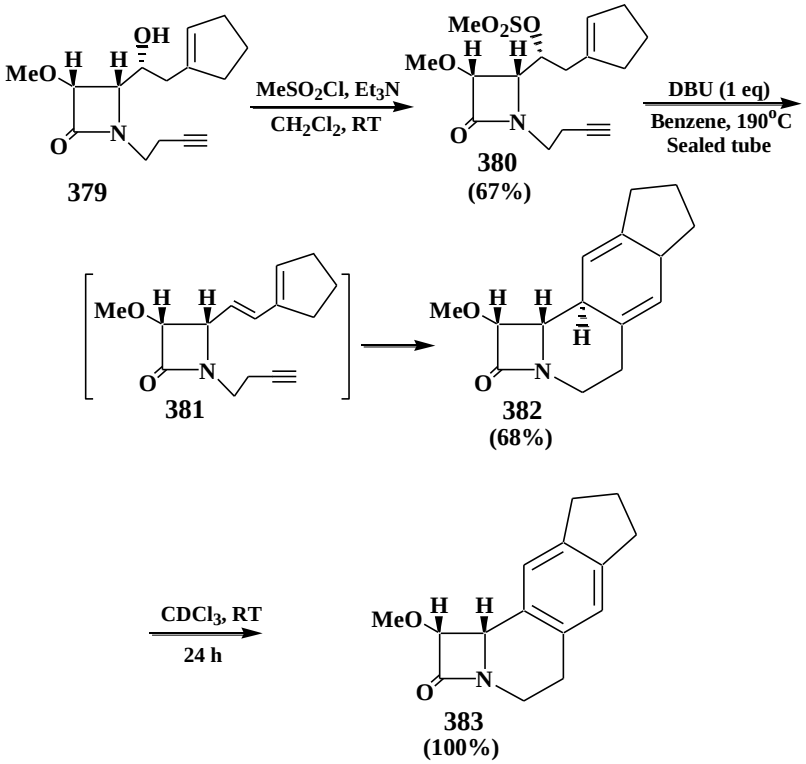
Alcaide,[87] has recently reported a novel methodology for the synthesis of the entiomerically pure homoallylic alcohols *via* the Lewis acid-promoted intermolecular carbonyl-ene reaction of the enantiopure 4-formyl β-lactams **(+)-376** afforded the homoallylic alcohols **(+)-378** as the only product in moderate to excellent yields (41-85%), Scheme 83. The homoallylic alcohol **(+)-379** were transformed into the corresponding mesylated derivatives **380** in reasonable yield (67%), which on heating in benzene in sealed tube with one equivalent of DBU underwent interamolecular Diels-Alder cycloaddition process to afford the corresponding adduct **382** in moderate yield (68%) *via* the formed *in situ* intermediate **381**. The obtained Diels-Alder adduct **382** underwent aromatization either on standing at room temperature or on heating for prolonged time to give the product **383** in quantitative yield, Scheme 84. The presence of the alkyn group at C3 on the β-lactam ring resulted in the formation of the aromatized products without separating the first formed intermediates. Alcaide has also reported an interesting result, thus the enantiomercally pure mesylates **(+)-384** and reacted with 1.5 equivalents of DBU in refluxing benzene to give

racemic mixture of the amides **(±)-385** in 61% to 69% yields, Scheme 84. It is believed that the excess of the base has affected the N1-C4-bond cleavage in the β-lactam ring.

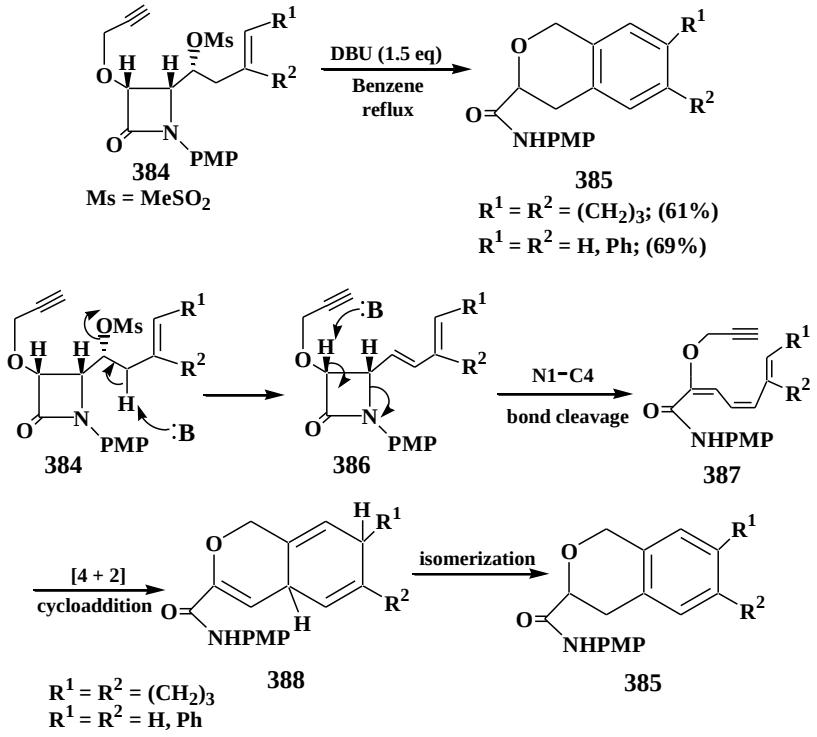


R^1 = OMe, OBn, OPh, O-Allyl, O-Propargyl, Phthlimido
R^2 = p-$MeOC_6H_4$, 2-Propenyl, 3-Butenyl, 2-Propynyl, 3-Butynyl
R^3 = R^4 = $(CH_2)_3$, $(CH_2)_4$, H, Ph; Lewis acid: $SnCl_4$, $BF_3.Et_2O$

Scheme 1



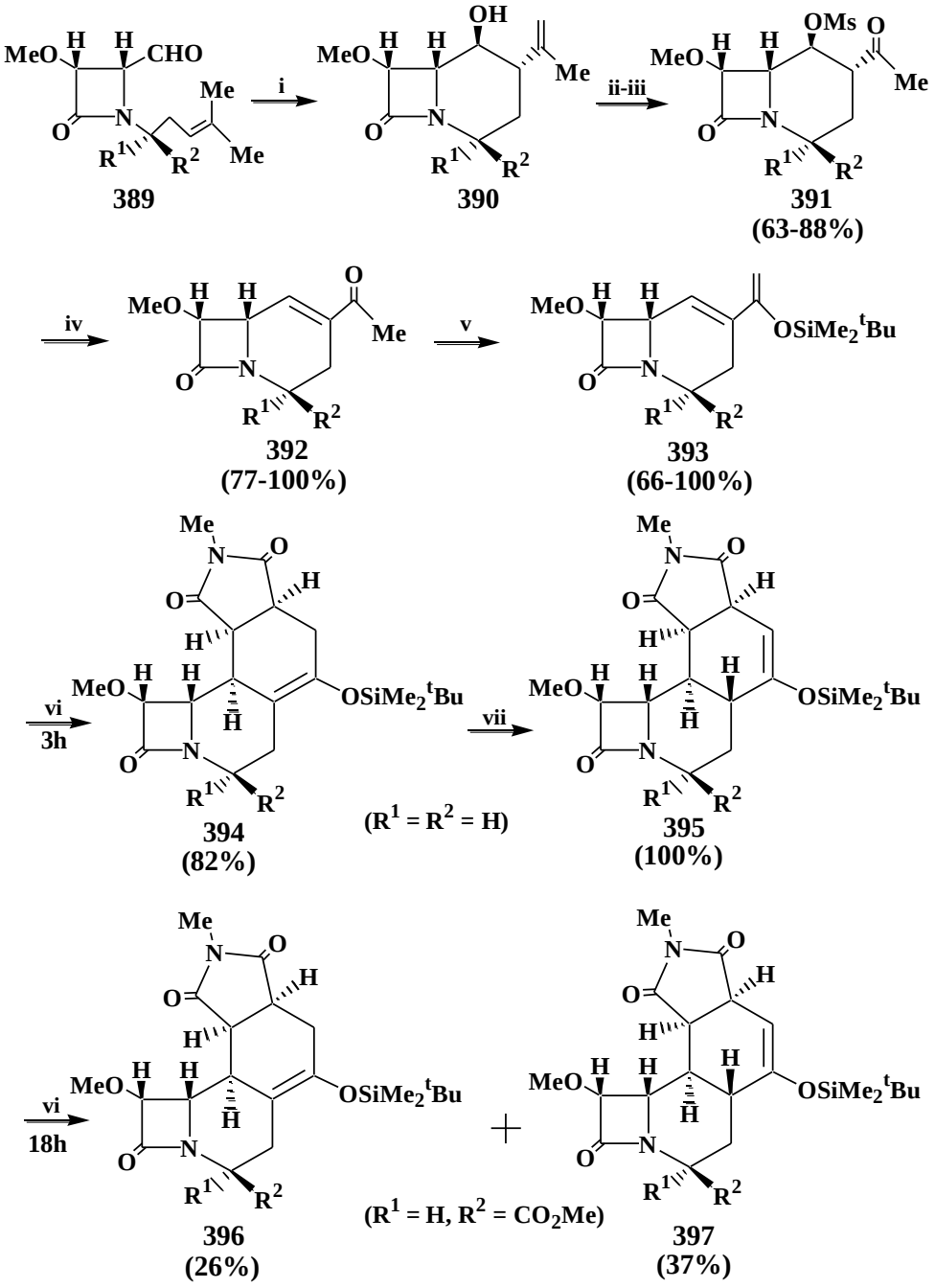
Scheme 84



Scheme 85

Alcaide [88] very recently reported that the enantiomerically pure 2-azetidiene tethered alkenylaldehydes **389** under Lewis acid catalysis afforded pure enantiomers of **390** in acceptable yields in stereoselective fashion. The obtained alkenyl alcohols were transformed into the corresponding mesylates **391** in acceptable to excellent yields (63-88%), followed by elimination of methanesulfonic acid by the effect of DBU in benzene at room temperature to form the enones **392** in 77-100% yields, which on the reaction with 1.2 equivalents of tert-butyldimethylsilyl trifluoromethanesulfonate in dichloromethane in the presence of triethylamine gave the Diels-Alder condidates **393** in acceptable to quantitative yields (66-100%). The activated bicyclic inner-ring-outer dienes **393** smoothly underwent Diels-Alder cycloaddition to afford the corresponding tetracyclic carbacephams in good to excellent yields (63-82%), Scheme 86. The diene **393** ($R^1 = R^2 = H$) gave good yield (82%) of the corresponding adduct **394**, which on standing at room temperature in $CDCl_3$ for only one hour gave the rearranged product **395** in quantitative yield. The isomerisation form **394** to **395** was observed only in $CDCl_3$

solvents probably due to the 1,3-migration of hydrogen catalysed by the acidic traces in the solvent, in C_6D_6 no isomerisation was observed. On the other hand, the diene **393** (R^1 = H, R^2 = CO_2Me) under the Diels-Alder conditions after 18 hours afforded a 63 % yield of the cycloadducts **396** and **397** in a 26:37 ratio, respectively.



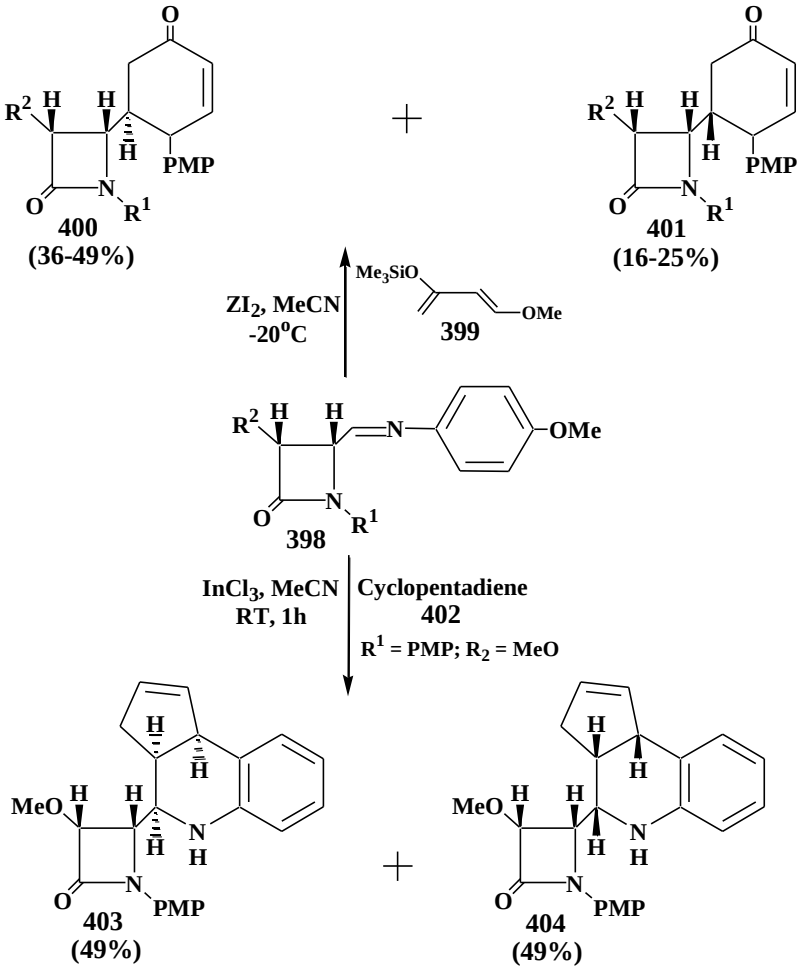
Ms = $MeSO_2$

Reagents and conditions: (i) $BF_3.Et_2O$, CH_2Cl_2, −78°C; (ii) $MeSO_2Cl$, Et_3N, RT; (iii) $RuCl_3$, 7% mol, $NaIO_4$ (4 eq), $ClCH_2CH_2Cl/H_2O$ (5:4), RT; (iv) DBU (1 eq), Benzene, RT; (v) $^tBuMe_2$ $SiSO_2CF_3$ (1.2 eq), CH_2Cl_2, 0°C; (vi) N-methylmaleimide, toluene, 145°C, sealed tube; (vii) $CDCl_3$, RT, 1h

Scheme 86

An interesting article came from Alcaide's laboratories showed the first synthesis of indolizidine alkaloids using the β-lactams as chiral building blocks *via* azo-Diels-Alder reaction of 2-azetidinone-tethered imines combined with N1-C2 bond

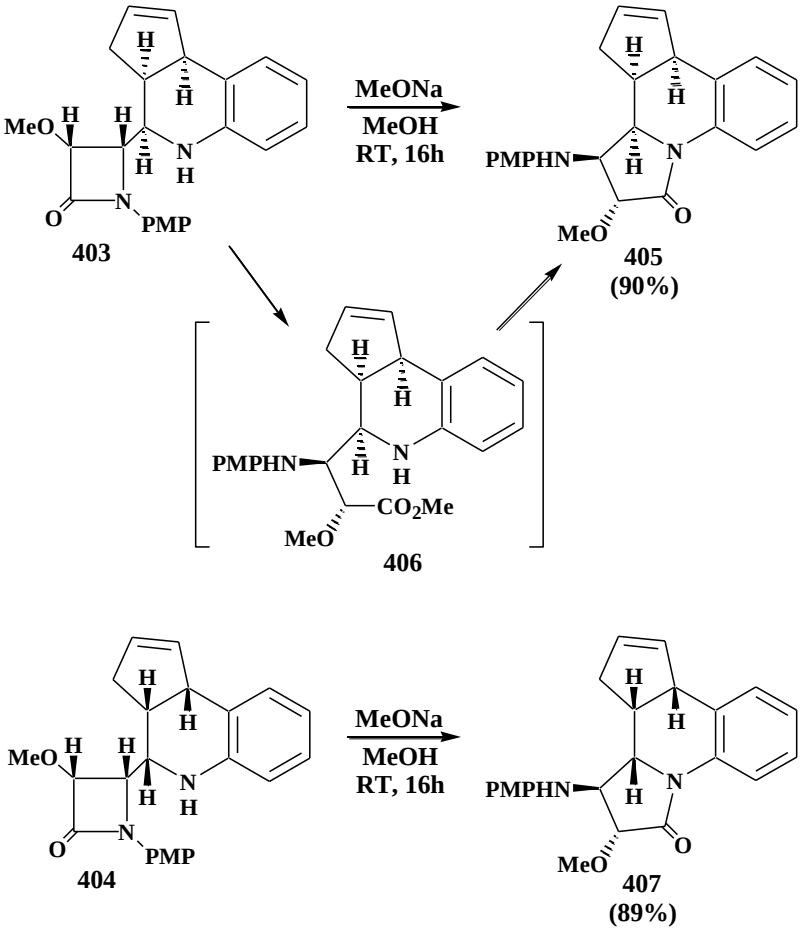
breakage and rearrangement reactions on the β-lactam ring.[89] Thus, [4+2] cycloaddition between the imines **398** and the 1-methoxy-3-trimethyl-silyloxy-1,3-butadiene (Danishfsky's reagent, a very reactive diene) **399** underwent smoothly in CH_3CN at low temperature (-20°C) in the presence of zinc iodide to give reasonable to good yields (52-74%) of separable isomeric mixtures of the corresponding cycloadducts **400** and **401** in ratio ranging from 36:16 to 49:25. Interestingly the imine **398** reacted with the less electron rich dienes (e.g. cyclopentadiene **402**) at room temperature to afford excellent yield (98%) of the separable diastereoisomers **403** and **404** in a 1:1 ratio. These results showed for the first time this imino-diene behaviour of the aliphatic aldimines, Scheme 87.[89,90]



Scheme 87

However, treating the cycloadduct **403** with MeONa in methanol at room temperature gave after 18 hours excellent

yield (90%) of the the indolizidine like system **405** through the firstly obtained β-amino ester **406**, Scheme 88. The other diastereoisomer **404** reacted analogously to afford 89% yield of the indolizidine derivative **407**.

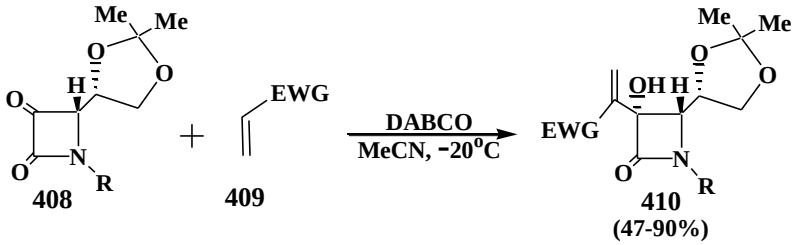


Scheme 88

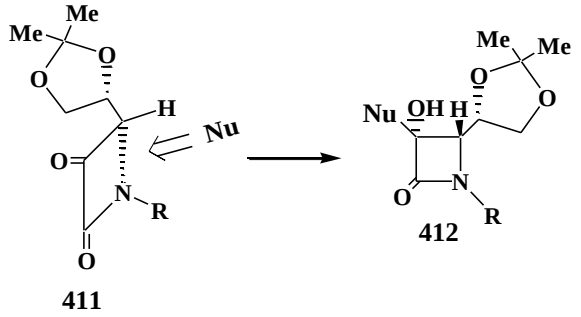
4.3 Baylis-Hillman Reactions:

Alcaide[91,92] very recently issued some elegant reports showing the use of the azetidin-2,3-ones as successful candidates for the Baylis-Hillman reaction. Thus the homochiral azetidin-2,3-ones **408** reacted smoothly with the activated alkenes **409** in acetonitrile at -20^{o}C in the presence of DABCO, to give the corresponding Baylis-Hillman adducts **410** in moderate to excellent yields (47-90%) with high stereoselectivity, Scheme 89. It is believed that the high stereoselectivity is due to the nucleophilic attack from the less

hindered face and away from the bulky chiral group at C4 on the β-lactam ring, Scheme 90.

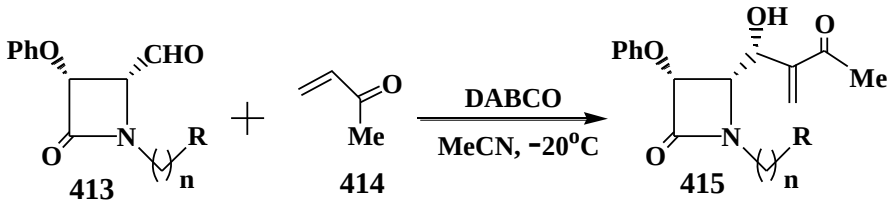


Scheme 89



Scheme 90

The 4-formyl β-lactam 413 reacted analogously to give the corresponding Baylis-Hillman adducts in acceptable to good yields (60-80%) with high diastereoselectivity ranges from 92 to >97%, Scheme 91.



a, n = 1, R = Vinyl, (80%, de = > 97%)
b, n = 1, R = Vinyl, (78%, de = 92%)
c, n = 2, R = Ethynyl, (67%, de = > 97%)
d, n = 3, R = Ethynyl, (60%, de = > 97%)

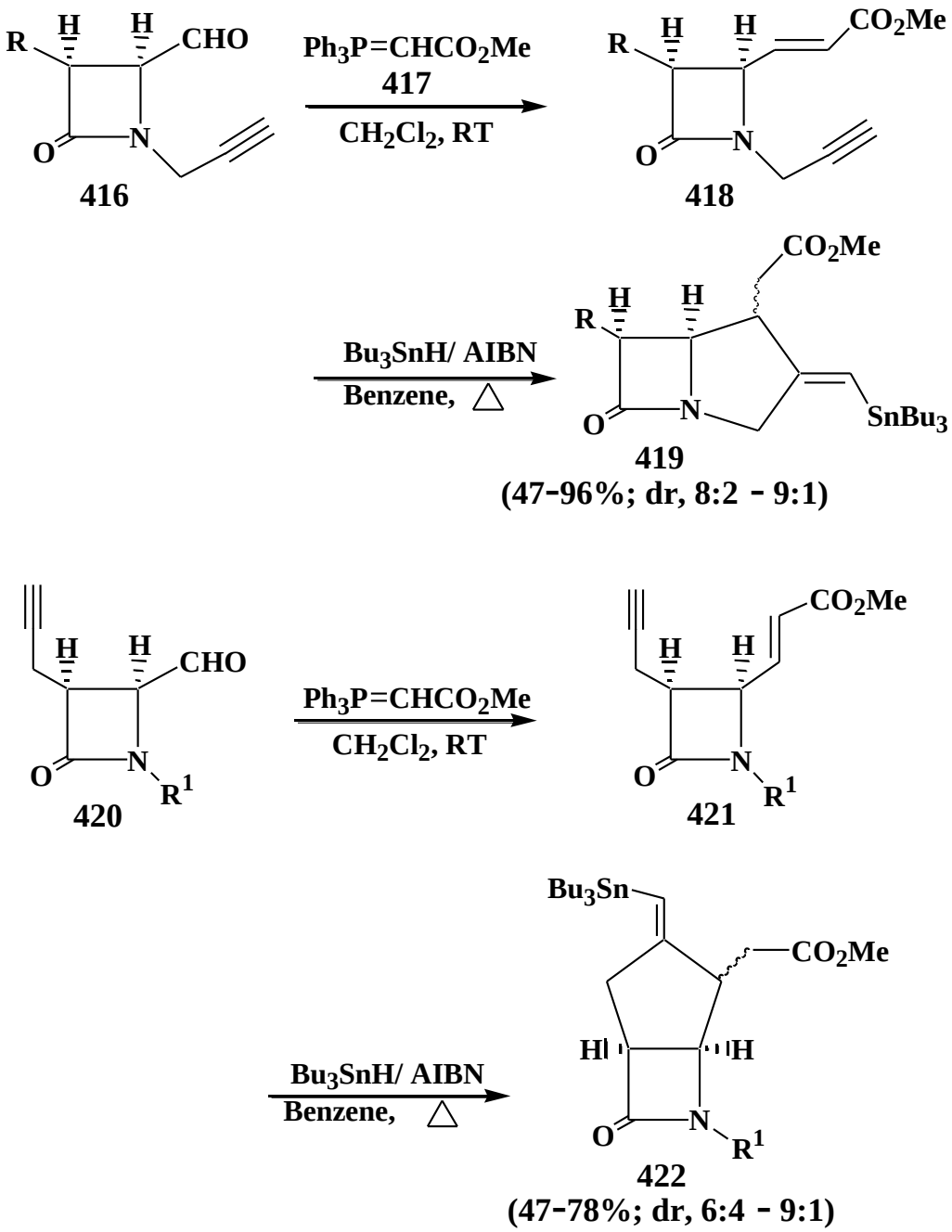
Scheme 91

4.4 The Radical Reactions:

The radical reactions are very powerful tool for the synthesis of five- and six-membered carbocycles and hetrocycles. The

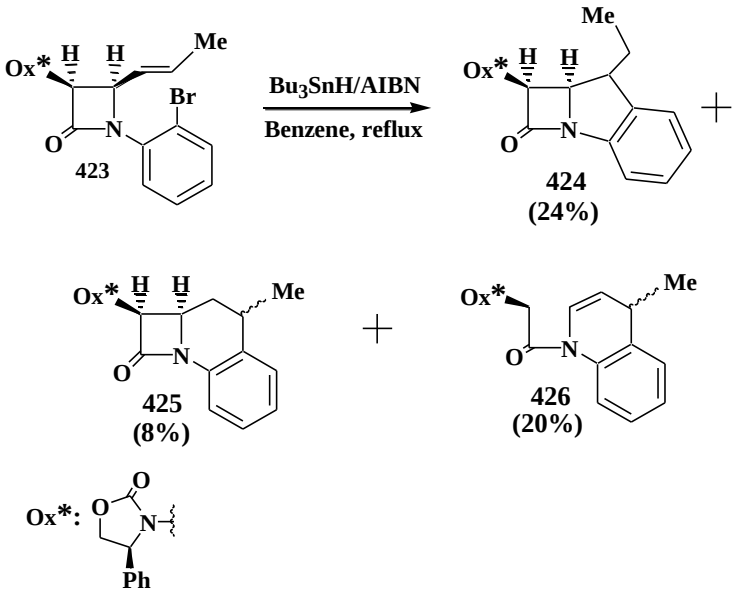
radical cyclization generally proceeds very smoothly with high degree of regio- and stereoselectivity.

The synthesis of fused bicyclic β-lactams resembles one of the benefits of the radical cyclization methodology. Thus, Wittig-olefination of the monocyclic β-lactam **416** afforded the enyne-β-lactam **418** in which the double bond acts as a radical acceptor during the reaction with Bn_3SnH in boiling benzene in the presence of AIBN (azoisobutyronitrile) to give the fused bicyclic β-lactams (vinyltin carbapenam) **419** in moderatae to excellent yield (47-96%) with high diastereoselectivity (8:2-9:1), Scheme 92.[93] However, the monocyclic β-lactams **420** under the same conditions afforded the 3,4-fused bicyclic β-lactams in moderate to good yields (47-78%) with the diastereomeric ratio ranges from 6:4 to 9:1.

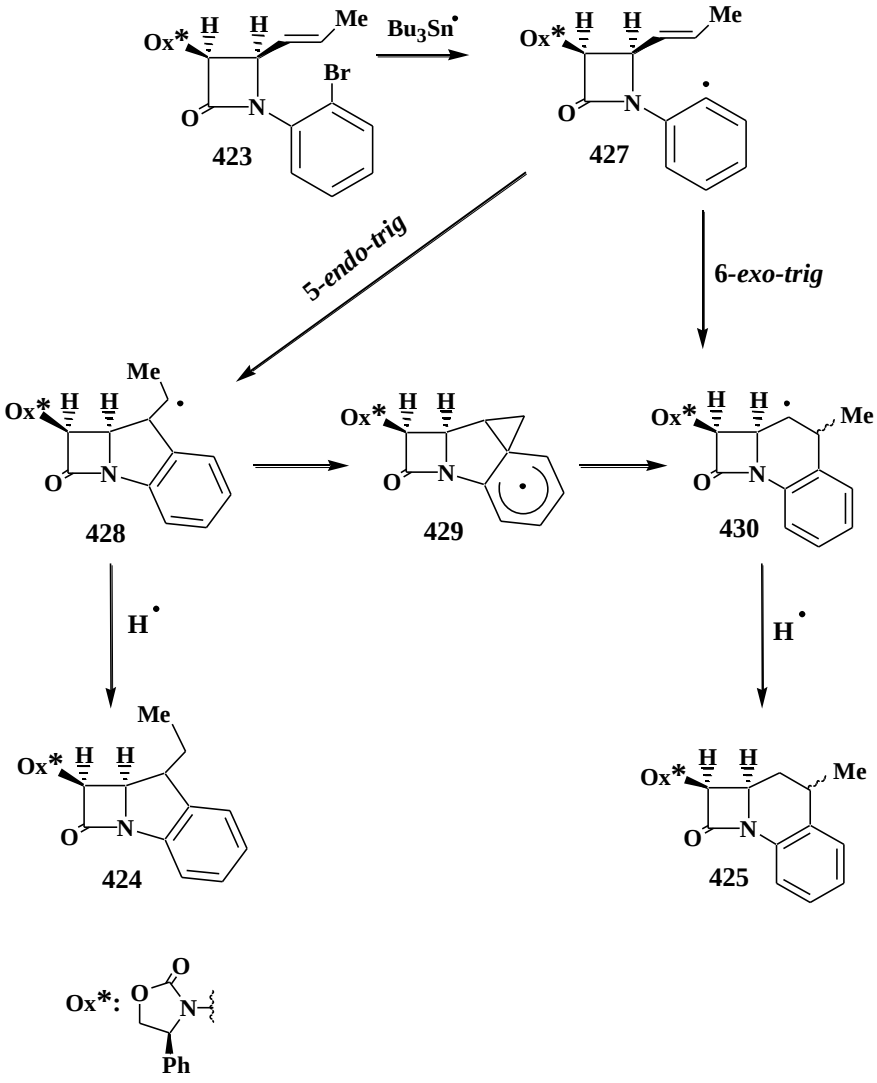


Scheme 92

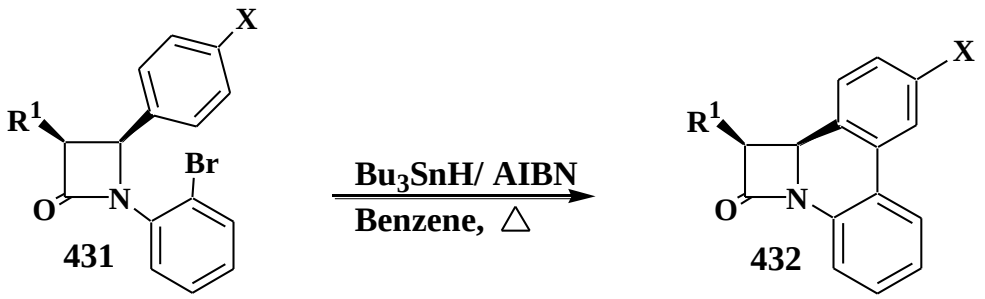
It was reported that treating the β-lactam **423** with Bu_3SnH in the presence of AIBN in boiling benzene afforded both the carbapenems **424** and cabacephems **425** together with the 1,4-dihydroquinoline **426** in 30, 8 and 20% yields, respectively, Scheme 93. The formation of **428** and **429** is represented in Scheme 94. On the other hand the β-lactam **432** under the same conditions resulted in the synthesis of the tetracyclic β-lactams **433**, Scheme 95.[94]


Ox*
H
H
Me
Br
N
O
423
Bu3SnH/AIBN
Benzene, reflux
424
(24%)
425
(8%)
426
(20%)
Ox*:
O
N
Ph

Scheme 93

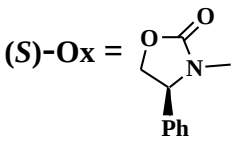

Ox*
H
H
Me
Br
N
O
423
Bu3Sn•
427
5-endo-trig
6-exo-trig
428
429
430
H•
424
425
Ox*:
O
N
Ph

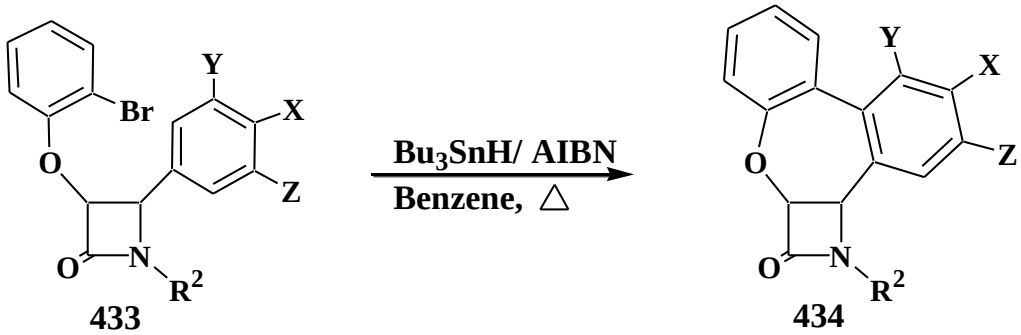
Scheme 94



R^1 = BnO, PhO, AcO and (*S*)-Ox

X = H, MeO





R^2 = *p*-$MeOC_6H_4$, $PhCH_2$

X = H, MeO

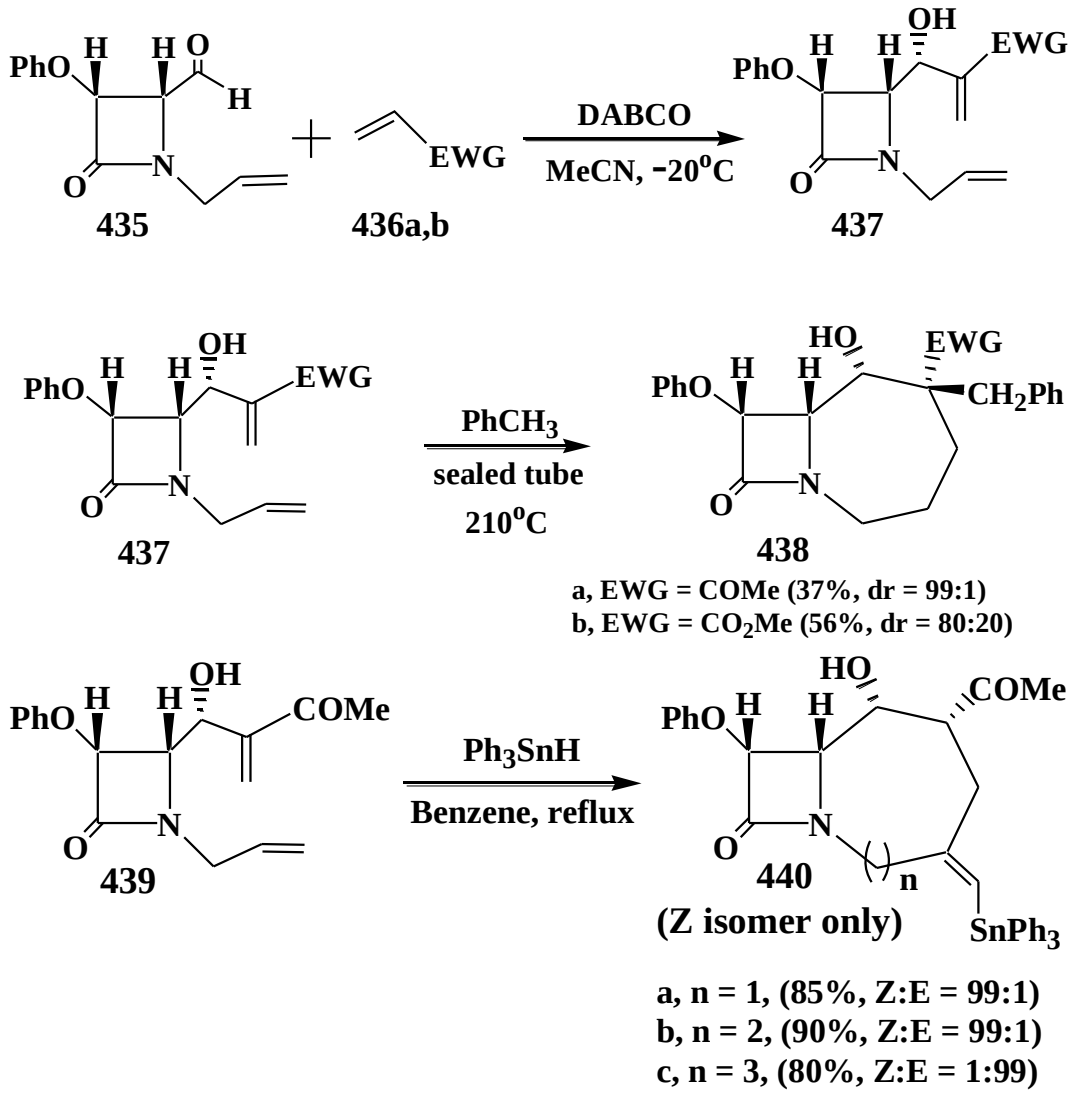
Y = H, MeO

Z = H, MeO

Scheme 95

Alcaide *et al.*[95,96] reported that heating the Baylis-Hillman adducts **437a** in toluene at 210^{o}C in sealed tube afforded single isomers of the bicyclic β-lactams **438a** in modest yield (37%) with excellent diastereoselectivity (99:1), however compound **437b** under similar conditions gave a slightly better yield (56%) of **438b** with poorer diastereoselectivity (80:20). However,

heating a mixture of **439a-c**, Ph_3SnH and AlBN in boiling benzene gave compounds **440a-c** in excellent yields (80-90%) with high stereoselectivity ranging from 99:1 to 1:99, Scheme 96.

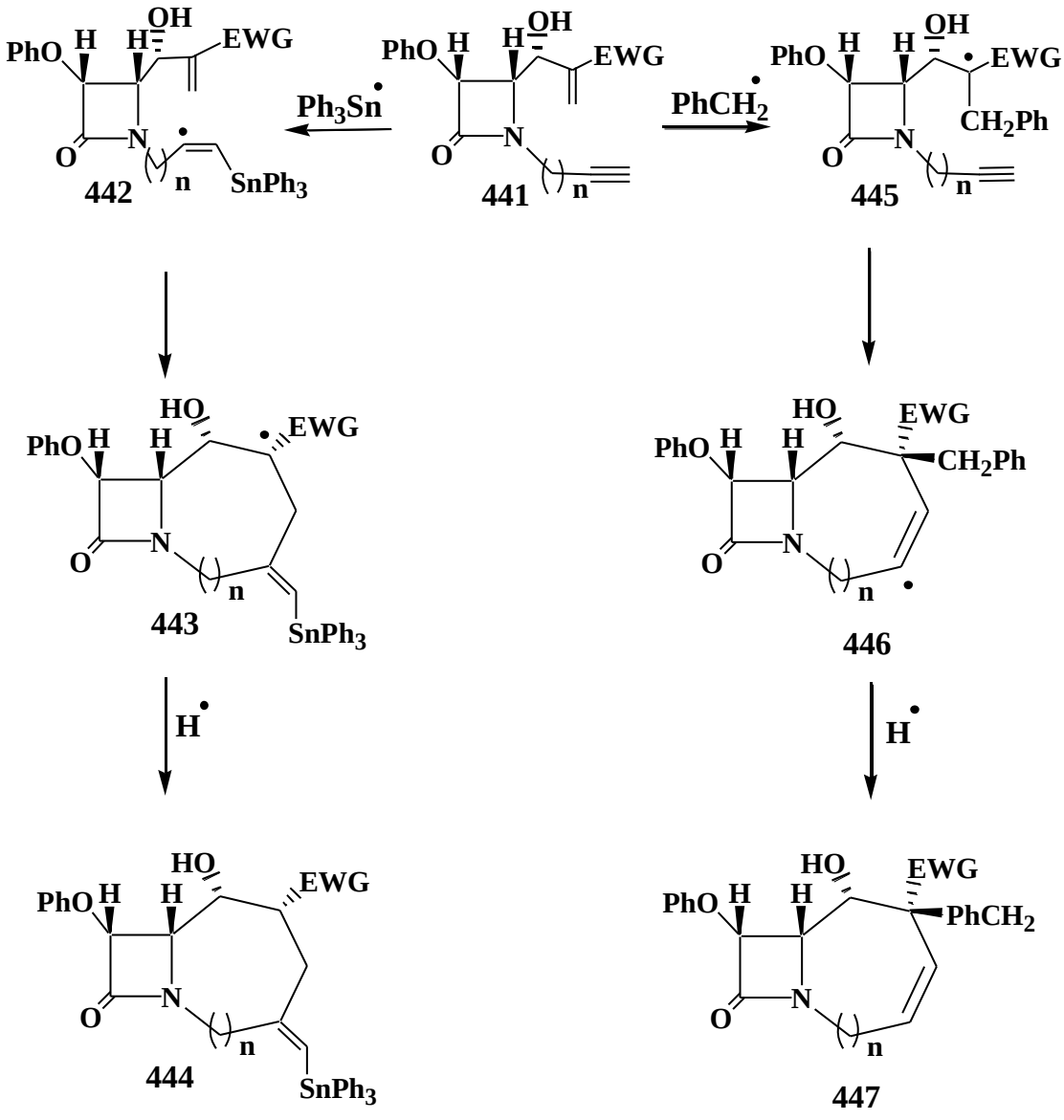


Scheme 96

Subjection of any organic molecules to a high enough temperature in the gas phase results in the formation of free radicals. When the molecule contains bonds with dissociation energies from 20-40 kcal/mol, cleavage can be caused in the liquid phase.[97] The dissociation energy of the $PhCH_2$-H bond is

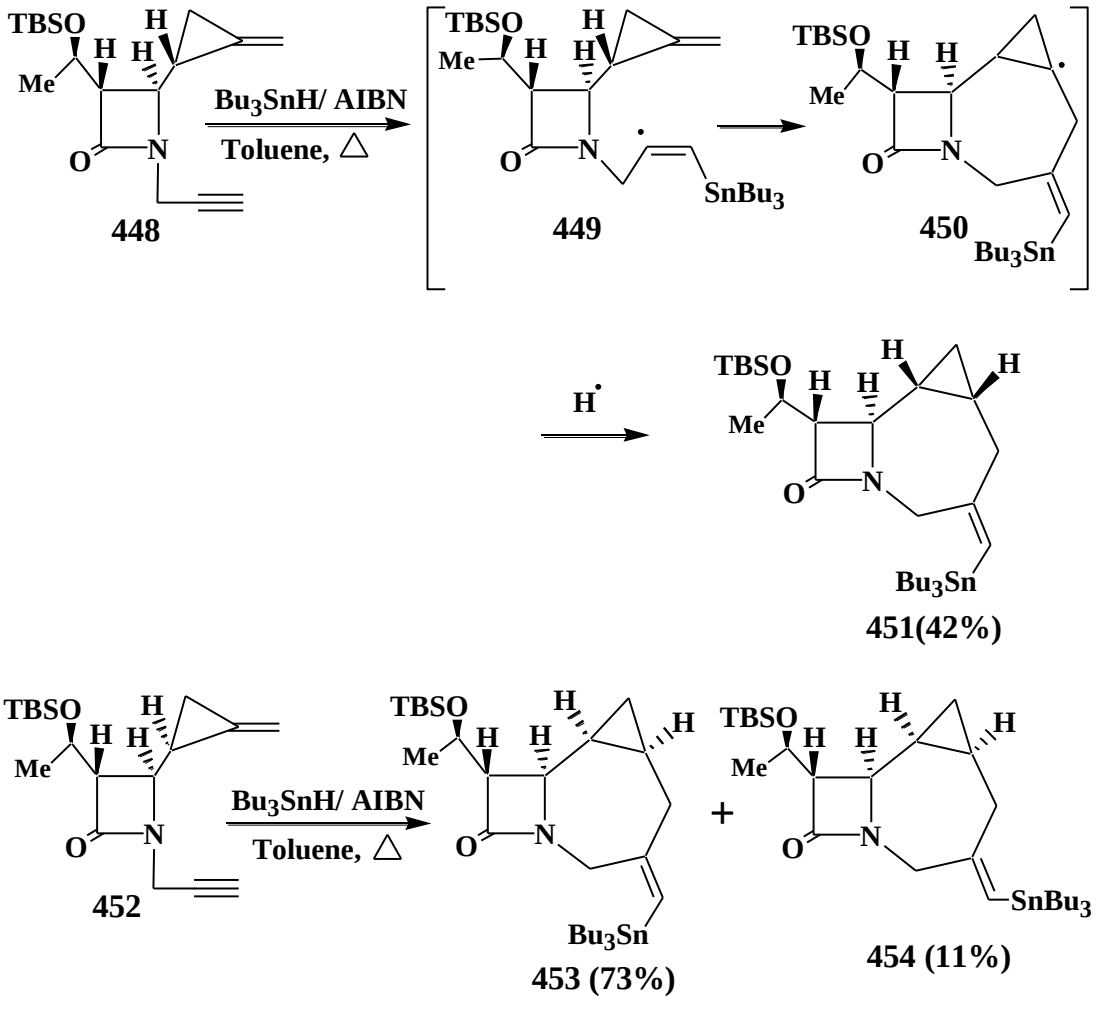
88 kcal/mol, so the generation of the benzylic radical ($PhCH^{\bullet}_2$) is an unexpected process via heating at usual temperatures.

The adducts **441** underwent a tandem Michael addition/endo cyclization or a tandem radical addition/Michael addition depending on the electronic nature of the radical promoter, the more nucleophilic benzylic radicals ($PhCH^{\bullet}_2$) attack the electron poor alkenes, whereas the more electrophilic radicals $Ph_3Sn^{\bullet}$ react readily with the electron rich alkynes, Scheme 97.[95,96]



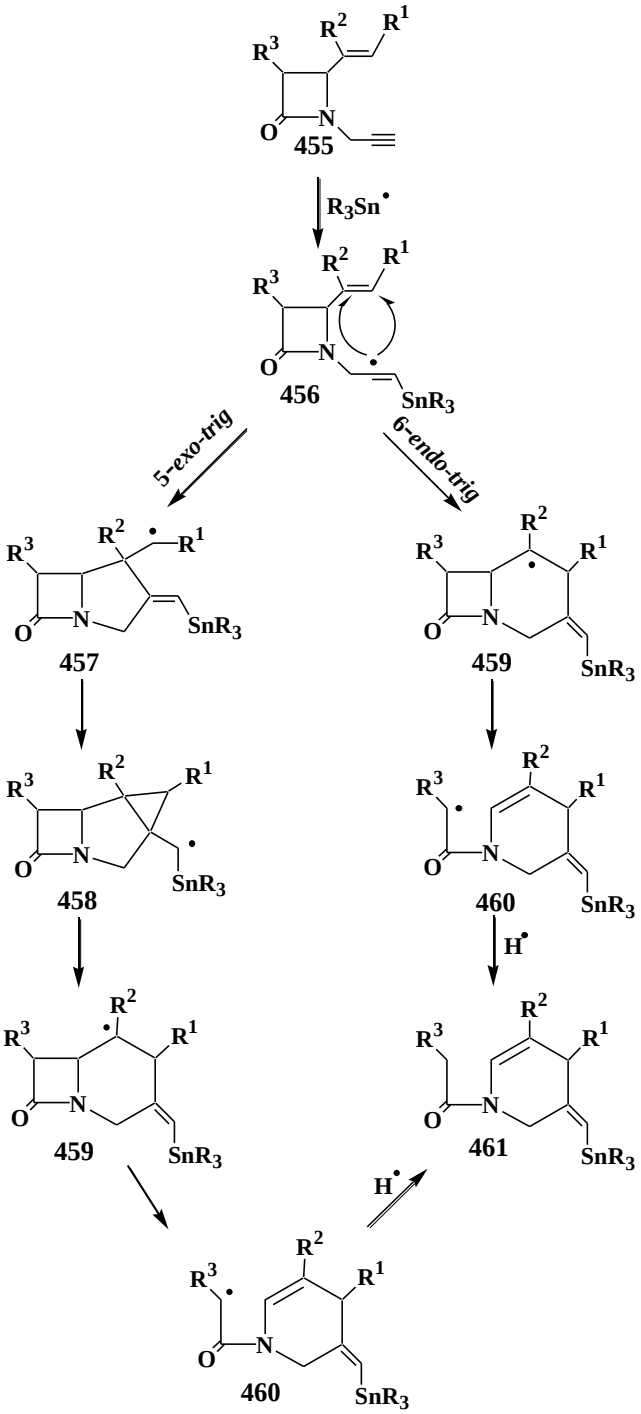
Scheme 97

It was reported that slow addition of Bu_3SnH/AIBN to a refluxing toluene solution of the enyne-2-azetidinone **448** gave the tricyclic vinylstaunane **451** in a 42% yield as a single stereoisomer, *via* a 7-*endo*-*trig* radical cyclization. However, the diastereomer **452** under similar conditions afforded the *Z* and *E* isomers **453** and **454** in 73 and 11% yields, respectively, Scheme 98.[98]



Scheme 98

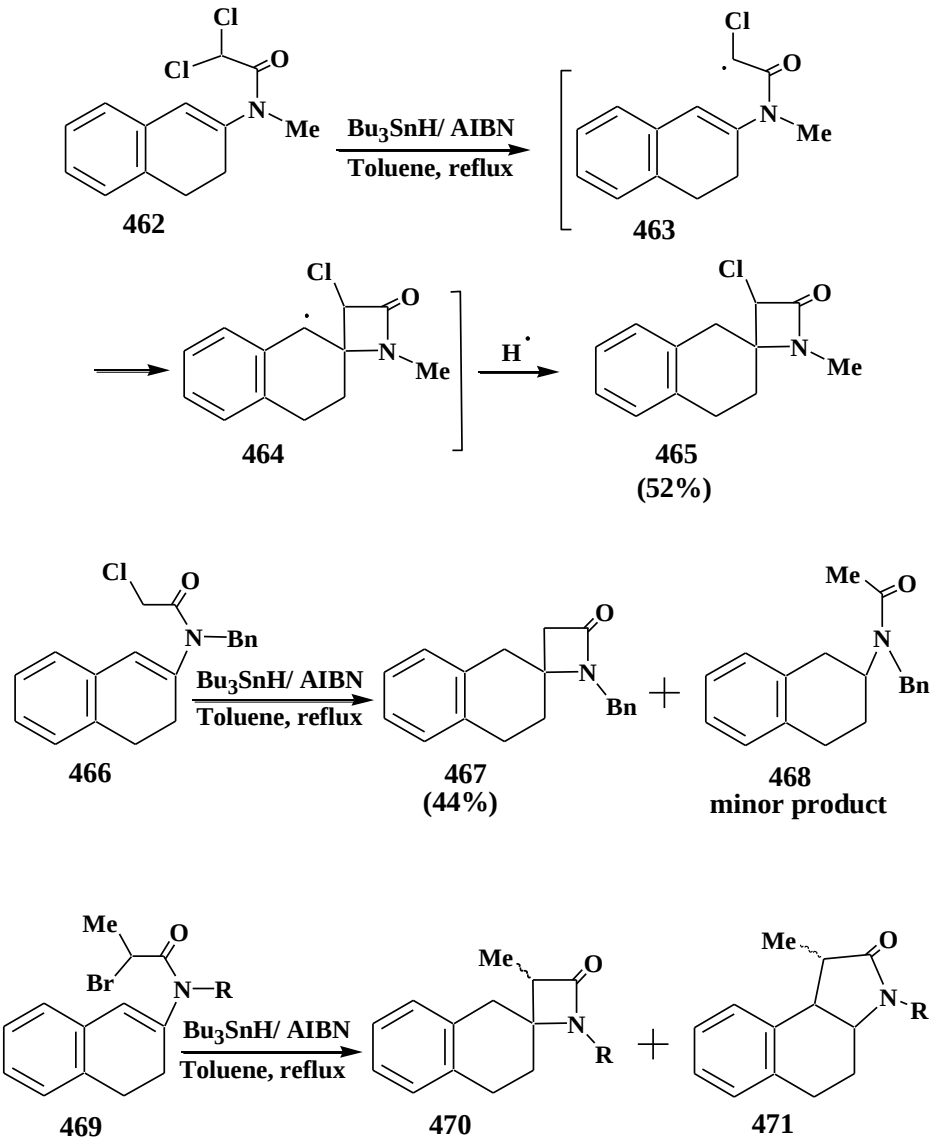
It was reported that the β-lactam derivative **455** under the Bu_3SnH/AIBN conditions gave the tetrahydropyridines **463**, Scheme 99. For activated double bonds a 5-*exo*-*trig* ring closure occurs yielding the expected carbapenams. Substitution at the acceptor carbon atom, or non-activated double bonds, essentially results in inhibition of of the cyclization process, even for activated double bonds. In these cases, reduction products are obtained as the main components of the reaction mixtures. However, the homolytic cleavage of C3-C4 bond is closely related to the cyclobutylcarbenyl radical cleavage. In the β-lactam case, the driving force for the cleavage may be the stability of the captodative radical, (R^3 = PhO) together with the strain in the β-Lactam ring.[93]



Scheme 99

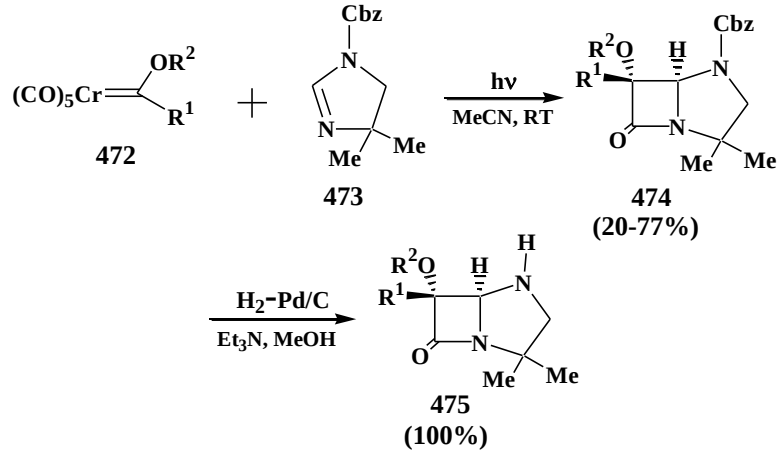
Ikeda and Ishibashi[99] have reported that a 4-*exo*-*trig* radical cyclization reaction of the 2,2-dichloroactamide **462** with Bu_3SnH (3.6 equiv) and catalytic amount of azoisobutyronitrile (AIBN) in boiling toluene afforded 52% yield of the spiro β-lactam **465**. However, 2-chloro-N-benzyl analogous **466** (bulky substituent on the nitrogen) afforded the spiro β-lactams **467** in

44% along with the reduction product **468**. On the other hand, the bromoacetamides **469** under similar conditions afforded the β-lactam **470** *via* a 4-*exo-trig* radical and γ-lacams **471** through 5-*endo-trig* and radical cyclization. Both the N-substituents and the reaction temperature affected the regioselectivity of the radical cyclization processes (*4-exo-trig* and 5-*endo-trig*), Scheme 100.



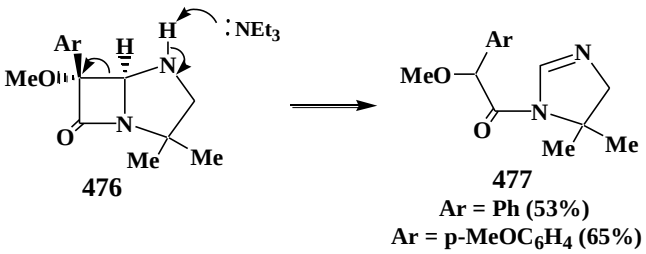
Scheme 100

Hegedus *et al.*[100] reported that the photolysis of chromium alkoxycarbene complexes **472** with imidazoline **473** under argon produced azapenams **474** in 20-77% yields. Hydrogenolytic removal of the N-protecting group in the presence of triethylamine gave quantitative yield of the azapenams **475** when R is an alkyl group, Scheme 101. However, when R is aryl group the deprotection of the aryl azapenams resulted in substantial amounts of ring cleaved products **477**, Scheme 102.



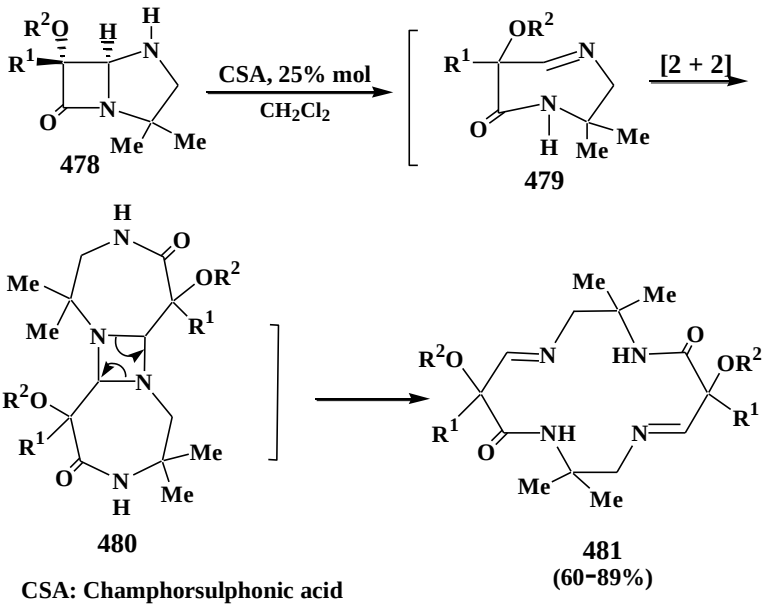
R^1 = $nC_{16}H_{33}$, cC_3H_5, iPr, cC_6H_{11}, tBu
R^2 = Et, Me

Scheme 101



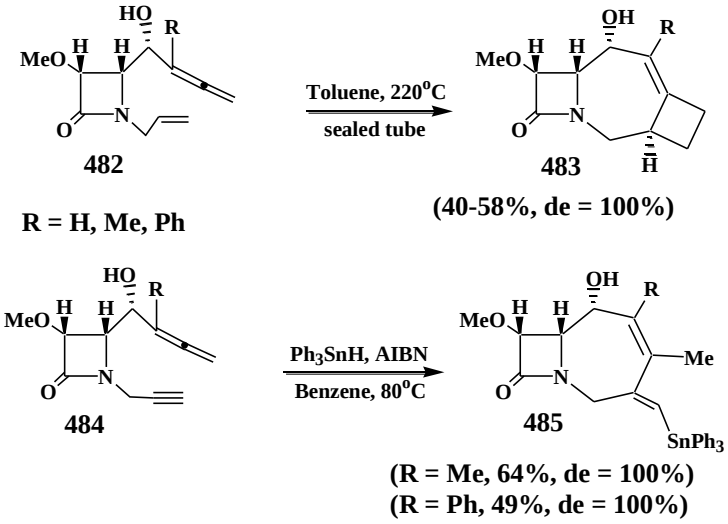
Scheme 102

They also showed that the azapenams **478** under the acid catalysis afforded the tetraaza macrocycles **481** in good yields (60-89%), Scheme 103.[101]



Scheme 103

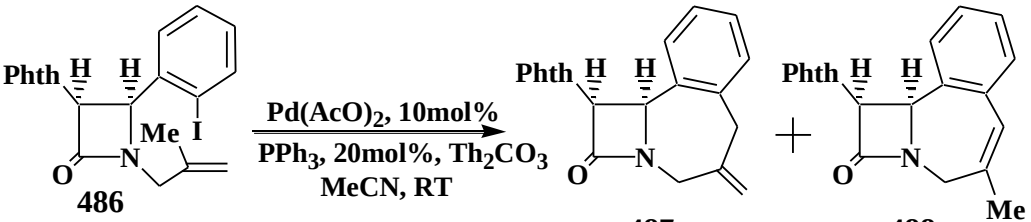
Alcaide[102] recently reported that both racemic and optically pure 2-azetidinone-tehered enallenyl alcohols **481** smothly underwent [2+2] cycloaddition reaction in regio- and stereospecific manner to give moderate yields of the tricyclic β-lactams **482** (40-58%). On the other hand, the allenes **483** by the effect of Ph_3SnH/AIBN system gave the corresponding bicyclic derivatives **484** in moderate to acceptable yields (49-64%) as single isomers, Scheme 104.



Scheme 104

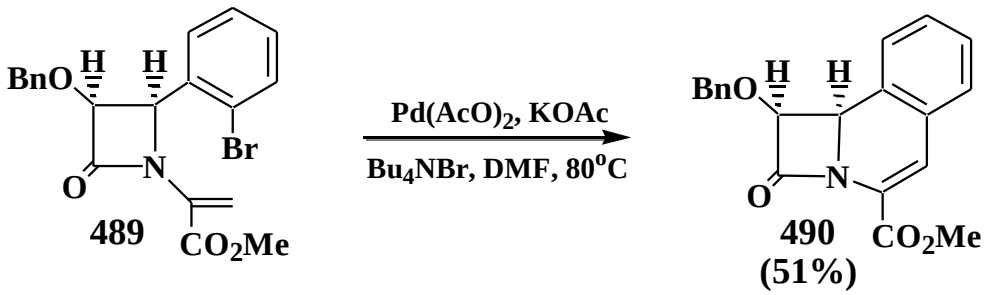
4.5 The Metal Promoted Reactions:

Grigg and co-workers,[103] described the synthesis of bricyclic β-lactams via palladium-catalyzed cyclizatoin indoaryl β-lactam using acatalyst system comprising 10 mol% $Pd(AcO)_2$, 20% mol% PPh_3 and Ti_2CO_3 (2 mol). A 7-*endo-trig* cyclization afforded a 8:1 mixture of double bonds isomers **487** and **488** in 62% total yield, Scheme 105.



Scheme 105

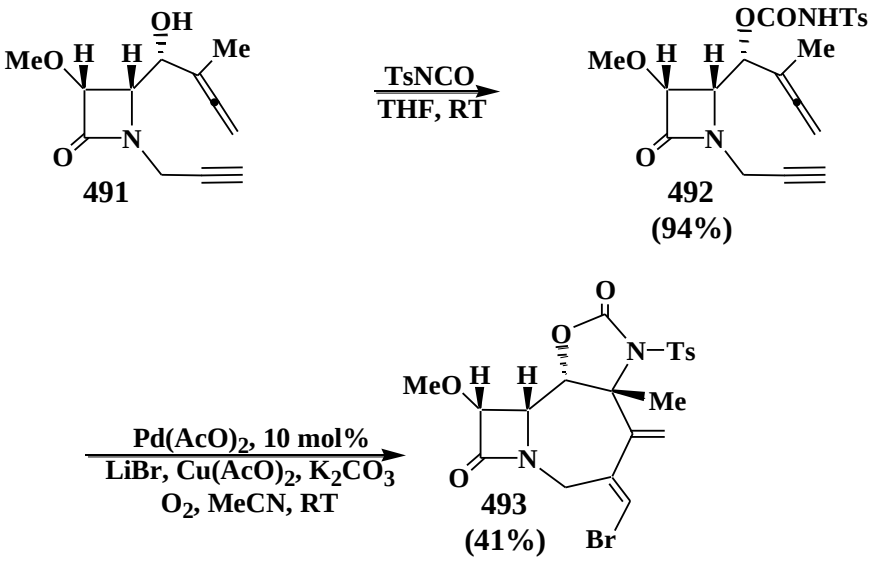
Alcaide *et al.*[104] reported a related example for the synthesis of tricyclic β-latcams ivolving Heck reaction by converting the β-lactam **489** into the corresponding benzocarbacephem **490** in 50% yield, Scheme 106.



Scheme 106

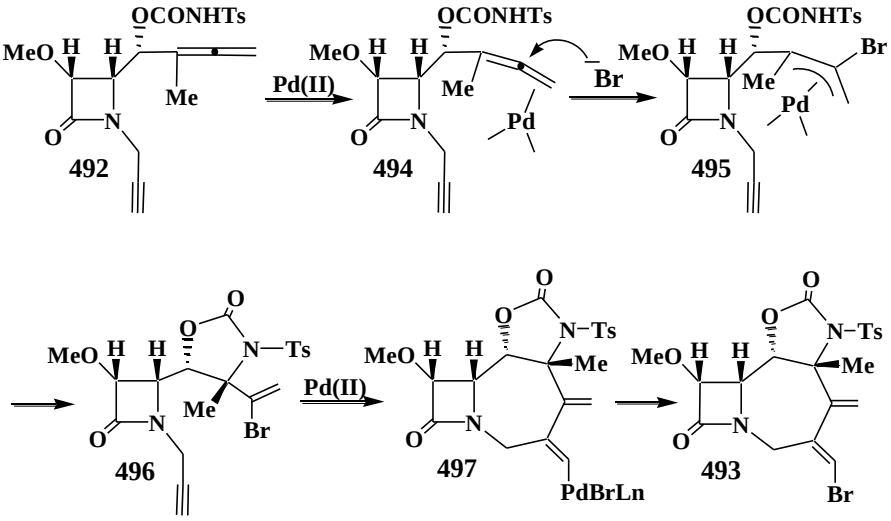
Alcaide *et al.*[105] have utilised successfully the palladium tandem reactions in constructing some interesting tricyclic β-lactams, which resemble a real challenge for synthetic chemists by the conventional synthetic methods. Thus, the β-lactam allenynol derivatives **491** reacted with tosyl isocyanate in THF at room temperature to give 94% yield of the carbamate derivative **492**, the obtained carbmate **492** was treated at room temperature with $Pd(AcO)_2$ 10 mol%, (5 equiv.) of LiBr,

$Cu(AcO)_2$ (2 equiv.) and K_2CO_3 (1.2 equiv.) in acetonitrile under an atmospheric pressure of oxygen to form the tricyclic β-lactam **493** in 41% yield, Scheme107.



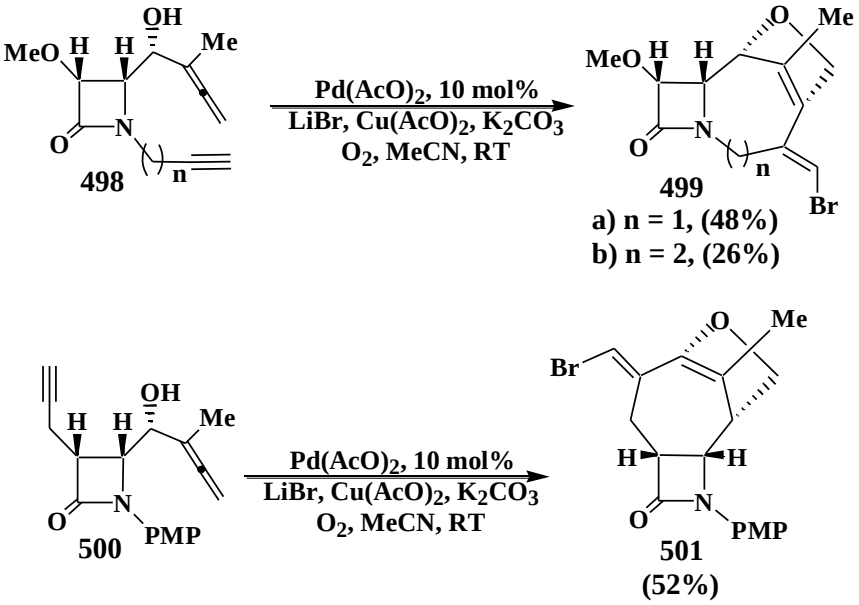
Scheme 107

The proposed mechanism is represented in Scheme 108 in which the nucleophilic attack on the allen-palladium complex **494** would afford the (π-allyl)palladium intermediate **495**, then an intramolecular amidation reaction would give **496** which undergoes Heck-type-coupling reaction to form **493** *via* the alkenyl paladium intermediate **497**.



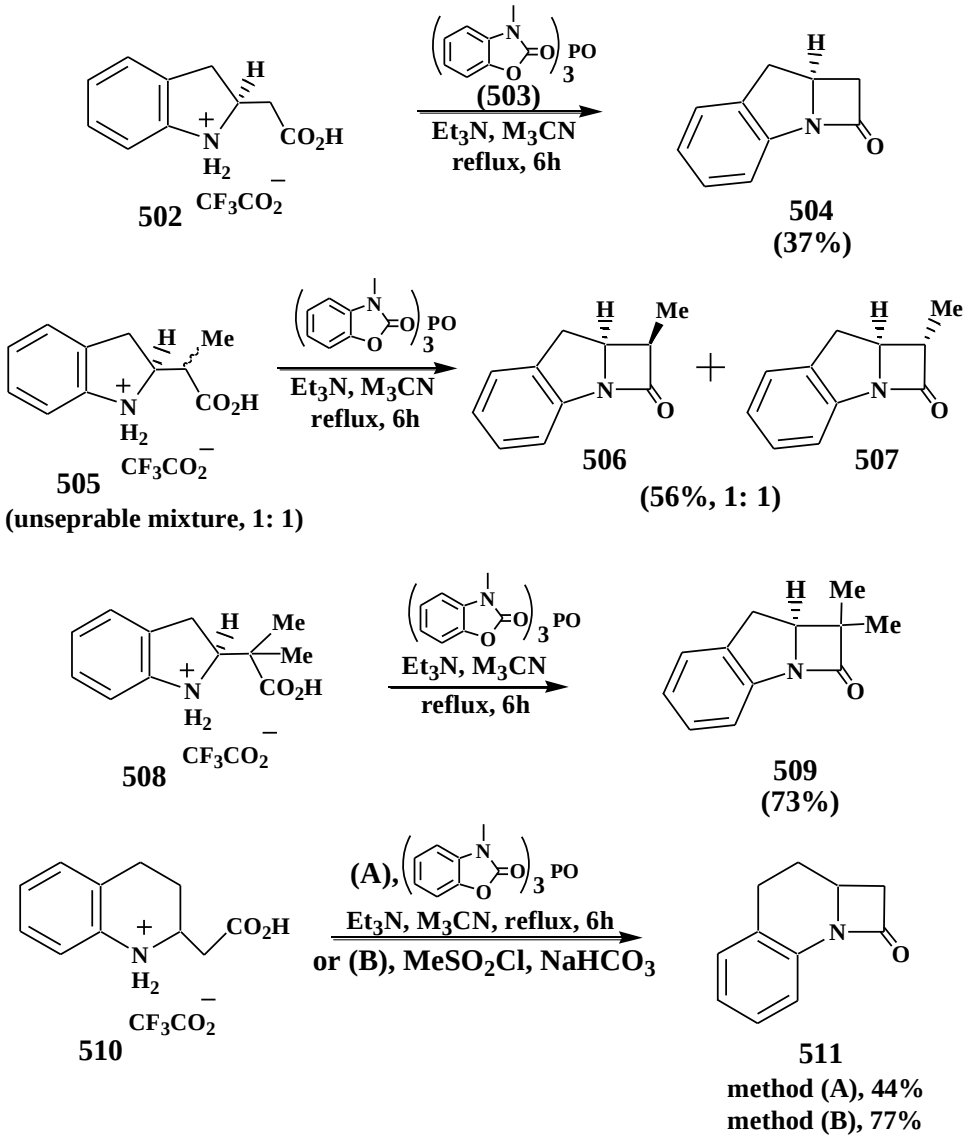
Scheme 108

However the same authors reported that the allenynols **498a,b** and **500** under the same cascade conditions, analogously underwent cyclization to afford the bridged medium-sized ring tricyclic β-lactams **499a,b** and **501** in moderat yields 48 , 26 and 52%, respectively, Scheme 109.



Scheme 109

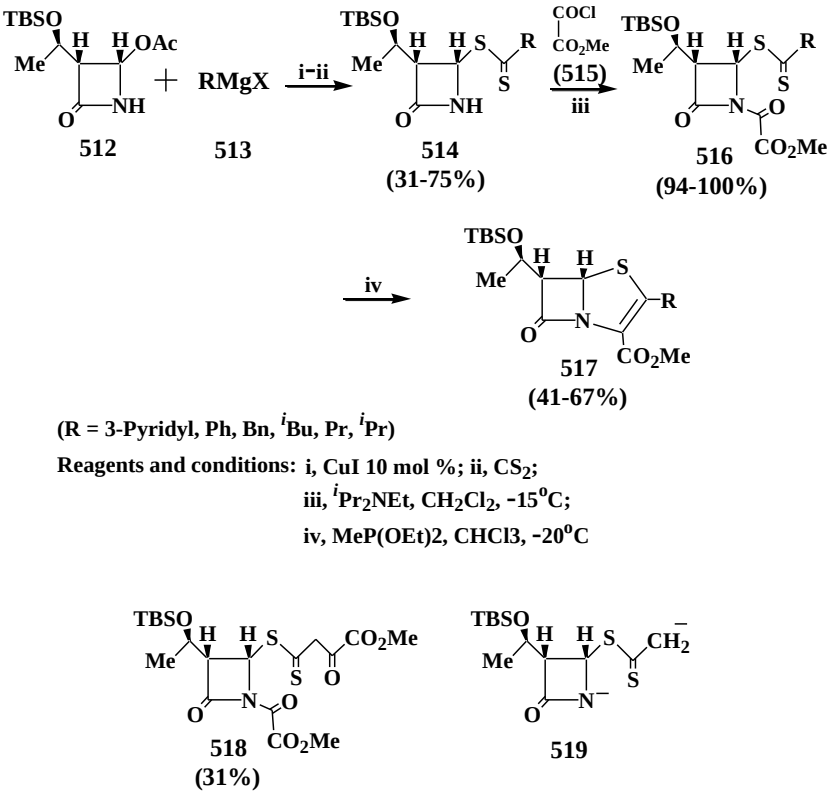
The salts of the 2,3-dihydro-IH-indole-2-acetic acid **502**, **505** and **508** reacted with the phosphine oxides **503** in the presence of Et_3N to give the corresponding benzocarbapenams **504,** a mixture of **506** and **507** and **509**, respectively in modest to acceptable yields (37-73%), Scheme 110. However, the Thorpe-Ingold effect was very well pronounced as the yield goes higher with the more substitution on the acetic residue. The tetrahdroquinoline **510** reacted analogously to give the corresponding benzocarbacephams **511** in a 44% yield (method A) and a 77% yield (method B).[106,107]



Scheme 110

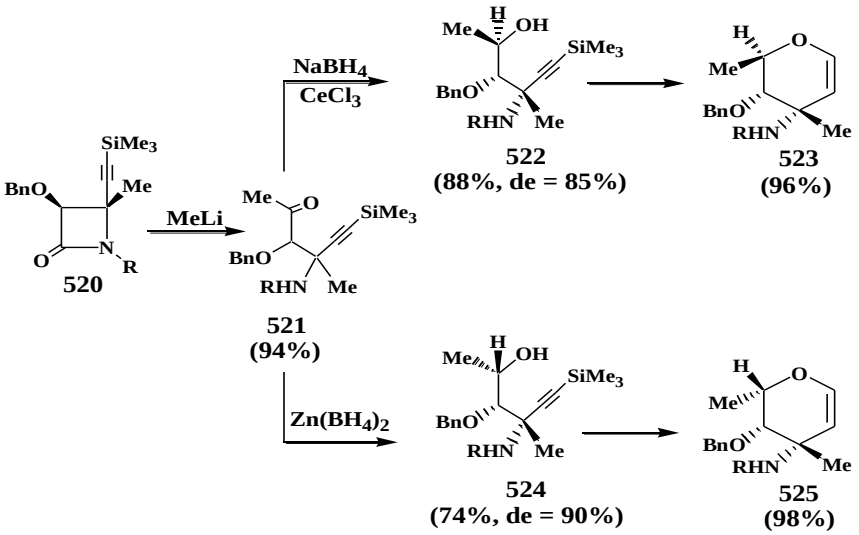
It was reported that the reaction of the allylmagnesium bromide **513** with CuI (10 mol%) and carbondisulphide at –20°c according to Westmijze's procedure, followed by addition of the 4-acetoxy β-lactam **512** gave the dithioesters **514** in modest to acceptable yields (31-75%). These dithioesters on acylation with methyl oxalyl chloride **515** in CH_2Cl_2 at –15°C in the presence of diisopropylethylamine afforded the corresponding oxalimides **516** in almost quantitative yields (94-100%), which underwent Wittig-cycliztion to give the 2-substituted penems **517** in moderate yields (41-67%), Scheme 111. However, when R = Me, the β-lactam derivative **518** was obtained in 31%, it is

presumably formed via the dianion **519** (obtained under the reaction condition).[108]



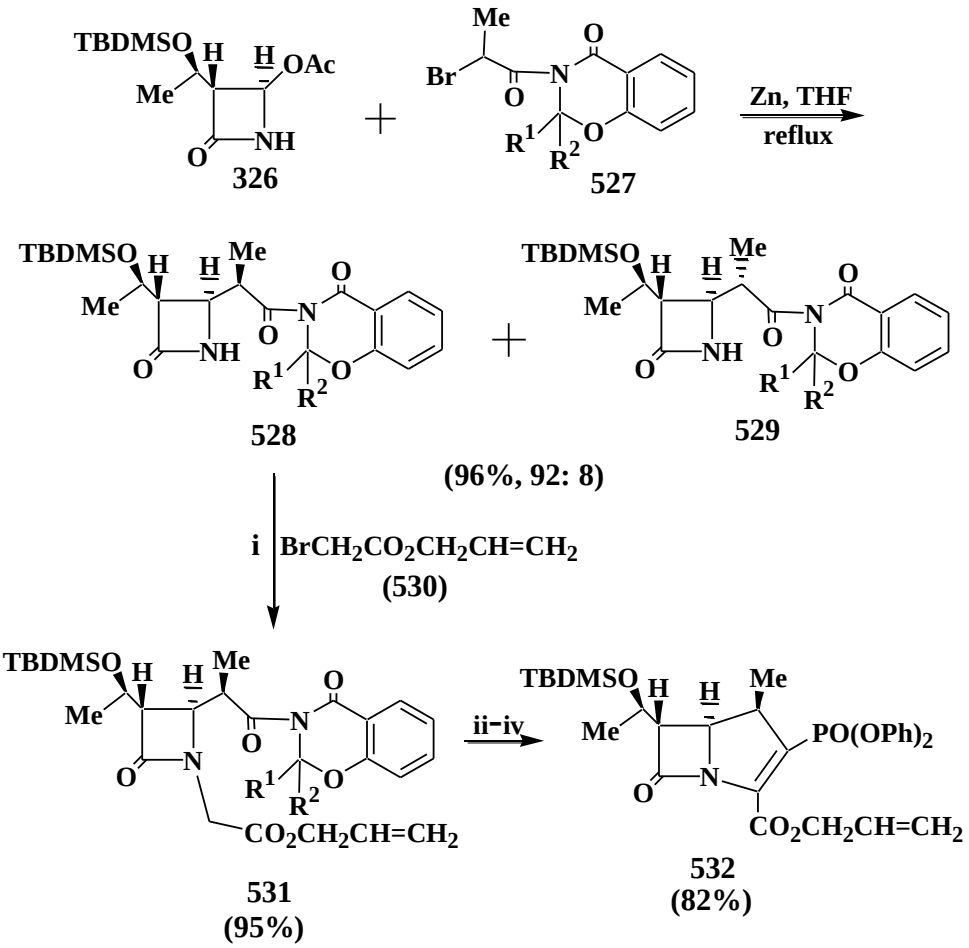
Scheme 111

Cutchins and McDonald[109] have reported that the reaction of the β-lactams **520** with MeLi gave excellent yields (94%) of the corresponding ketones **521** through N1-C2 bond cleavage, the obtained ketones **521** on the reaction with $NaBH_4/CeCl_3$ or $Zn(BH_4)_2$ afforded the alkynals **522** and **524** in excellent yields with high diastereoselectivity (88%, 85% de) and (74%, 90 de), respectively. The alkynals **522** and **524** underwent a tungsten-catalysed cycloisomerization to give almost quantitative yields 96% and 98%, of the vancosamine and saccharosamine glycols **523** and **525**, respectively, Scheme 112.



Scheme 112

Kondo *et al.*[110] reported that the reaction of the 4-acetoxyazetidienone **526** with 3-(2-bromopropionyl)1,3-benzoxazinone **527** and 3 equivalents of Zn dust in boiling tetrahydrofuran resulted in the 4-substituted-β-lactam **528** and **529** in a total yield 96% with high diastereoselectivity (92:8). The derivative **528** was reacted with allyl bromoactate and sodium bis(trimethylsilylamide) in tetrahydrofuran at –50 to –40^{o}C to afford the N-alkylated-β-lactam **531** in a 95% yield, which was easily cyclized by the effect of bis(trimethylsilylamide) and trimethylsilyl chloride in tetrahydrofuran at –35 to –25^{o}C and then the mixture was treated with diphenyl phosphochloridate at 0^{o}C to give **532** in 82% yield, Scheme 113.

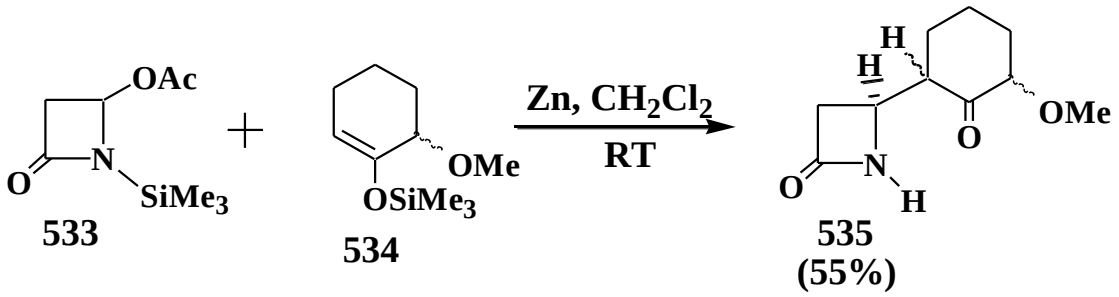


$R^1 = R^2 = -(CH_2)_5-$

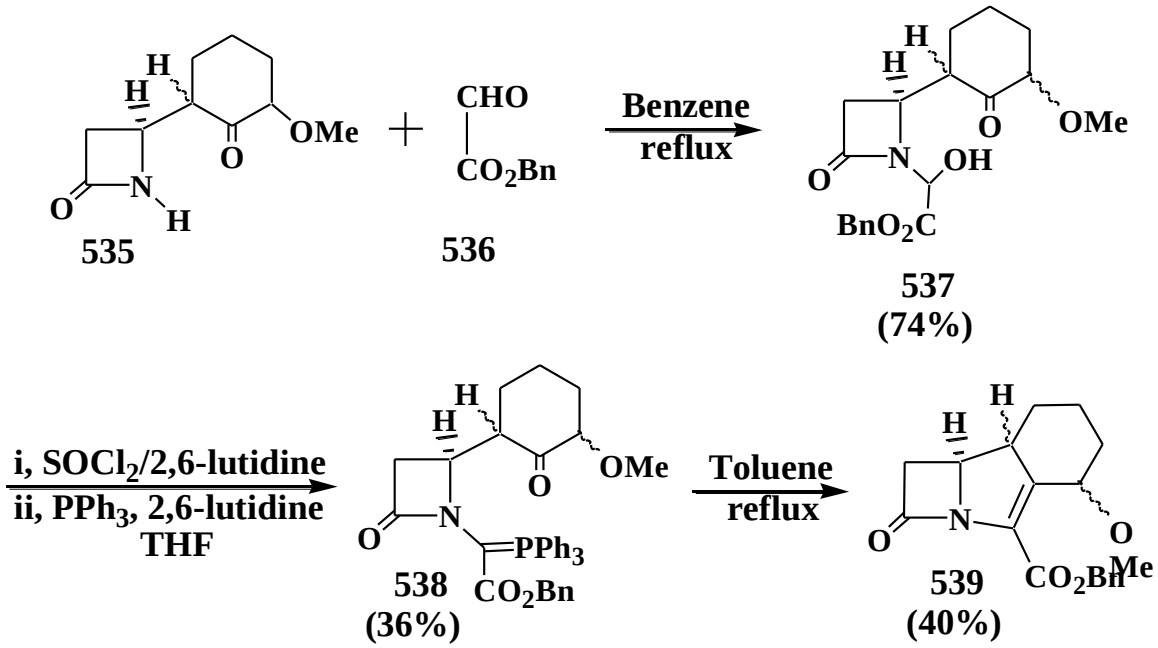
Reagents and coditions: i = $NaN(SiMe_3)_2$, THF, -50 to -40°C;
ii = $NaN(SiMe_3)_2$, THF, -35 to -25°C; iii = Me_3SiCl, THF, -35 to -25°C
iv = $ClPO(OPh)_2$, 0°C

Scheme 113

Donati,[111] showed that N-silylated azetidin-2-one **533** coupled with slightly excess (1.2 equivalent) of the silyl enol ether **534** in the presence of $ZnCl_2$ in CH_2Cl_2 at room temperature to give an isomeric mixture of the β-lactams **535** in a total 55% yield, Scheme 114. Compounds **535** were heated with benzylglyoxalate to afford the alcohols **537** which on treatment with $SOCl_2$/2,6-lutidine and then PPh_3/2,6-lutidine gave the phosphorane which under Wittig intramolecular cyclization resulted in the trinem ring system, Scheme 115.

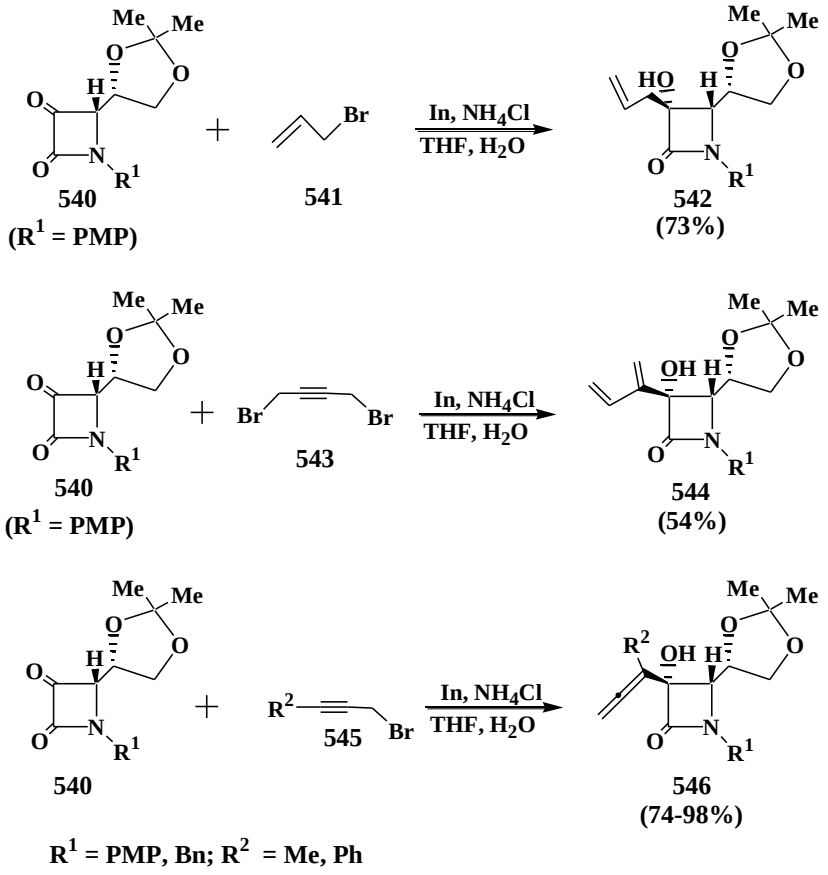


Scheme 114



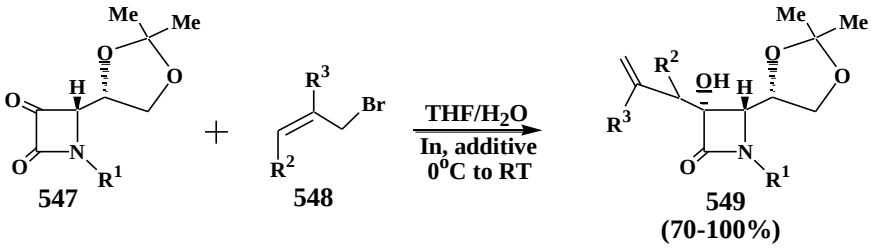
Scheme 115

Alcaide *et al.*[112] reported that the homochiral azetidin-2,3-one **540**
(R = PMP: *p*-$MeOC_6H_4$) reacted with the allybromide **541** and 1,4-dibromobut-2-yn **543** in the presence of indium metal in aqueous THF to afford the Barbier-type product **542** and the diene derivative **544** in 73 and 54% yields, respectively. However, treating a mixture of **540** (R = PMP, Bn) and 1-bromobytyns **545** with indium metal in aqueous THF afforded the allenyl derivatives **546** in good to excellent yields (74-98%), Scheme 116.



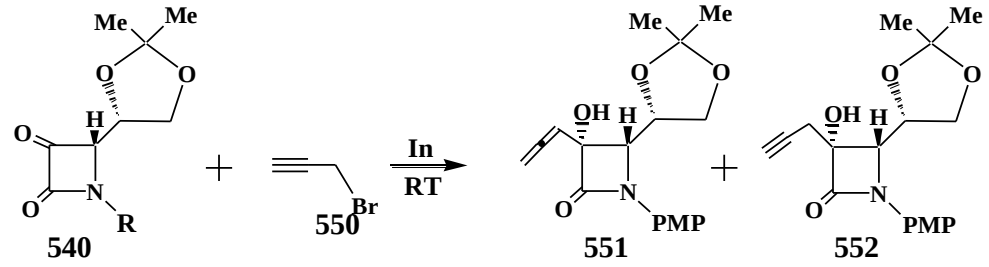
Scheme 116

Alcaide[113] reported that the homochiral azetidin-2,3-diones **547** reacted smoothly with the allyl bromides **548** under indium-mediated Barbier-type reaction condition to give the 3-allylated-3-hydroxy-β-lactam **549** in good to excellent yields (70-100%) in a total diastereoselectivity, Scheme 117. On the other hand, the azetidin-2,3-dione **540** (R = PMP) reacted with propargyl bromide **550** under the same conditions to give 50% yield of 2 regioisomers **551** and **552** in 58:42 ratio. However, changing the solvent system (using a saturated aqueous solution of NH_4Cl in THF instead of aqueous THF) has reversed the regioselectivety (29:71) with slightly higher yield (67%), Scheme 118.



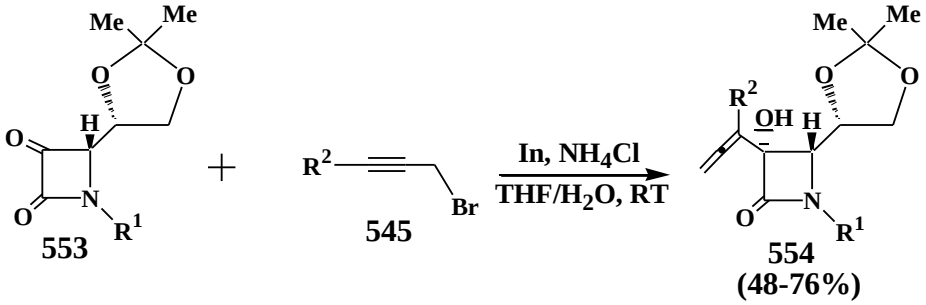
R^1 = *p*-$MeOC_6H_4$, 2-propenyl, 3-butenyl,2-propynyl, 3-butynyl;
R^2 = H, Me; R^3 = H, CO_2H; additive = NH_4Cl, $InCl_3$, $HfCl_4$

Scheme 117



Scheme 118

In contrast, azetidin-2,3-ones **553** reacted regioselectivety with propargyl bromides **545** bearing aliphatic or aromatic substituent at the tirminal position 2 to give the α-allenic alcohols **554** as the only products in yields ranging from 48 to 76%, Scheme 119.

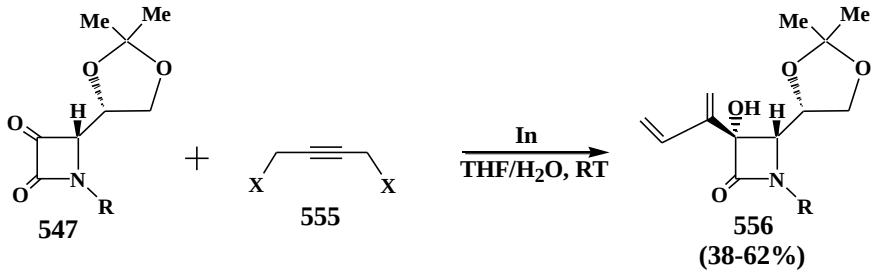


R^1 = *p*-$MeOC_6H_4$, 2-propenyl, 2-propynyl; R^2 = Me, Ph

Scheme 119

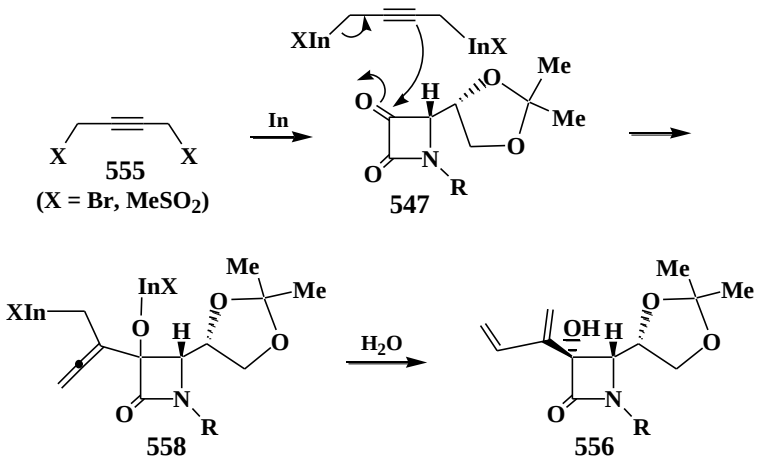
Finally, the enantiopure azetidin-2,3-ones **547** reacted regio- and stereoselectively with 1,4-bis(methanesulfonyl)-2-butyne **555** or under the indium-mediated Barbier-type reaction in aqueous THF (1:1) at room temperature to give the 3-(1,3-

butadiene-2-yl)-3-hydroxy-β-lactams **556** in moderate yields (38-62%), Scheme 120. The mechanism of such 1,3-butadiene-2-ylation process is shown in Scheme 121.



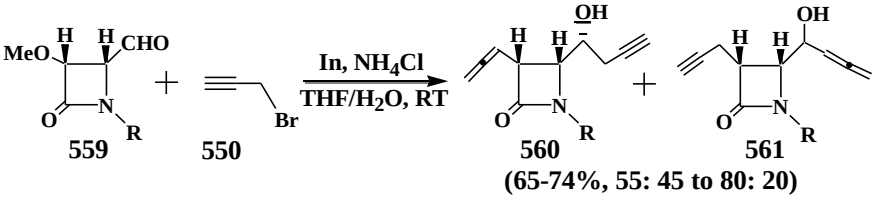
R = *p*-MeOC$_6$H$_4$, 2-Propenyl, 3-Butenyl, 2-Propynyl, 3-Butynyl
X = MeSO$_2$

Scheme 120



Scheme 121

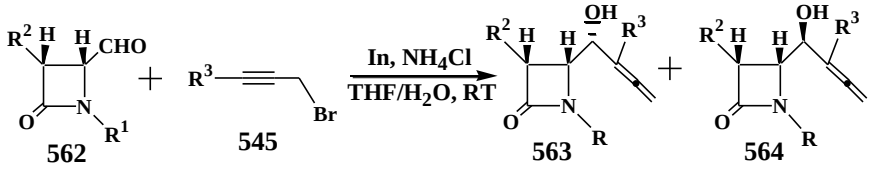
The enantiopure 4-formyl β-lactams 559 as the carbonyl component in the indium-mediated Babier-type reaction reacted with the propargyl bromide itself to give, yet again, regioisomeric mixtures of **560** and **561** in 65-74% yields with a poor to acceptable regioselectivety ranges form 55:45 to 80: 20, Scheme 122.



R = *p*-MeOC$_6$H$_4$, 2-propenyl, 2-propynyl, 4-pentynyl

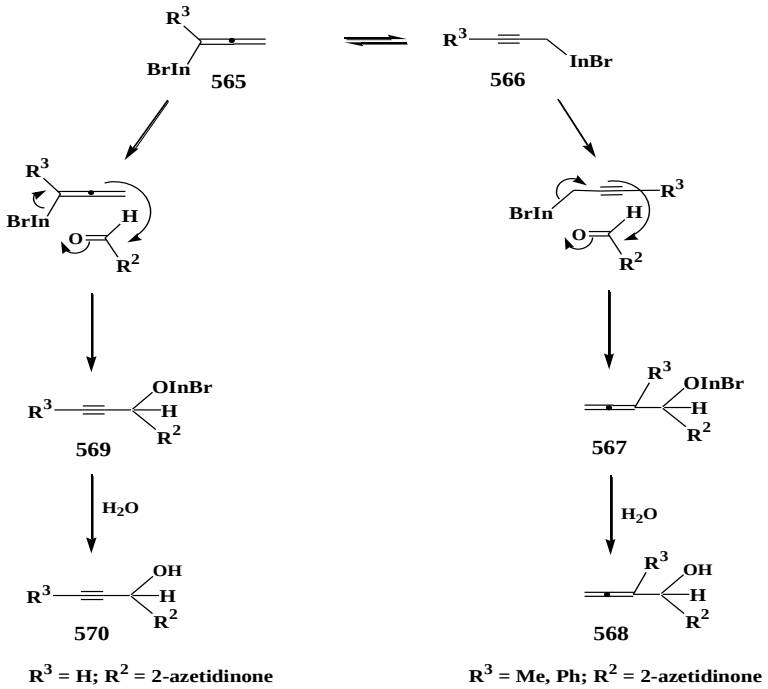
Scheme 122

However, the 3-substituted propargyl bromides **545** under similar conditions gave only the regioisomers **563** and **569** in resonable to excellent yields (60-92%) with high distereoselectivity, Scheme 123. Explanation of the regioselectivity in the indium-mediated propargylation-allenylation reaction for the 4-formyl β-lactams is given in Scheme 124, it seems that the isomerization of the propargylindium to the allenylindium is sterically dependent on the terminal substituent R^1.



R^1 = *p*-$MeOC_6H_4$, 2-Propenyl, 3-Butenyl, 2-Propynyl, 3-Butynyl;
R^2 = MeO, PhO, 2-Propenyloxy, Ethenyl, 2-Propenyl, 2-Propynyl;
R^3 = Me, Ph

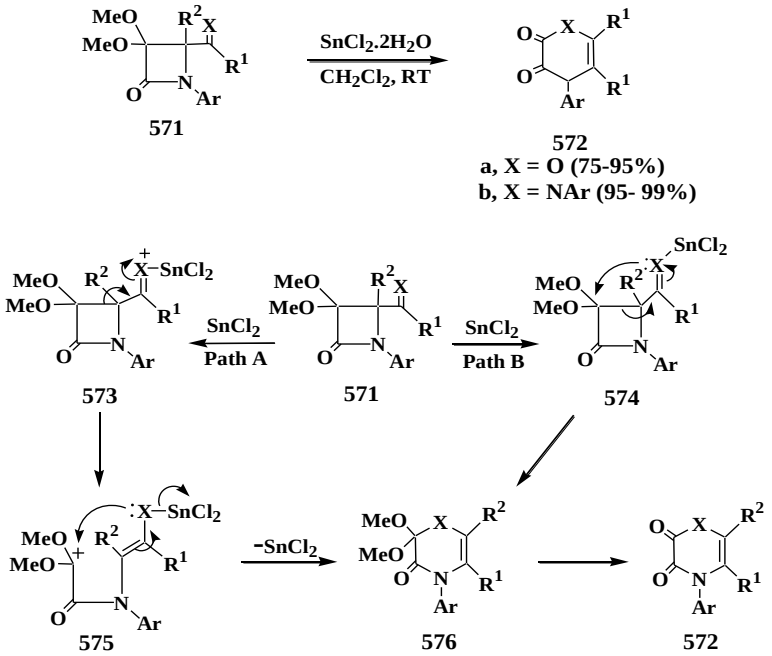
Scheme 123



Scheme 124

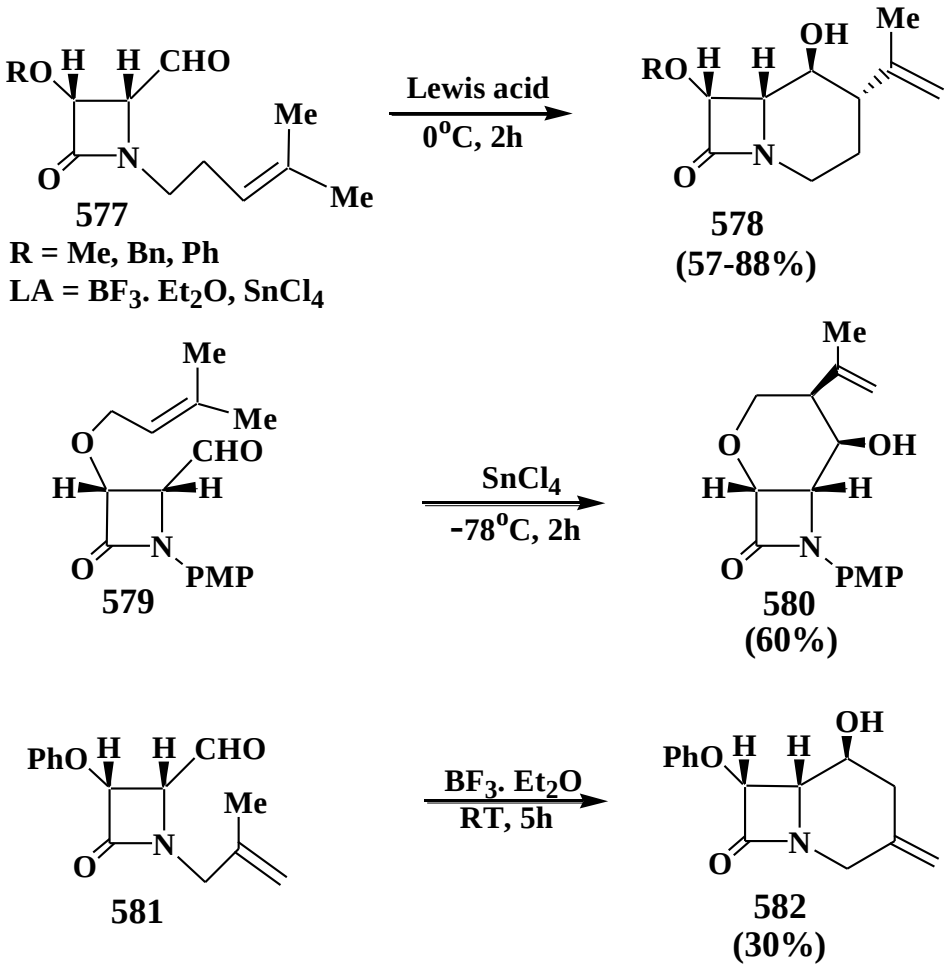
Alcaide[114] has reported that the tendency C3-C4 bond breakage–carbocationic rearrangement of the 4-acyl- or 4-imino-3,3-dimethoxy-2-azetidine-2-one **571** promoted by tin(II)

chloride gave excellent to quantitative yields of the corresponding dihydro-1,4-oxazine or pyrazine-2,3-diones **572a,b**, respectively, Scheme 125. They suggested that either path **(A)** or path **(B)** would lead to the intermediate **576** which finally gives the 2,3-diones.



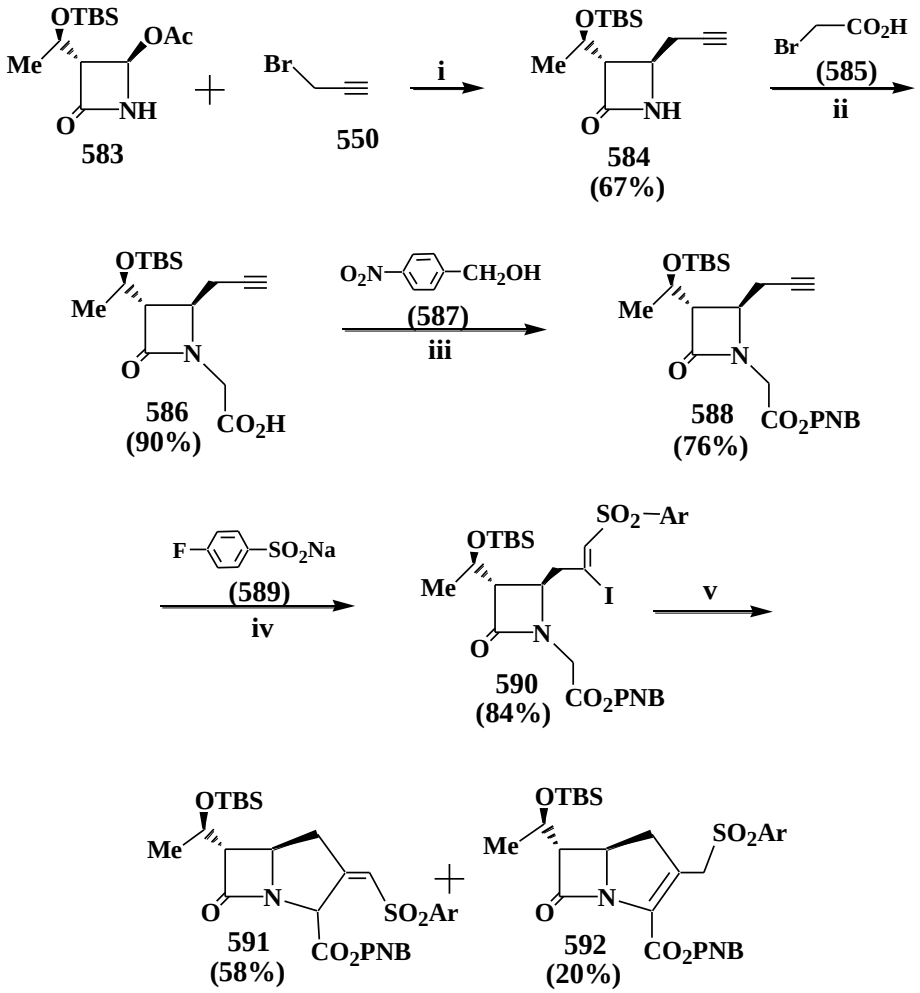
Scheme 125

On the other hand, the 2-azetidinone-tethered alkenyl aldehydes **577**, **579** and **581** under Lewis acid catalysis underwent carbonyl-ene reaction to give the bicyclic β-lactams **578**, **580** and **582**, respectively in low to high yields (30-88%) with high stereoselectivity, Scheme 126.[72]



Scheme 126

It was reported that the Zn/Et_2AlCl-promoted Reformatsky-like reaction of the *trans*-4-acetoxy-β-lactam **583** with propargyl bromide **550** afforded the β-lactam **584** in 67% yield, which reacted with bromoacetic acid **585** and the resulting acid dervative **586** was converted to the *p*-nitrobenzyl ester **588** under standard conditions. chemo- and regioselective, which on iodo-sulphonylation afforded the iodovinyl sulphone **590** in 84% yield. A basic addition-elimination ring closure of **590** afforded a mixture of the exocyclic-double bonded compound **591** and the endocyclic-double bonded product **592** in 58 and 20% yields, respectively, Scheme 127.[115]



TBS = Bu_3Si, Ar = *p*-FC_6H_4, PNB = *p*-$NO_2C_6H_4CH_2$

Reagents and conditions:

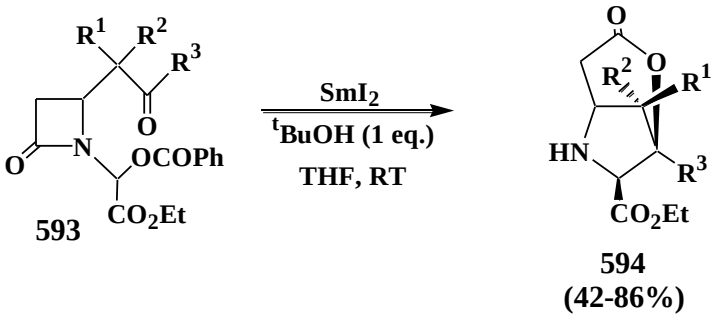
i) Zn/Et_2AlCl, THF, 0^oC, 2h; ii) NaH, THF/DMF, 0^oC to RT, 15h;

iii) THF, DCC, DMAP, RT, 15h; iv) I_2, AcOEt/H_2O, hν 0.5h;

v) 1-1.5 eq $LiN(SiMe_3)_2$, THF, -78^oC, 45min

Scheme 127

It was reported that the β-lactams **593** underwent reductive cyclization to give the functionalised proline derivative **594** in low to high yields (42-86%), Scheme 128.[116]



593 **594**
(42-86%)

Scheme 128

5. Selected Readings:

(I) For books see for example:

a- "*The Organic Chemistry of β-Lactams"*, G.I. Georg, *Ed. VCH Publishers:* New York, **1993**.

b- "*Asymmetric Syntheses by Means of the β-Lactam Synthon Method, Advances in Asymmetric Synthesis"*, I.Ogima, *JAI Press Inc*. **1995**, *vol 1*, pp. 95-146.

c- "*Understanding Antibacterial Action and Resistance"*, A.D. Russell and I. Chopra, *Ellis Horwood Limited*, New York, **1990**.

d- "*Introduction to Organic & Biochemistry"*, Third Edition **1998**, F.A. Bettelheim and J. March, *Harcourt Brace College Publishers*, Fort Worth, Chapter *12*, pp. 375-388.

e- Wilson and Gisfold, in "*Text Book of Organic medicinal and Pharmaceutical Chemistry",* Ninth Edition **1991**, Ed. J.N. Delgado and W.A. Remers, J.B. Lippincott Company, Philadelphia, *Chapter 7*, pp. 227-271.

f- "*Antibiotics: Penicillins*, in *Medicinal Chemistry"*, Second Edition 2000, International Publishers, New Delhi, Chapter *21*, pp. 454-465.

(II) For reviews see for example:

a- I. Ojima. *Acc. Chem. Res.* **1995**, *28*, 383.

b- I. Ojima and F. Delaloge, *Chem. Soc. Rev.* **1997**, *26*, 377.

c- M. Gomez-Gallego, M.J. Mancheno and M.A. Sierra, *Tetrahedron* **2000**, *56*, 5743.

d- B. Alcaide and P. Almendros, *Current Org. Chem*. **2002**, *6*, 245. *C.A.: 137*, 278986e**, 2002.**

e- B. Alcaide and P. Almendros, *Current Med. Chem*. **2004**, *11*, 1917.

f- B. Alcaide and P. Almendros, *Chem. Soc. Rev.* **2001**, *30*, 226. *C.A.: 135*, 288596a**, 2001.**

g- C. Palomo, J.M. Aizpurua, I. Ganoba and M. Oiarbide, *Eur. J. Org. Chem.* **1999**, 3223.

h- A. Kamal and P.B. Sattur, *Hetereocycles* **1987**, *26*, 1051.

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1- B.D. Wladkowski, S.A. Chenoweth, J.N. Sanders, M. Krauss and W.J. Stevens, *J. Am. Chem. Soc.* **1997**, *119*, 6423. *C.A.: 127*, 343273e**, 1997.**

2- A.H. Berko, *Tetrahedron*, **1996**, *52* , 331.

3- G.S. Georg, *Recent Advances in the chemistry and Biology of β-Lactam and β-Lactam Antibiotics. Bioorg. Med. chem. Letters (Symposium in print No 8)*, **1993**, *3*, 2159.

4- G. Bonfiglio and D.M. Livermore, *J. Antimicrob. Chemother*. **1994**, *33*, 465.

5- R. Kluger, *Synlett* **2000**, *12*, 1708.

6- Y. Song, R. Kluger, *Bioorg. and Med. Chem. Lett*. **1994**, *4*, 1225.

7- G. Martelli, G. Spunta, M. Pannunzio, *Tetrahedron Lett.*, **1998**, *39*, 6257. *C.A.: 129*, 260247q**, 1998.**

8- M. Pannunzio, S. Bacchi, E. Campana, L. Fiume and P. Vicennati, *Tetrahedron Lett.*, **1999**, *40*, 2495.

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المقرر:

Metabolism

الكلية : العلوم

الفرقة : الرابعة كيمياء خاص

اعداد:

Ass. Prof. Dr. Hussien Temerik

Content

Metabolism

The biochemical reactions that happen inside the body.

Metabolism divided into to process

1- Catabolim

2- Anabolism

Catabolism

The biochemical processes of metabolism by which large molecules are breakdown to small molecules or oxidizing to producing energy.

Anabolism

The biochemical processes of metabolism by which molecules are synthesized or built up.

Note

Catabolism and anabolism are separated process, catabolism process occur to produce energy, but anabolism need energy.

INTRODUCTION

The carbohydrates are source of energy for animal nutrition. The

monosaccharides and oligosaccharides are efficiently metabolized by simple stomach animals. On the other hand, ruminants contain microbes, which secrete enzymes capable of degrading cellulose. Glycogen is a polysaccharide found in animal and fungal cells. Glycogen is a storage form of carbohydrate and is readily utilized when there is deficiency of energy.

Digestion

The dietary carbohydrates that are most important nutritionally are polysaccharides and disaccharides, since free monosaccharides are not commonly present in the diet in significant quantities. There is, however, some free glucose and fructose in honey, in certain fruits, and in the carbohydrates that are added to processed foods. The cellular use of carbohydrates depends on their absorption from the Gastrointestinal (GI) tract into the blood stream, a process normally restricted to monosaccharides. Therefore, poly saccharides and disaccharides must be hydrolyzed to their constituent monosaccharide units. The hydrolytic enzymes involved are collectively called glycosidases, or, alternatively, carbohydrases.

1 Disaccharides

Virtually no digestion of disaccharides or small oligo saccharides occurs in the mouth or stomach. In the human it takes place entirely in the upper small intestine. Unlike amylase, disaccharidase activity is associated with the mucosal cells of the microvilli or brush border rather than with the intestinal lumen. Among the types of enzyme activities located in the mucosal cells are lactase, invertase (sucrase), and isomaltase. The latter is not a disaccharidase but instead hydrolyses branched dextrins, as mentioned in an earlier section. Lactase catalyses the cleavage of lactose to equimolar amounts of galactose and glucose, and sucrase hydrolyses sucrose to yield glucose and one fructose residue; sucrase also hydrolyses maltose and maltotriose to free glucose.

2 Polysaccharides

The glycosidase, a-amylase, assumes a particularly important role in polysaccharide digestion because of its specific hydrolytic action on the α-1,4 bonds of the starches. Resistant to the action of this enzyme, therefore, are the β-1,4 bonds of cellulose and the α -1,6 linkages that form branch points in the starch amylopectin. The a-amylase hydrolyses the unbranched amylose rapidly into units of the disaccharide maltose and into the trisaccharide malltotriose, the latter subsequently undergoing slower hydrolysis to maltose and glucose. The enzyme's hydrolytic action on amylopectin produces, in addition to glucose, maltose, and maltotriose, a mixture of branched oligo saccharides, or dextrins, the smallest of which are tetrasaccharides and pentasaccharides. Together with the complementary activity of another glycosidase, α-dextrinase, which hydrolyses the α-1, 6 bonds at the branches, the dextrins are consequently hydrolysed to free glucose.

Metabolism of carbohydrates

- تحليل الجلوكوز Glycolysis
- دورة كربس Krebs Cycle
- بناء الجلايكوجين Glycogenesis
- إستحداث الجلايكوجين Gluconeogenesis
- تحليل الجلايكوجين Glycogenolysis

Glycolysis

Glycolysis is, by definition, the pathway by which glucose is converted into two units of lactic acid, a triose. The pathway can function anaerobically, and in situations in which oxygen debt is in effect, as in times of strenuous exercise, lactate accumulates in the muscle cells, causing the aches and

pains associated with overexertion. The importance of glycolysis in energy metabolism is that it provides the initial sequence of reactions necessary for glucose to be oxidized completely to CO_2 and H_2O via the citric acid cycle. In cells that lack mitochondria, such as the erythrocyte, the pathway of glycolysis is the sole provider of ATP by substrate level phosphorylation of ADP. The glycolytic enzymes function within the cytoplasmic matrix of the cell, while the enzymes catalyzing the citric acid (Krebs) cycle reactions are located within the mitochondrion (pp. 8, 9). Further metabolism of the products of glycolysis in the Krebs cycle allows complete oxidation of glucose to CO_2 and H_2O, with maximal energy production. Some of the energy liberated is salvaged as ATP, while the remainder maintains body temperature. Many cell types are involved in glycolysis, but most of the energy derived from carbohydrates originates in liver, muscle, and adipose tissue. The pathway of glycolysis, showing the entry of dietary fructose and galactose, the following are comments on selected reactions:

1 .The hexokinase/glucokinase reaction consumes 1mol ATP/mol glucose. Hexokinase (not glucokinase) is negatively regulated by the product of the reaction, glucose 6-phosphate.

2 .Glucose phosphate isomerase catalyses this inter-conversion of isomers.

3 .The phosphofructokinase reaction, an important regulatory site, is modulated negatively by ATP and citrate and positively by AMP.

Another ATP is consumed in the reaction.

3 .The aldolase reaction results in the splitting of a hexose bisphosphate into two triose phosphates.

4 .The isomers glyceraldehyde 3-phosphate and dihydroxyacetone phosphate (DHAP) are interconverted by the enzyme triosephosphate isomerase. In an isolated system the equilibrium favors DHAP formation. However, in the cellular environment it is shifted completely toward the production of glyceraldehyde 3- phosphate, since this metabolite is being continuously removed from the equilibrium by the subsequent reaction catalysed by glyceraldehyde 3-phosphate dehydrogenase.

5 .In this reaction, glyceraldehyde 3-phosphate is oxidised to a carboxylic acid, while inorganic phossphate is incorporated as a high-energy anhydride bond. The enzyme is glyceraldehyde 3-phosphate dehydrogenase, which uses NAD as its hydrogen accepting substrate. Under aerobic conditions, the NADH formed is deoxidized to NAD by O_2 via the electron transport chain in the mitochondria. The reason the O_2 is not necessary to sustain this reaction under anaerobic conditions is that the NAD consumed is restored by a subsequent reaction

6 .This reaction, catalyzed by phosphoglycerate kinase, exemplifies a substrate level phosphorylation of ADP. Do a little extensive reading, for a more detailed review of this mechanism by which ATP can be formed from ADP by the transfer of a phosphate from a high-energy donor molecule.

7 .Phosphoglyceromutase catalysis the transfer of the phosphate group from the carbon-3 to carbon-2 of the glyceric acid.

8 .Dehydration of 2-phosphoglycerate by the enzyme enolase introduces a double bond that imparts high energy to the phosphate bond.

9 .The product of reaction (9), phosphoenolpyruvate (PEP), donates its phosphate group to ADP in a reaction catalysed by pyruvate kinase. This is the second site of substrate level phosphorylation of ADP in the glycolytic pathway.

10 .The lactate dehydrogenase reaction transfers two hydrogen from NADH and H+ to pyruvate, reducing it to lactate. NAD is formed in the reaction and can replace the NAD consumed in reaction (6) under anaerobic conditions. It must be emphasized that this reaction is most active in situations of oxygen debt, as in prolonged muscular activity. Under normal, aerobic conditions, pyruvate enters the mitochondrion for complete oxidation. A third important option available to pyruvate is its conversion to the amino acid alanine through trans-amination with the amino group donor glutamate. This, together with the fact that pyruvate is also the product of the catabolism of various amino acids, makes it an important link between protein and carbohydrate metabolism.

11 .These two reactions provide the means by which dietary fructose enters the glycolytic pathway. Fructose is an important factor in the average American diet, since nearly half of the carbohydrate consumed is sucrose, and high fructose corn sugar is becoming more popular as a food sweetener. Reaction 12 functions in extrahepatic tissues and involves the direct phosphorylation by hexokinase to form fructose 6-phosphate. This is a relatively unimportant reaction. It is slow and occurs only in the presence of high levels of the ketose. Reaction 13 is the major means by which fructose is converted to glycolysis metabolites.

The phosphorylation occurs at carbon-l and is catalysed by

fructokinase, an enzyme found only in hepatocytes. The fructose lphosphate is subsequently split by aldolase, designated aldolase B to distinguish it from the enzyme acting on fructose 1,6-bisphosphate, forming DHAP and glyceraldehyde. The latter can then be phosphorylated by glyceraldehyde kinase (or triokinase) at the expense of a second ATP to produce glyceraldehyde 3-phosphate. Fructose is therefore converted to glycolytic intermediates and as such can follow the pathway to pyruvate formation and Krebs cycle oxidation. Alternatively, they can be used in the liver to produce free glucose by a reversal of the first part of the pathway through the action of gluconeogenic enzymes.

Glucose formation from fructose would be particularly important

if fructose provides the major source of carbohydrate in the diet.

Since the phosphorylation of fructose is essentially the responsibility of the liver, the ingestion of large amounts of the ketose can cause a depletion of hepaatocyte ATP, leading to reduction in the rate of various biosynthetic processes such as protein synthesis.

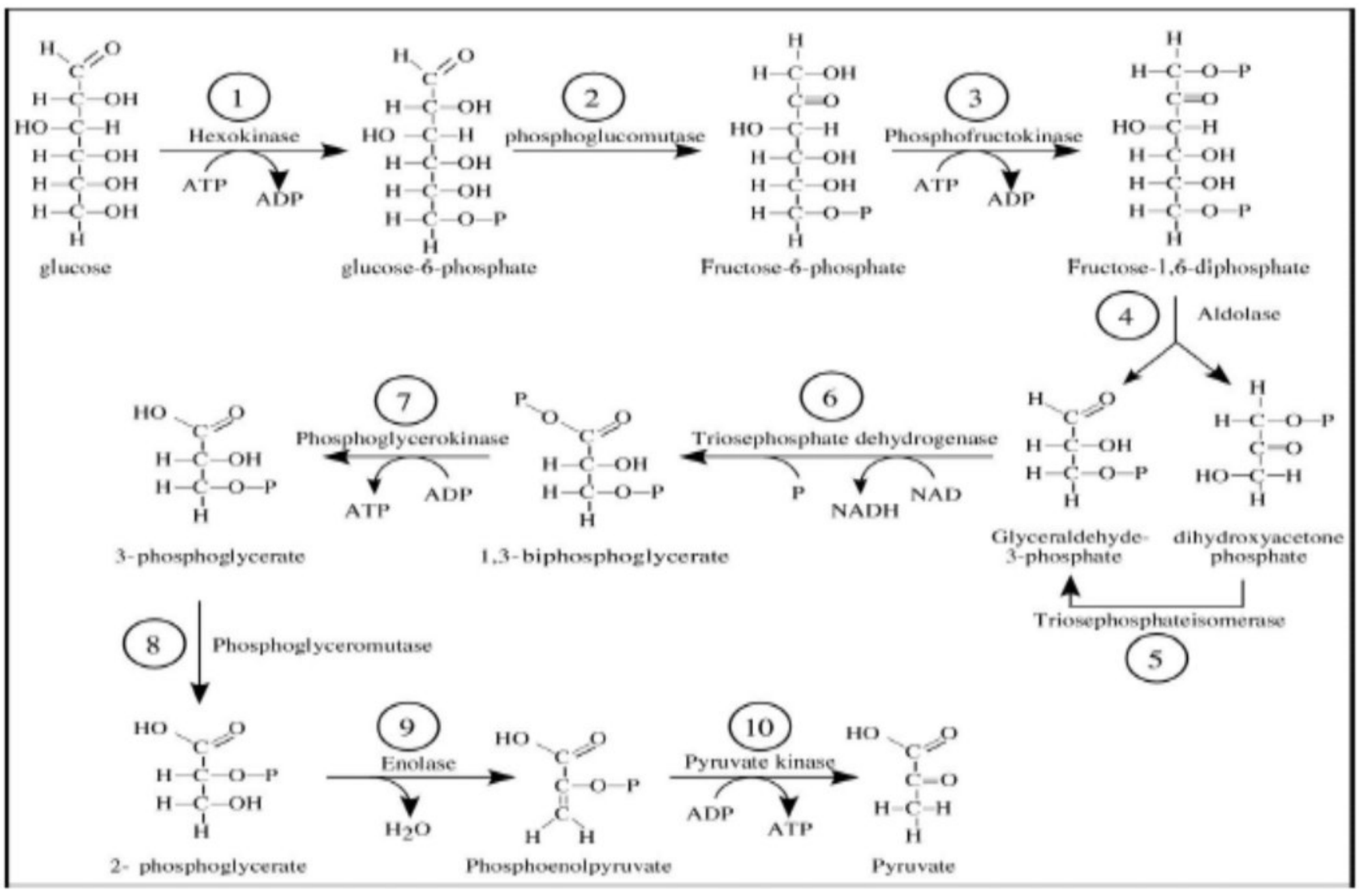
12 Like glucose and fructose, galactose is first phosphorylated. The transfer of the phosphate from ATP is catalysed by galactokinase and the resulting phosphate ester is at carbon-l of the sugar. The major dietary source of galactose is lactose, from which the monosaccharide is hydrolytically released by lactase.

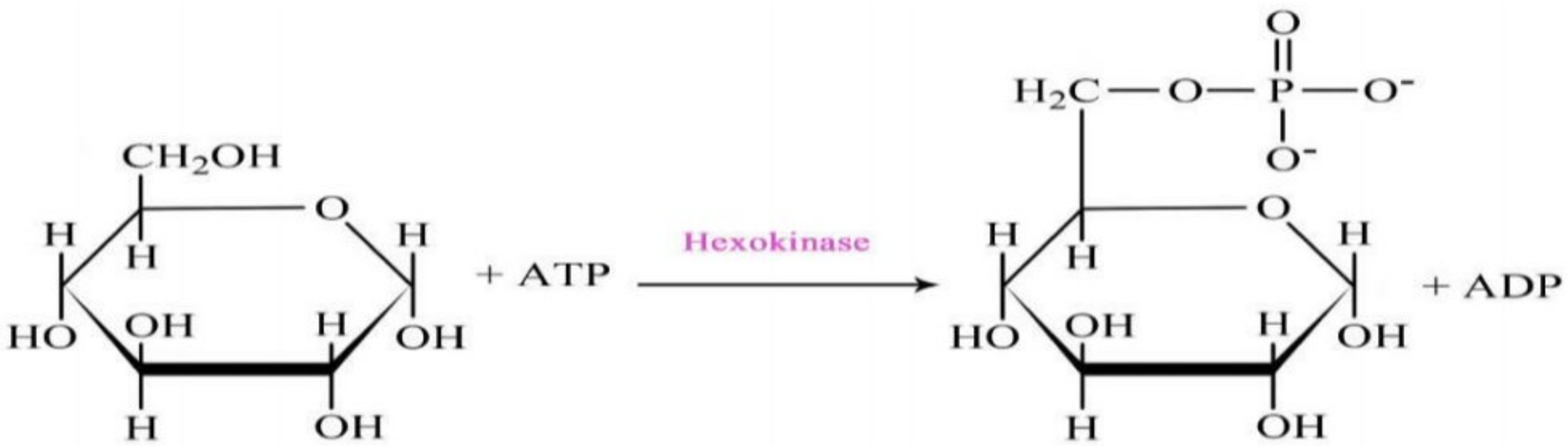
13 .Galactose 1-phosphate can be converted to glucose l phosphate by the enzyme galactose 1-phosphate uridyl transferase. The reaction involves the transfer of a uridyl phosphate residue from UDP glucose to the galactose l-phosphate, yielding glucose 1-phosphate and UDP galactose. As glucose 1-phosphate, galactose can be incorporated into glyycogen through reactions discussed previously. It can enter the

glycolytic pathway following isomerisation to glucose 6-phosphate and be hydrolysed to free glucose in liver cells.

14 .This indicates the entry of glucose 6-phosphate into another pathway called the hexose monophosphate shunt (pentose phosphate pathway), which will be considered next.

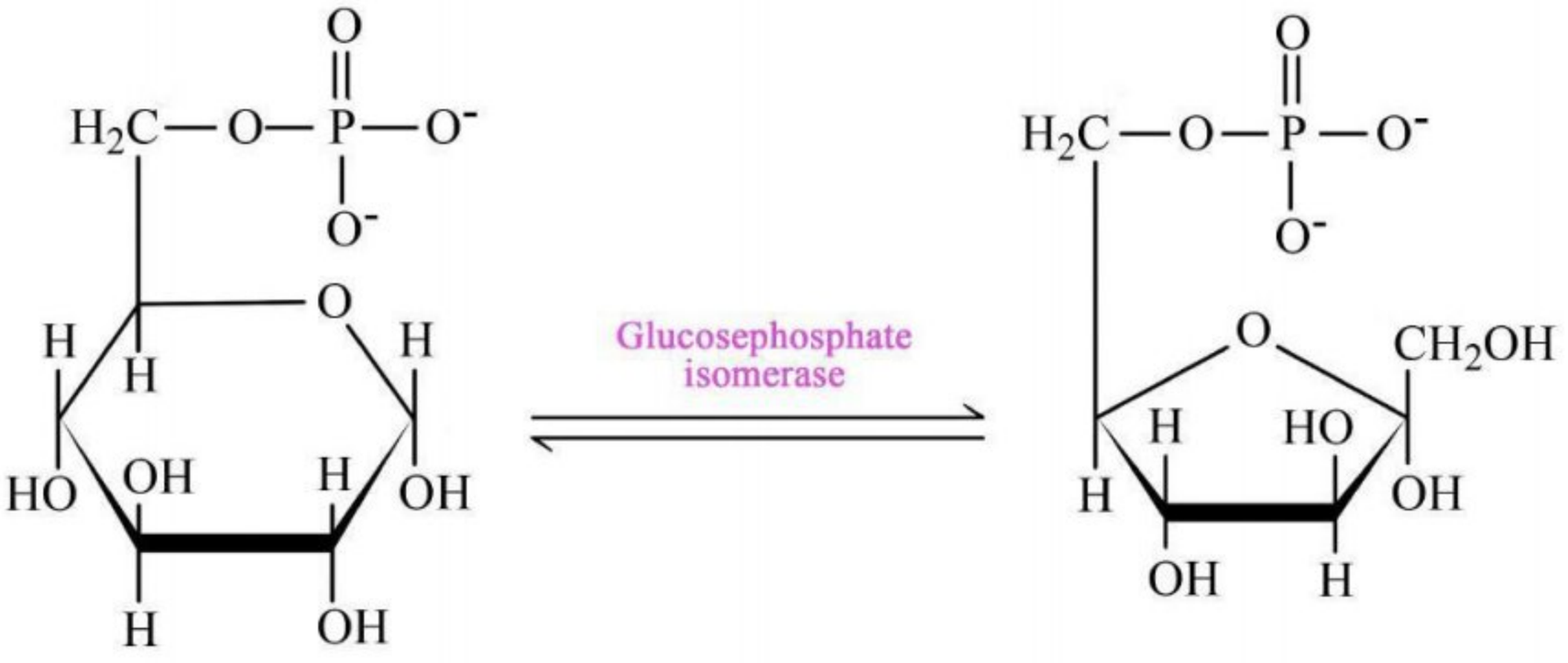
Glucose + 2 Pi + 2 ADP ⟶ 2 Pyruvate + 2 ATP





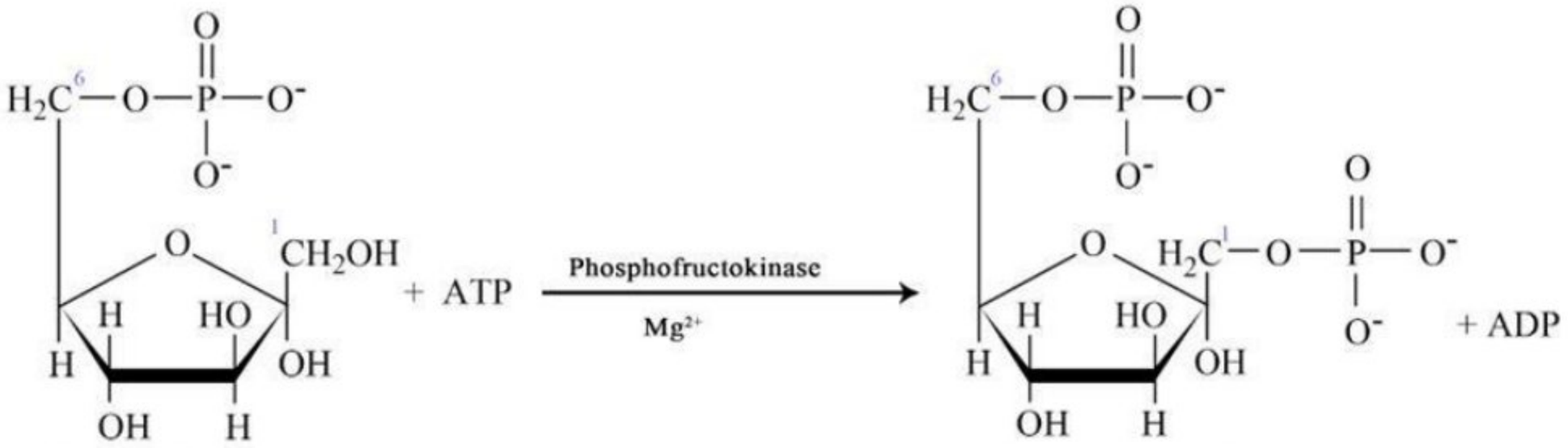
Glucose

Glucose-6-phosphate



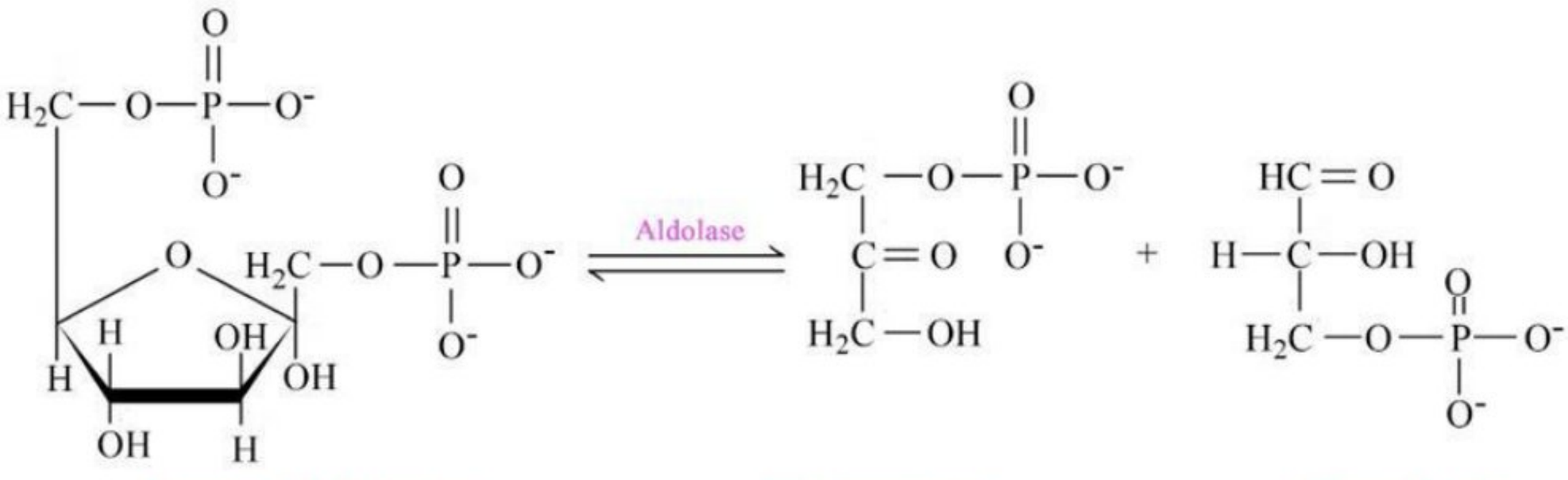
Glucose-6-phosphate

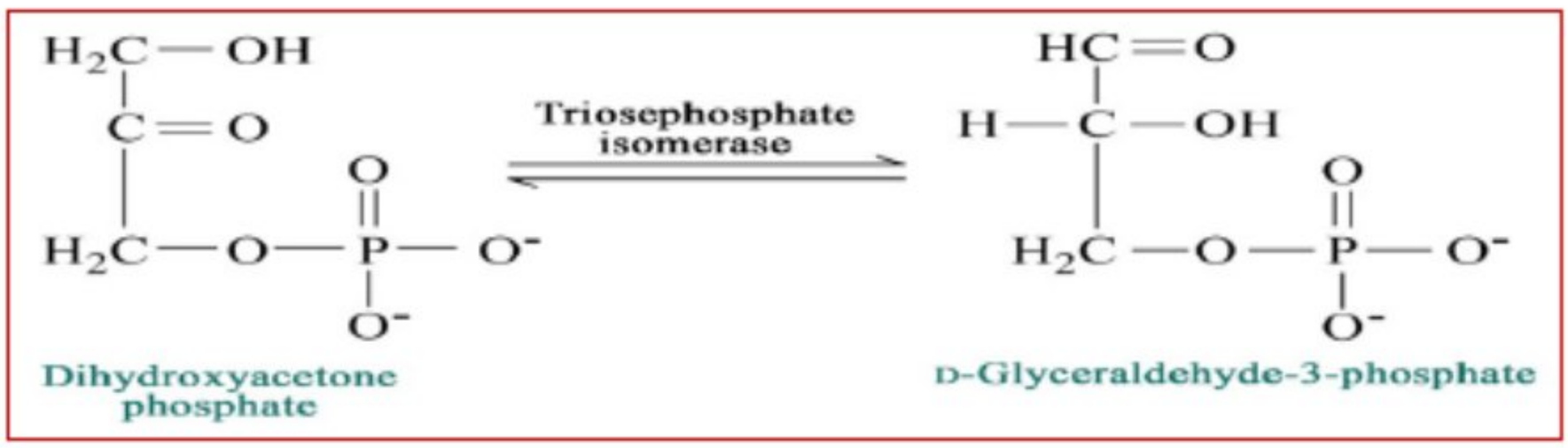
Fructose-6-phosphate

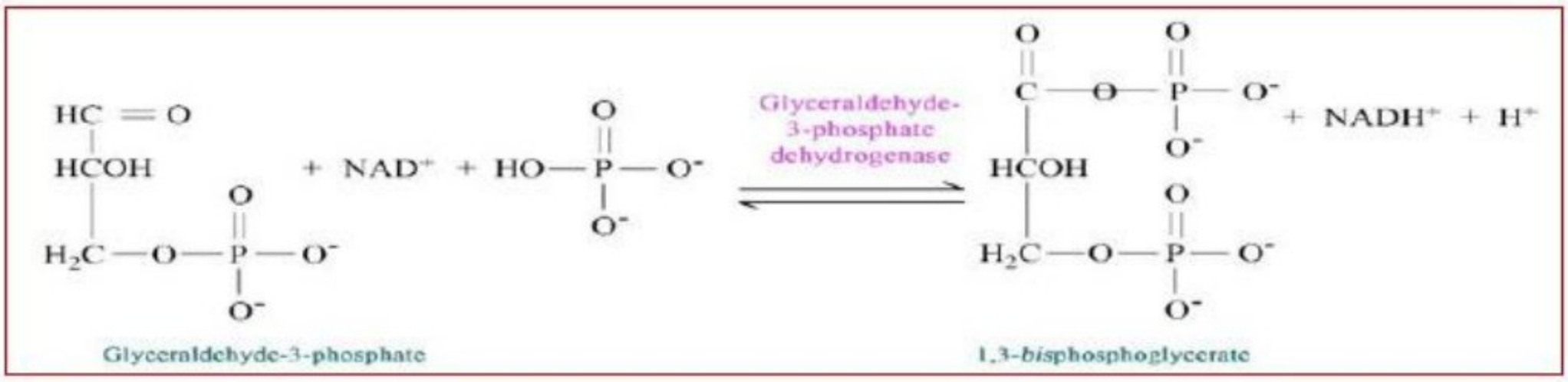


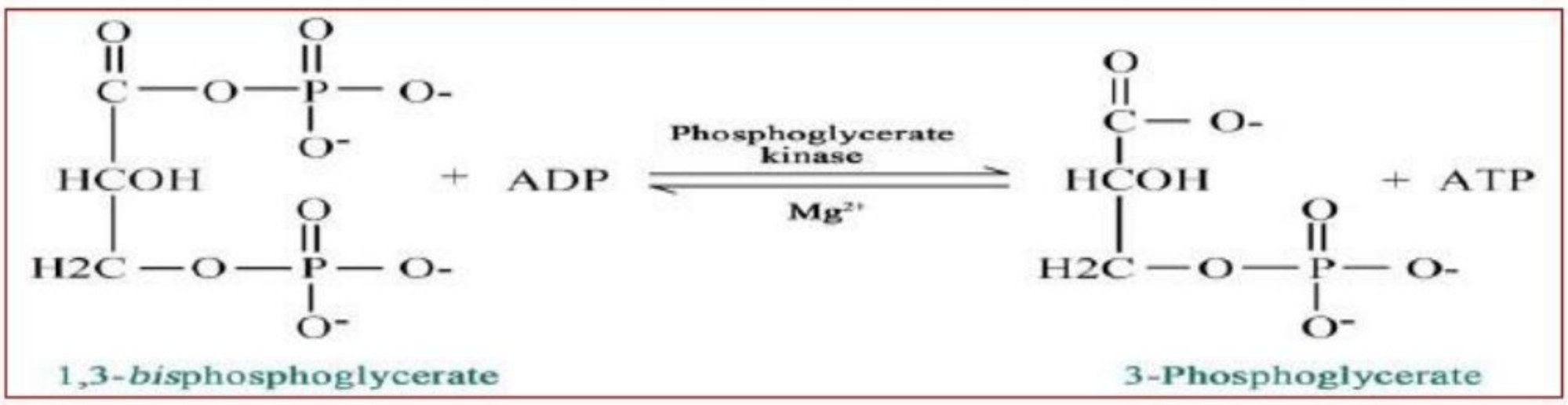
Fructose-6-phosphate

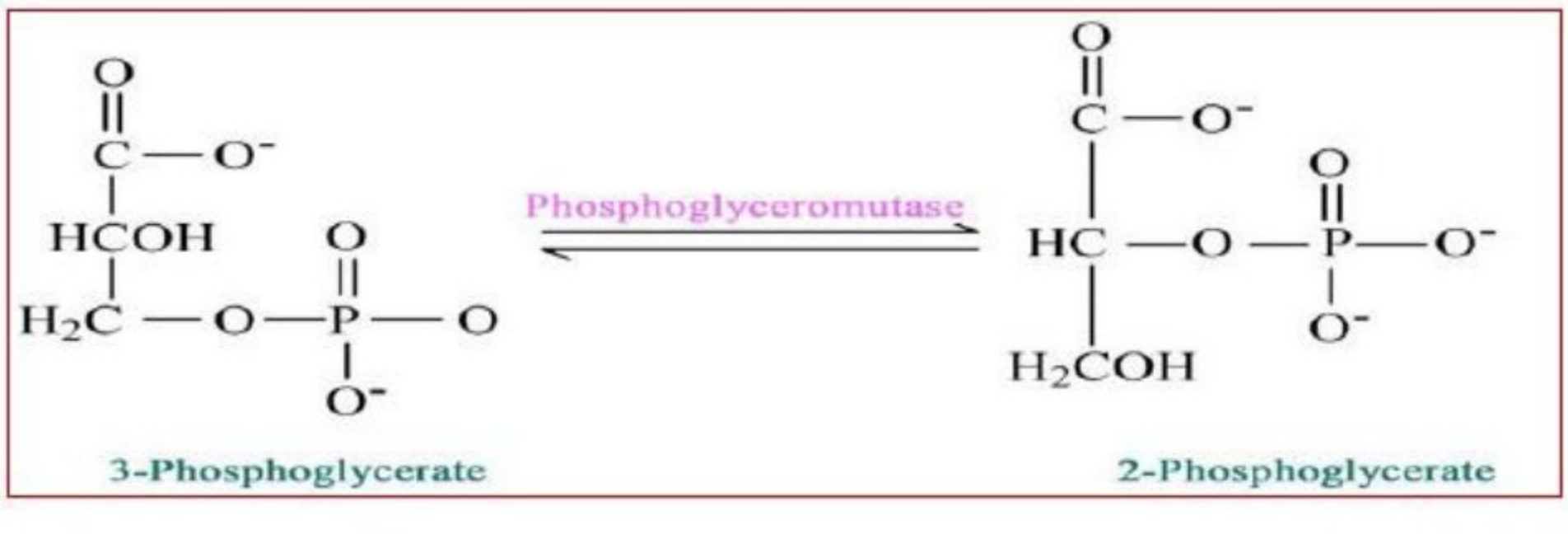
Fructose-1,6-*bis*phosphate

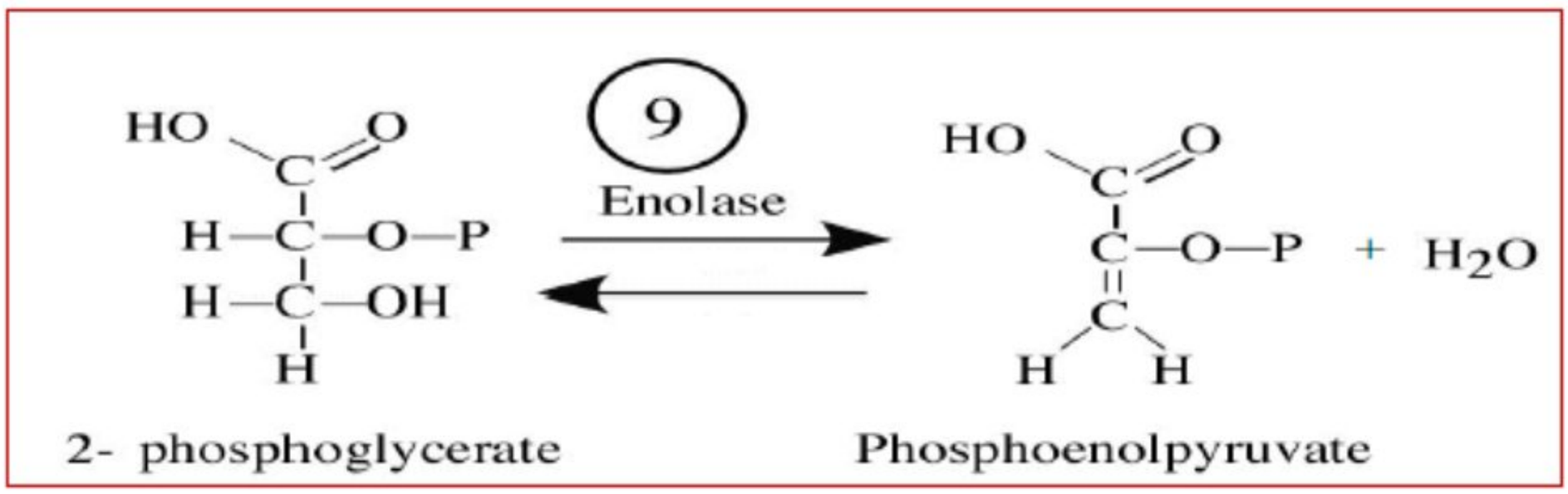


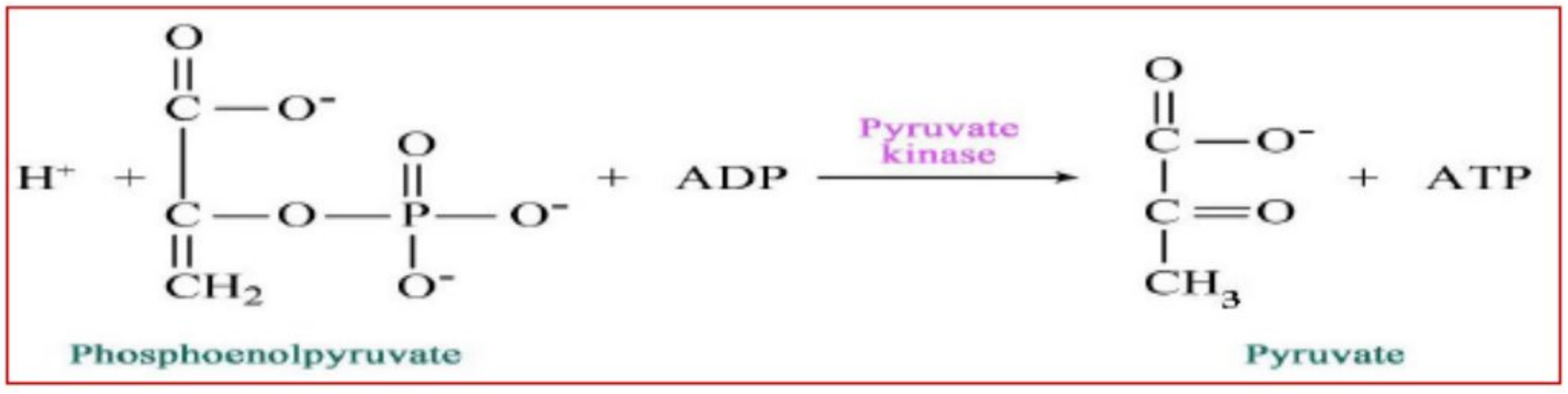


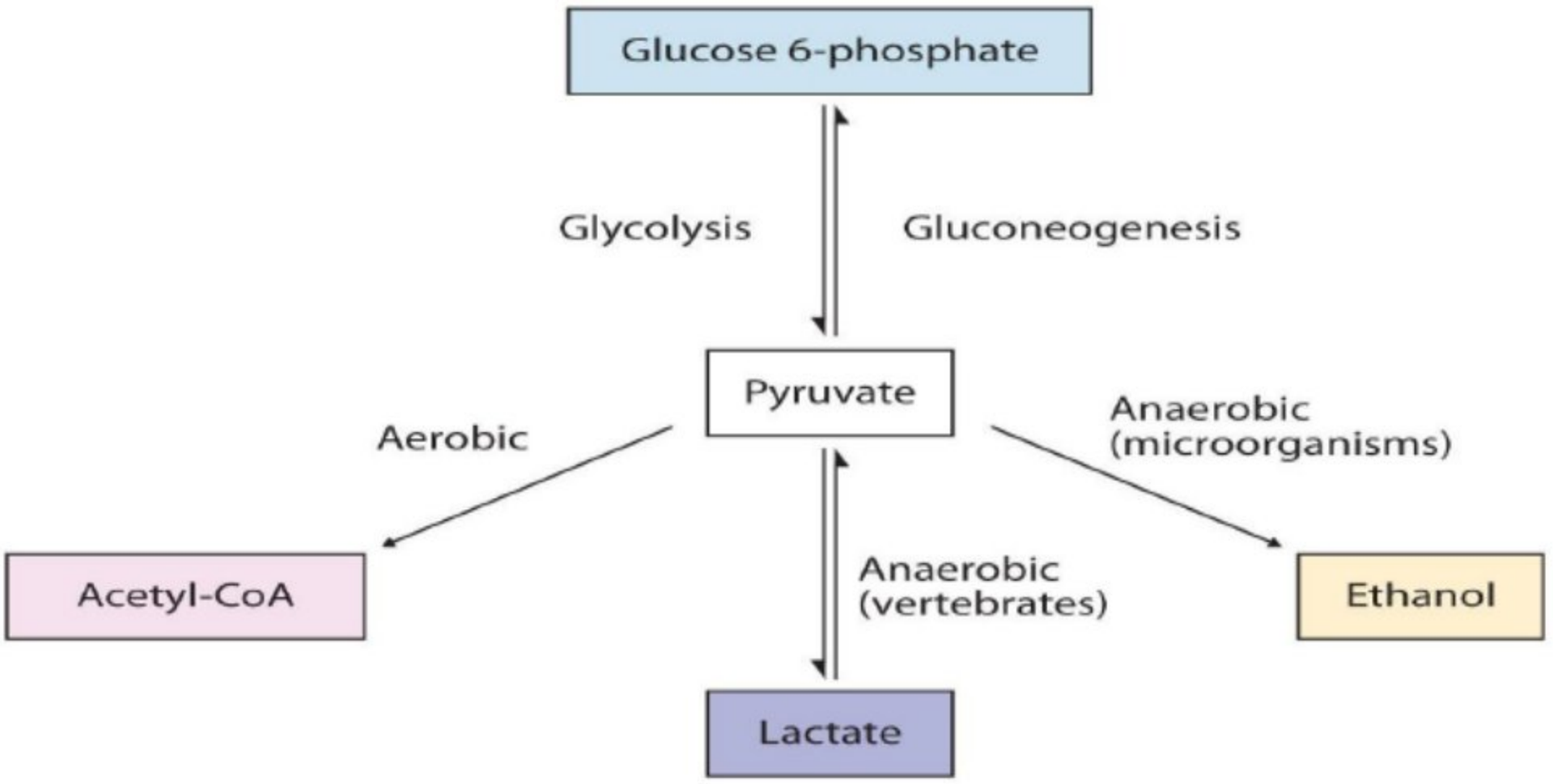


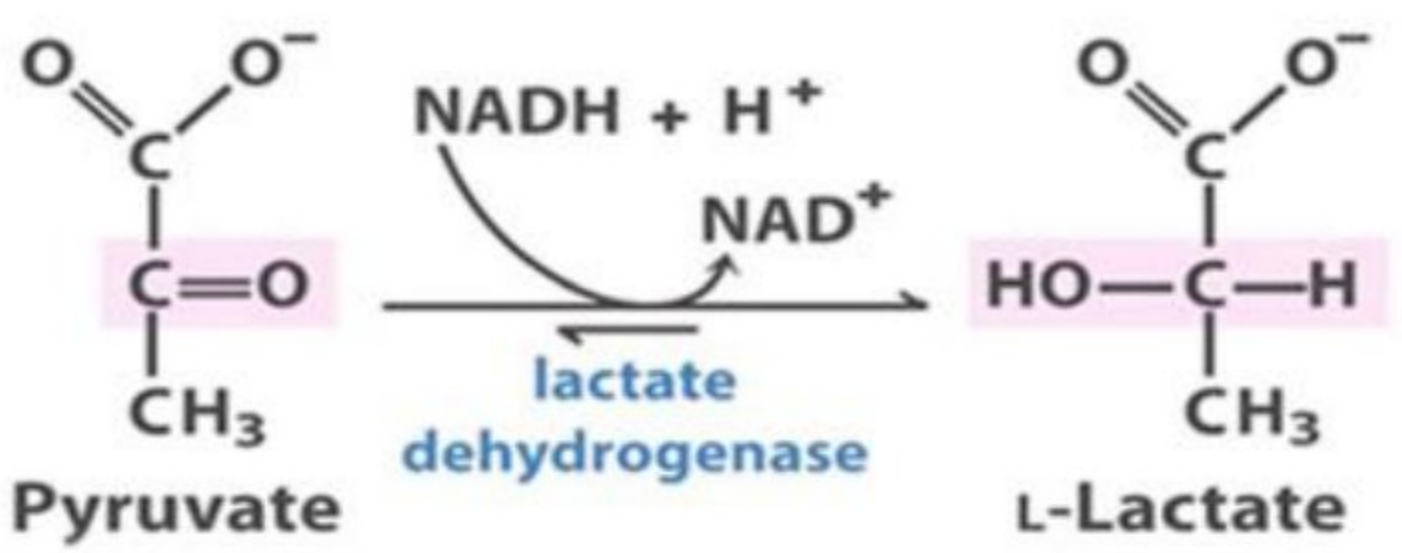


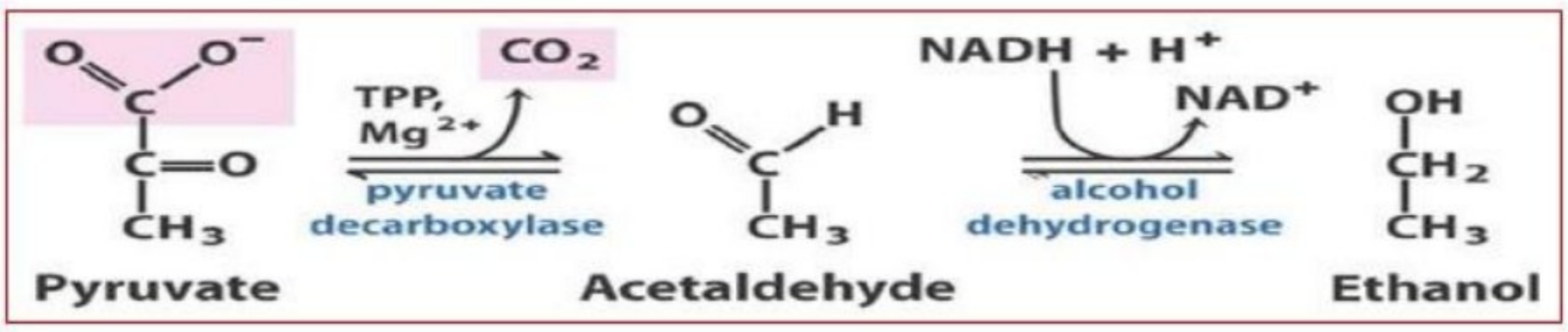


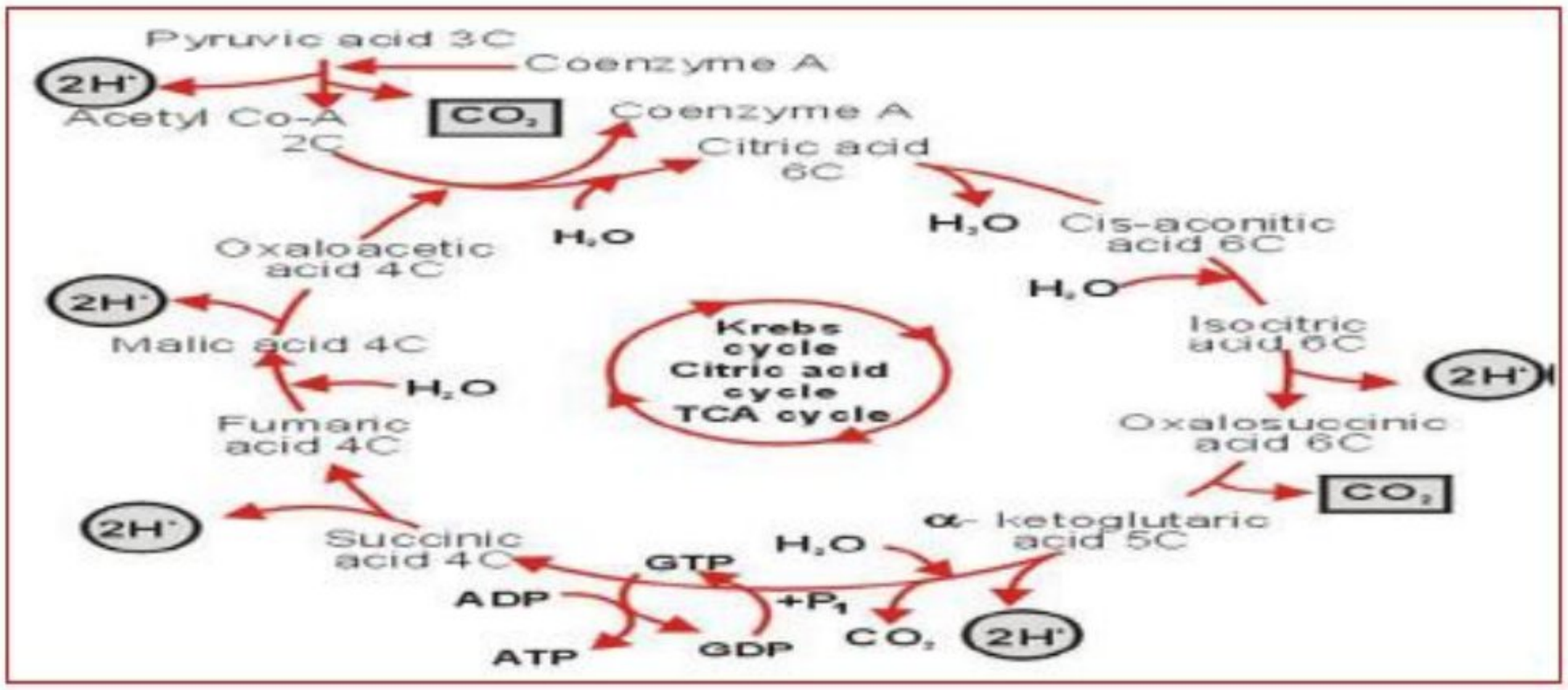












Krebs Cycle

Alternatively designated the tricarboxylic acid cycle or the citric acid cycle, this sequence of reactions represents the forefront of energy metabolism in the body. It can be thought of as the common and final catabolic pathway because products of carbohydrate, fat, and amino acids feed into the cycle where they can be totally oxidised to CO_2 and H_2O, with the accompanying generation of large amounts of ATP. Not all entrant substances are totally oxidised. Some Krebs cycle intermediates are used to form glucose by the process of gluconeogenesis, which will be discussed in the next section, and some can be converted to certain amino acids by transamination. However, the importance of the cycle as the nucleus of energy production is evidenced by the estimation that over 90 per cent of energy released from food occurs here.

The high energy output of the Krebs cycle is attributed to mitochondrial electron transport, with oxidative phosphorylation providing the means for ATP formation. The oxidation reactions occurring in the cycle are actually dehydrogenations in which an enzyme catalyses the removal of two hydrogens to an acceptor co-substrate such as NAD or FAD. Since the

enzymes of the cycle and the enzymes and electron carriers of electron transport are both compartmentalised within the mitochondria,

the reduced cosubstrates, NADH and FADH2 are readily reoxidised by O_2 via the electron transport chain. In addition to its production of the reduced co-substrates NADH and FADH2, which furnish the energy through their oxidation via electron transport, the Krebs cycle produces most of the carbon dioxide through decarboxylation reactions. Viewing this in its proper perspective with regard to glucose metabolism, it must be recalled that two pyruvates are produced from one glucose during cytoplasmic glycolysis. These pyruvates are in turn transferred into the mitochondria, where decarboxylation leads to the formation of two acetyl CoA units and two molecules of CO_2. The two carbons represented by the acetyl CoA are additionally lost as CO_2 through Krebs cycle decarboxylations. Most of the CO_2 produced is exhaled through the lungs, although some is used in certain synthetic reactions called carboxylation. The Krebs cycle is shown in figure below. It is usually visualized as beginning with the condensation of acetyl CoA with oxaloacetate to form citrate. The acetyl CoA is formed from numerous sources, including the breakdown of fatty acids, glucose (through pyruvate), and certain amino acids. Its formation from pyruvate will be considered now, since this compound links cytoplasmic glycolysis to the mitochondrial Krebs cycle activity. The reaction shown below is generally referred to as the pyruvate dehydrogenase reaction. However, the reaction is a complex one requiring a multienzyme system and various cofactors. The enzymes

and cofactors are contained within an isolable unit called the pyruvate dehydrogenase complex. The cofactors include coenzyme A (CoA)thiamine diphosphate (TDP), Mg+2, NAD, FAD, and lipoic acid. Four

vitamins are therefore necessary for the activity of the complex pantothenic acid (a component of CoA), thiamine, niacin, and riboflavin.

The role of these vitamins and others as precursors of coenzymes will be discussed in another unit. The enzymes include pyruvate decarboxylase, dihydroolipoyl dehydrogenase, and dihydrolipoyl transacetylase. The net effect of the complex results in decarboxylation and dehydrogenation of pyruvate with NAD serving as the terminal hydrogen acceptor. This reaction therefore yields energy, since the reoxidation by electron transport of the NADH produces three mol of ATP by oxidative phosphorylation. The reaction is regulated negatively by ATP and by NADH. The condensation of acetyl CoA with oxaloacetate initiates the Krebs cycle reactions. The following are comments on reactions:

1 .The formation of citrate from oxaloacetate and acetyl CoA is catalysed by citrate synthetase. The reaction is regulated negatively by ATP. The isomerisation of citrate to isocitrate involves cis aconitate as an intermediate. The isomerisation, catalysed by aconitase, involves dehydration followed by sterically reversed hydration, resulting in the repositioning of the-OH group onto an adjacent carbon. The first of four

dehydrogenation reactions within the cycle, the isocitratede hydrogenase reaction supplies energy through the respiratory chain reoxidation of the NADH. Note that the first loss of CO_2 in the cycle occurs at this site. It arises from the spontaneous decarboxylation of an intermediate compound, oxalosuccinate. The reaction is positively modulated by ADP and negatively modulated by ATP and NADH.

2 .The decarboxylation/dehydrogenation of aglutarate is mechanistically identical to the pyruvate dehydrogenase complex reaction in its multi-enzyme/cofactor requirement. In the reaction, referred to as the α

ketoglutarate dehydrogenase reaction, NAD serves as hydrogen acceptor, and a second carbon is lost as CO_2 The pyruvate dehydrogenase, isocitrate dehydrogenase, and aglutarate dehydrogenase reactions account for the loss of the three-carbon equivalent of pyruvate as CO_2.

3 .Energy is conserved in the thioester bond of succcinyl CoA. The hydrolysis of that bond by succinyl thiokinase releases enough energy to drive the phosphorylation of guanosine diphosphate (GDP) by inorganic phosphate. The resulting GTP is a high energy phosphate anhydride compound like ATP; as such, GTP can serve as phosphate donor in certain phosphorylation reactions. One such reaction occurs in the gluconeogenesis pathway.

4 .The succinate dehydrogenase reaction uses FAD instead of NAD as hydrogen acceptor. The FADH2 is reoxidised by electron transport to O_2, but only two ATPs are formed by oxidative phosphorylation instead of three.

5 .Fumarase incorporates the elements of H_2O across the double bond of fumarate to form malate.

6 .The conversion of malate to oxaloacetate completes the cycle. NAD acts as a hydrogen acceptor in this dehydrogenation reaction catalysed by malate dehydrogenase. It is the fourth site of reduced co substrate formation and therefore of energy release in the cycle.

In summary the complete oxidation of glucose to CO_2 and H_2O can be shown by the equation:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6\ CO_2 + 6\ H_2O + \text{energy}.$$

This is achieved by the combined reaction sequences of the glycolytic and Krebs cycle pathways. The amount of released energy conserved as ATP under aerobic conditions is as follows:

The glycolytic sequence, glucose →2 pyruvates, produces two ATPs by substrate level phosphoryllation and either four or six by oxidative phosphoorylation, depending on the shuttle system for NADH-reducing equivalents. Generally, six will be formed due to the overall greater activity of the malate shuttle system. The intra mitochondrial pyruvate dehydrogenase reaction yields two mol of NADH, one for each pyruvate oxidised and therefore six additional ATPs by oxidative phosphorylation.

The oxidation of 1 mol of acetyl CoA in the Krebs cycle yields a total of

12 ATPs. The sites of formation, indicated by reaction number, follow.

3 - 3 .ATP

4 -3 .ATP

5 -1 .ATP (as GTP)

6 -2 .ATP

8-3 .ATP

Total 12 ATP

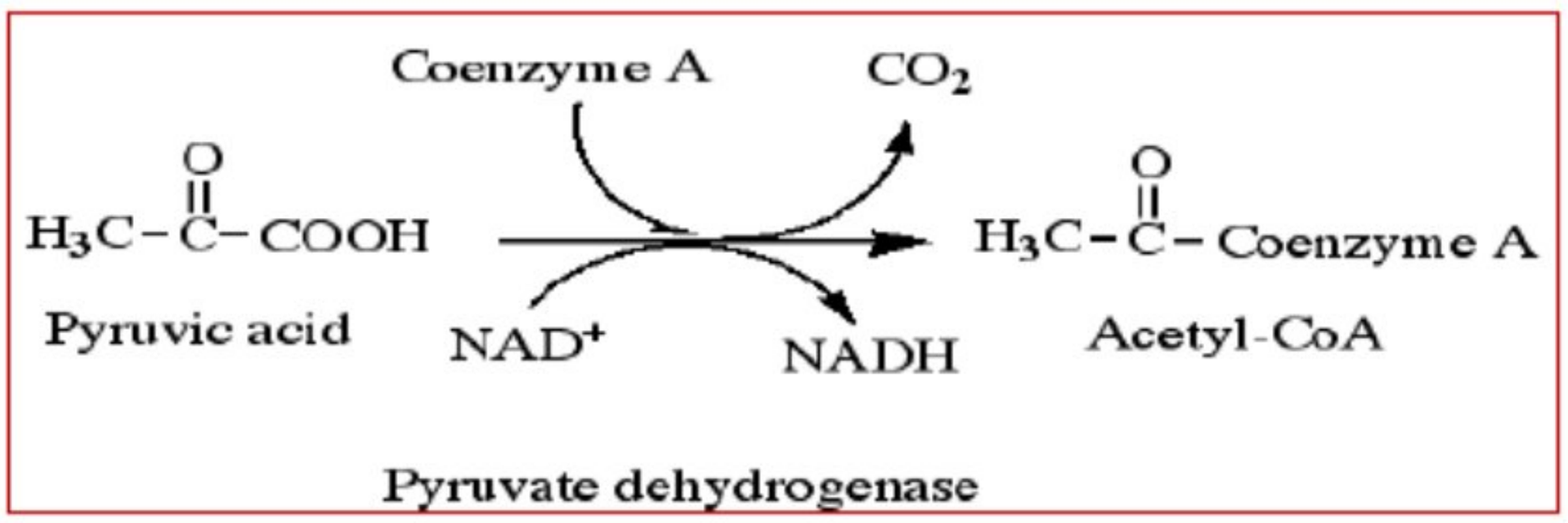
Since 2 mol acetyl CoA derived from one glucose, however, the actual

total is 24 ATPs. The total number of ATPs realized for the complete oxidation of 1 mol of glucose is therefore 38, equivalent to 262.8 kcal. It will be recalled that this figure represents only about 40% of the total energy released by mitochondrial electron transport. The remaining 60 per cent, or approximately 394 kcal, is released

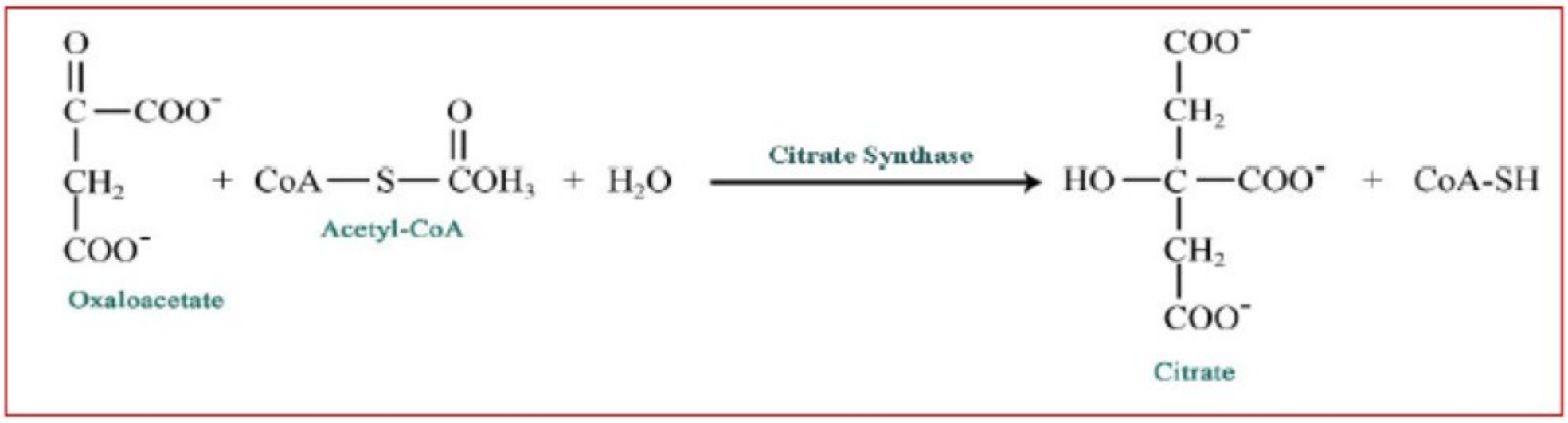
as heat to maintain body temperature has already been mentioned that acetyl CoA is produced by fatty acid oxidation and amino acid catabolism as well as from the glycolytically

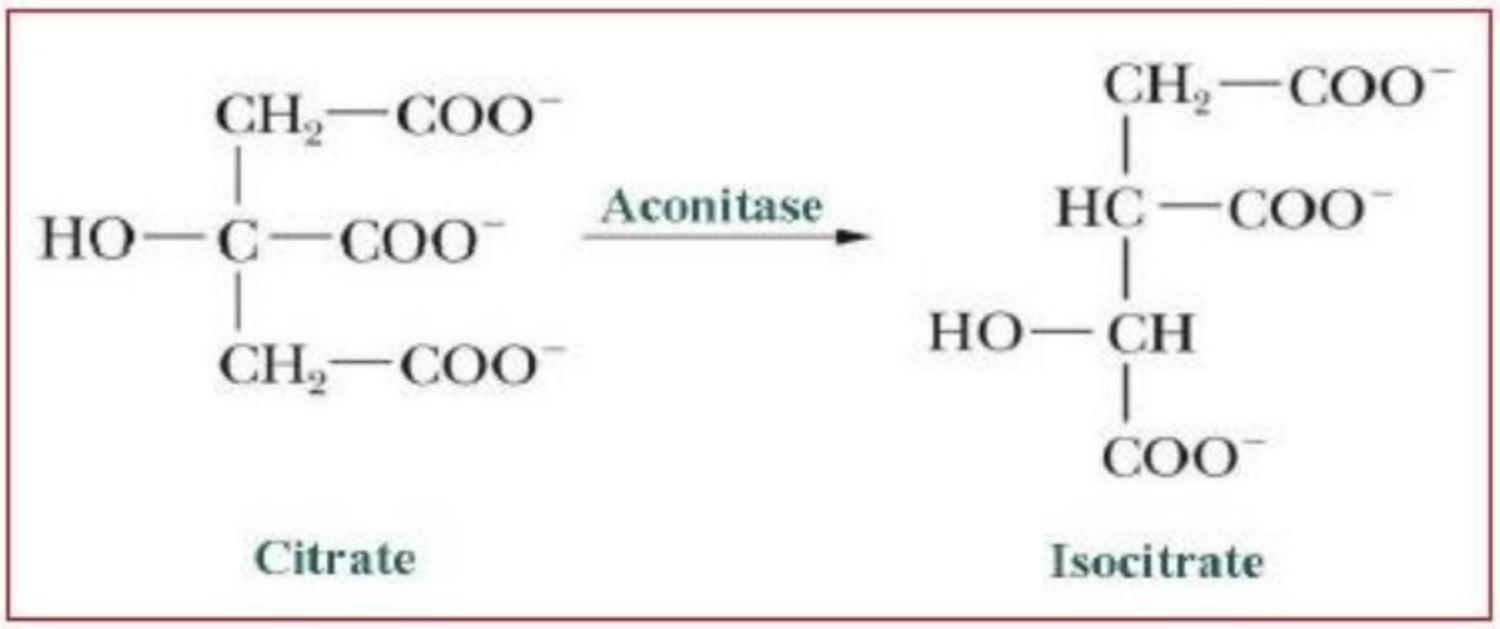
derived pyruvate. This clearly leads to an imbalance between the amount of acetyl CoA and oxaloacetate, which condense one to one stoichiometrically in the citrate synthetase reaction. It is therefore important that oxaloacetate and/or Krebs cycle intermediates, which can form oxaloacetate, be replenished in the cycle. Such a mechanism does indeed exist. Oxaloacetate, fumarate, succinyl CoA, and a rate can all be formed from certain amino acids, but the single most important mechanism for ensuring an ample supply of oxaloacetate is the reaction

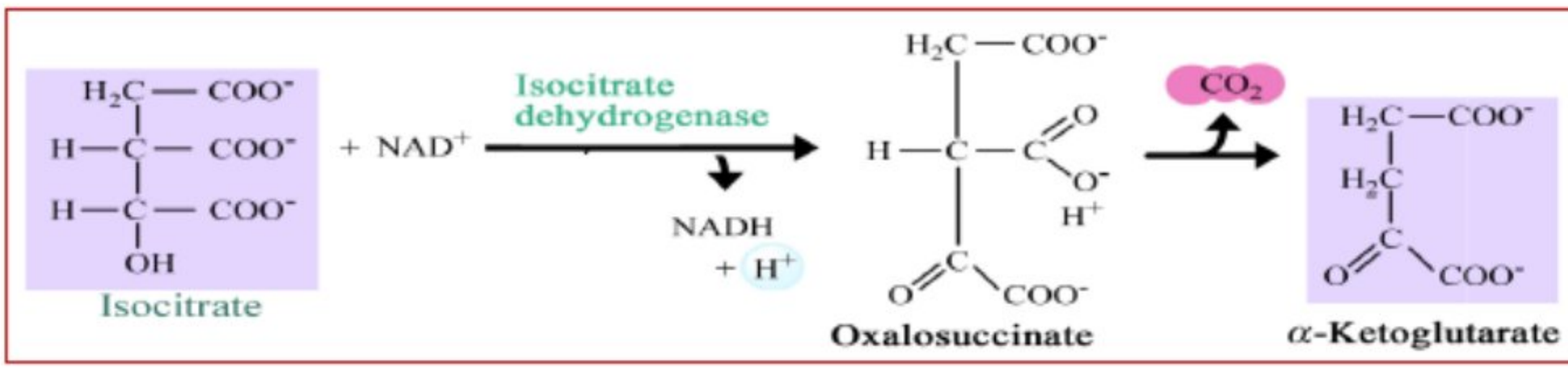
by which it is formed directly from pyruvate. This reaction, shown below, is catalysed by pyruvate carboxxylase. The "uphill" incorporation of CO_2 is accomplished at the expense of ATP, and the reaction requires the participation of biotin. The diversion of pyruvate into oxaloacetate is called an anaplerotic (filling up) process because of its role in restoring oxaloacetate to the cycle. It is of interest that pyruvate carboxylase is regulated positively by acetyl CoA, thereby accelerating oxaloacetate formation in answer to increasing levels of acetyl CoA.

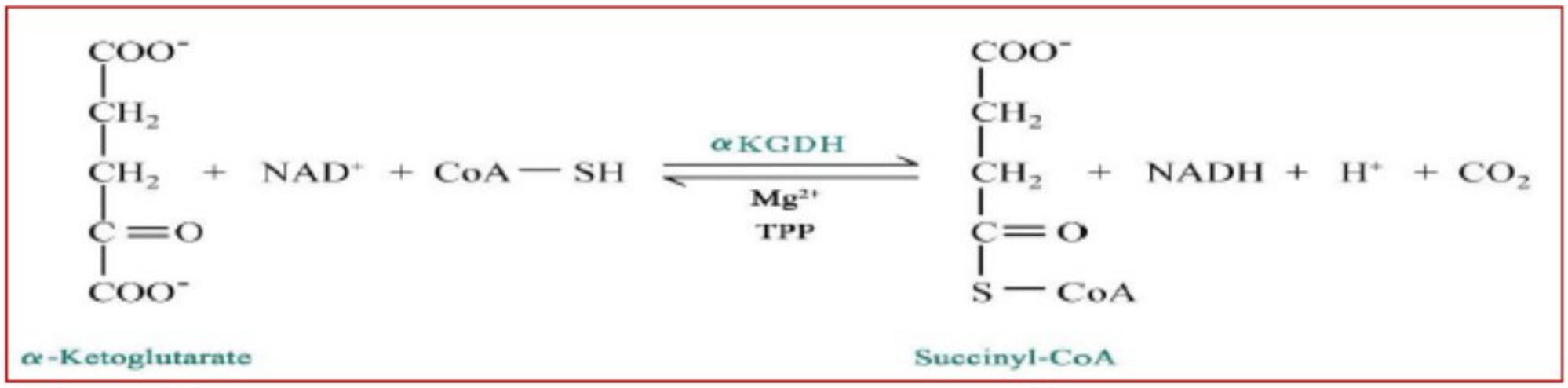


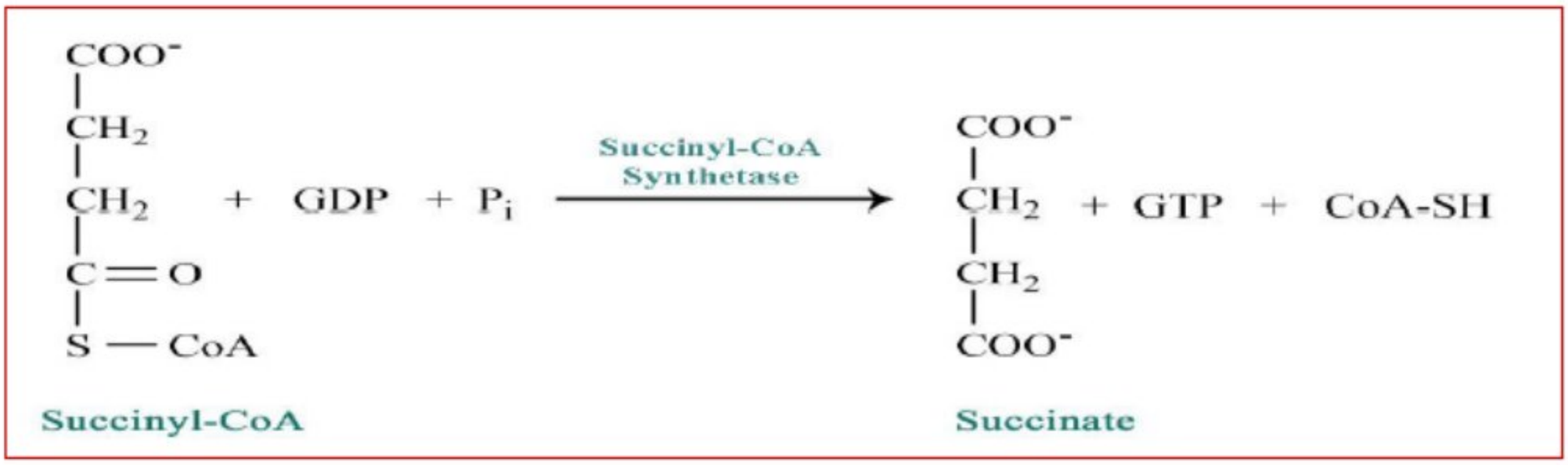
خطوات دورة كربس

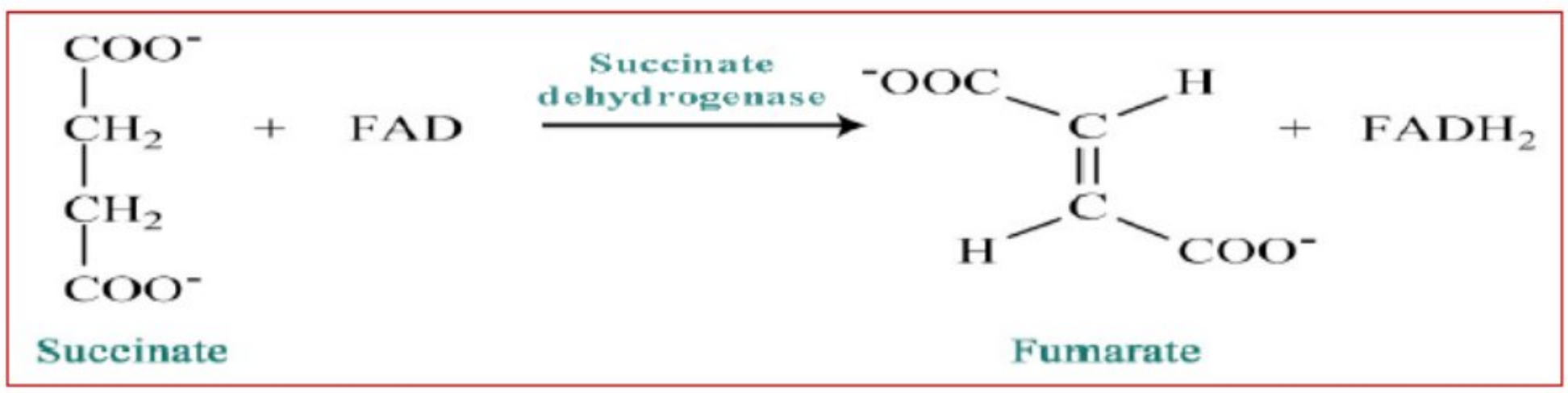


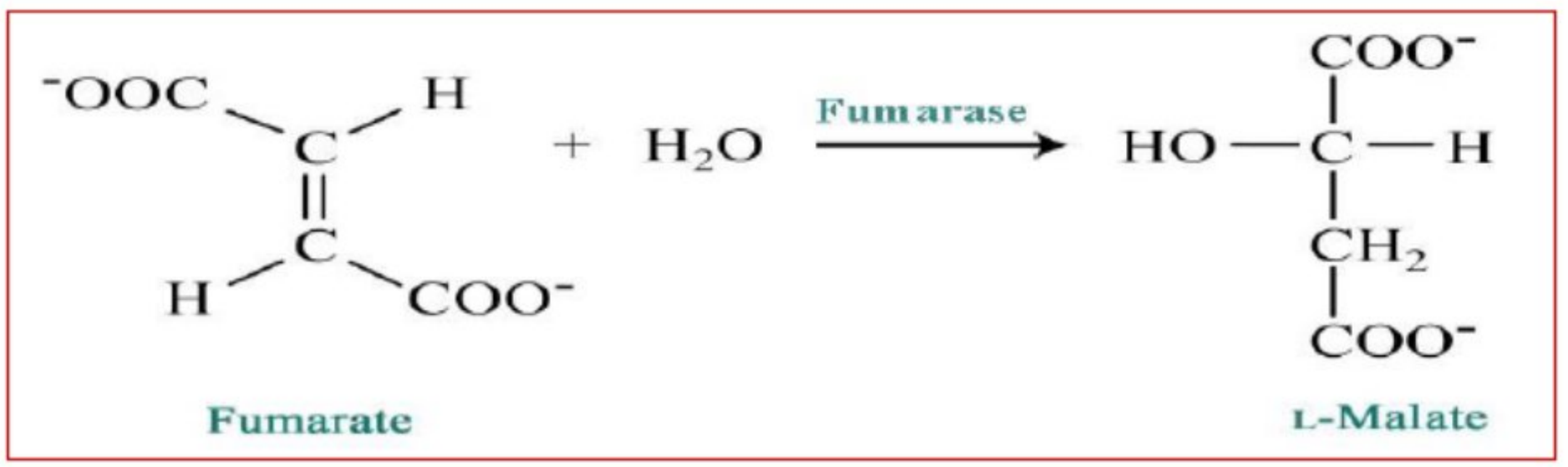


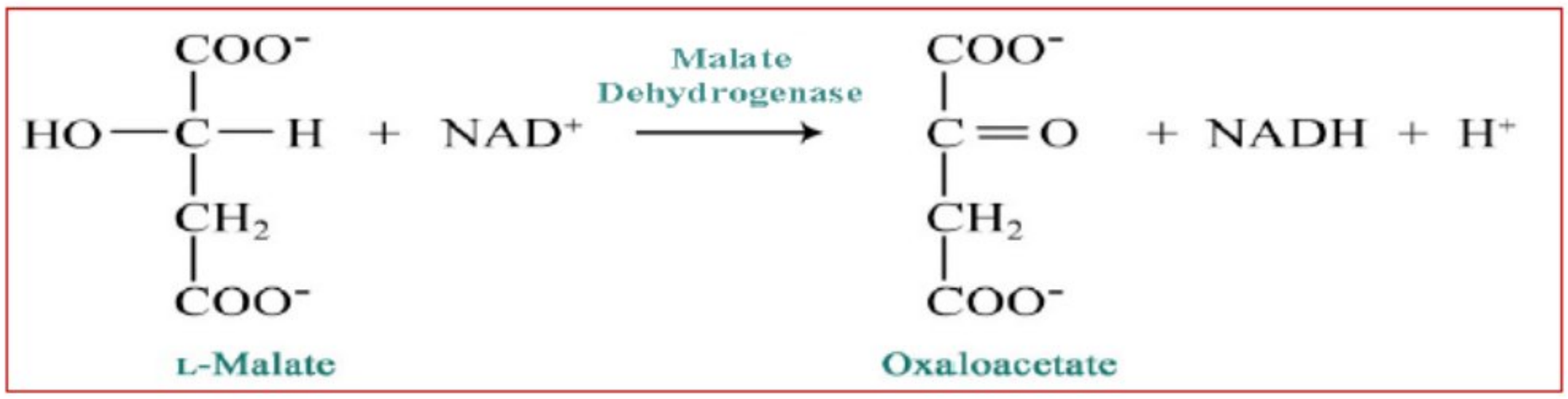




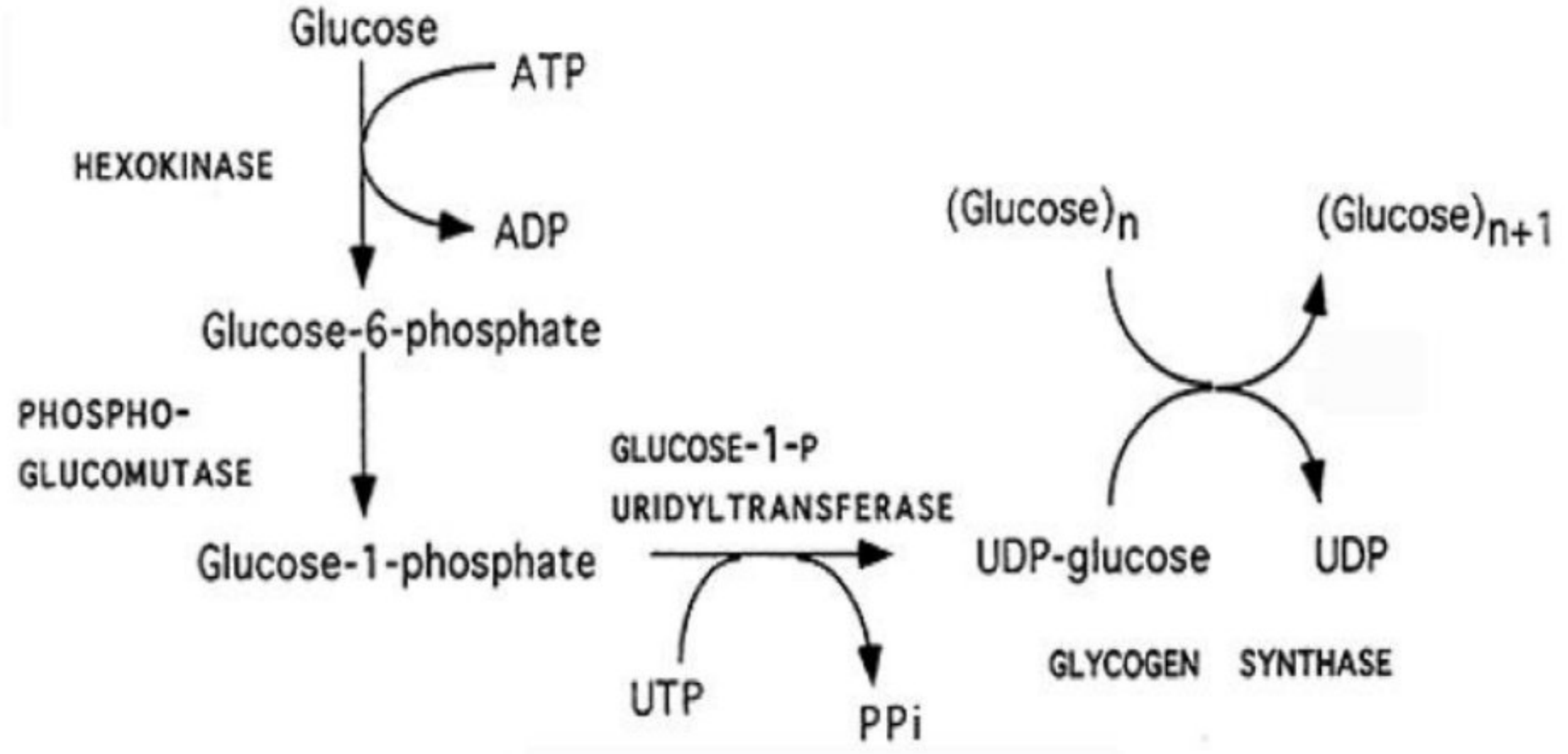




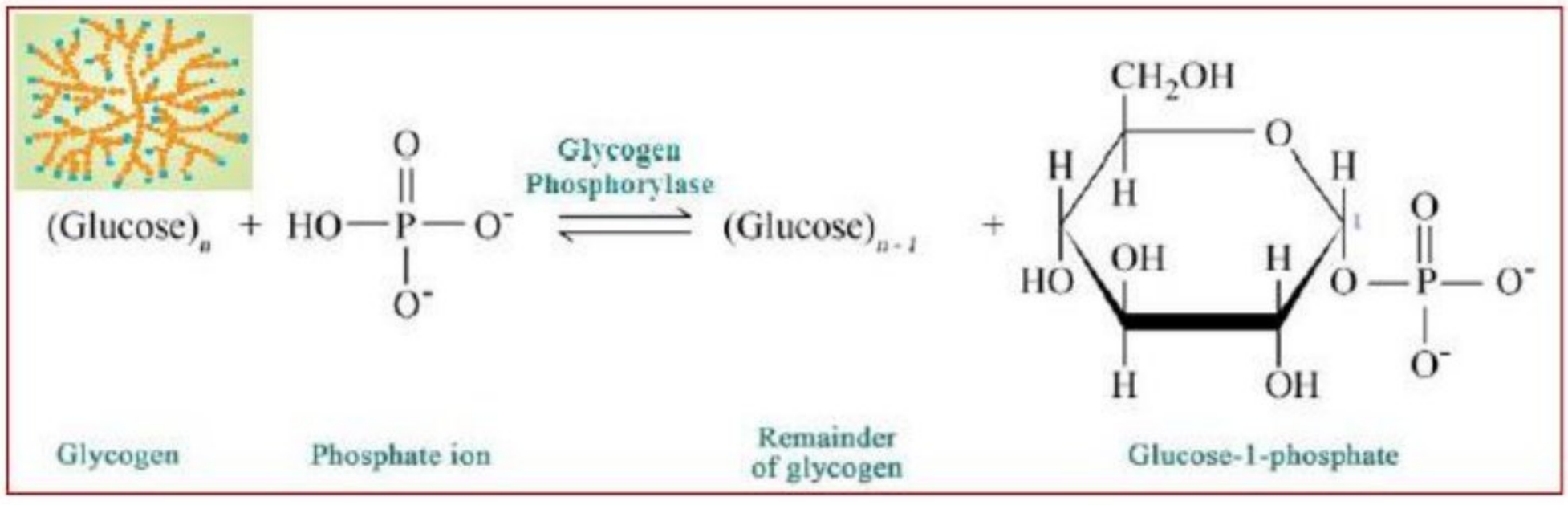


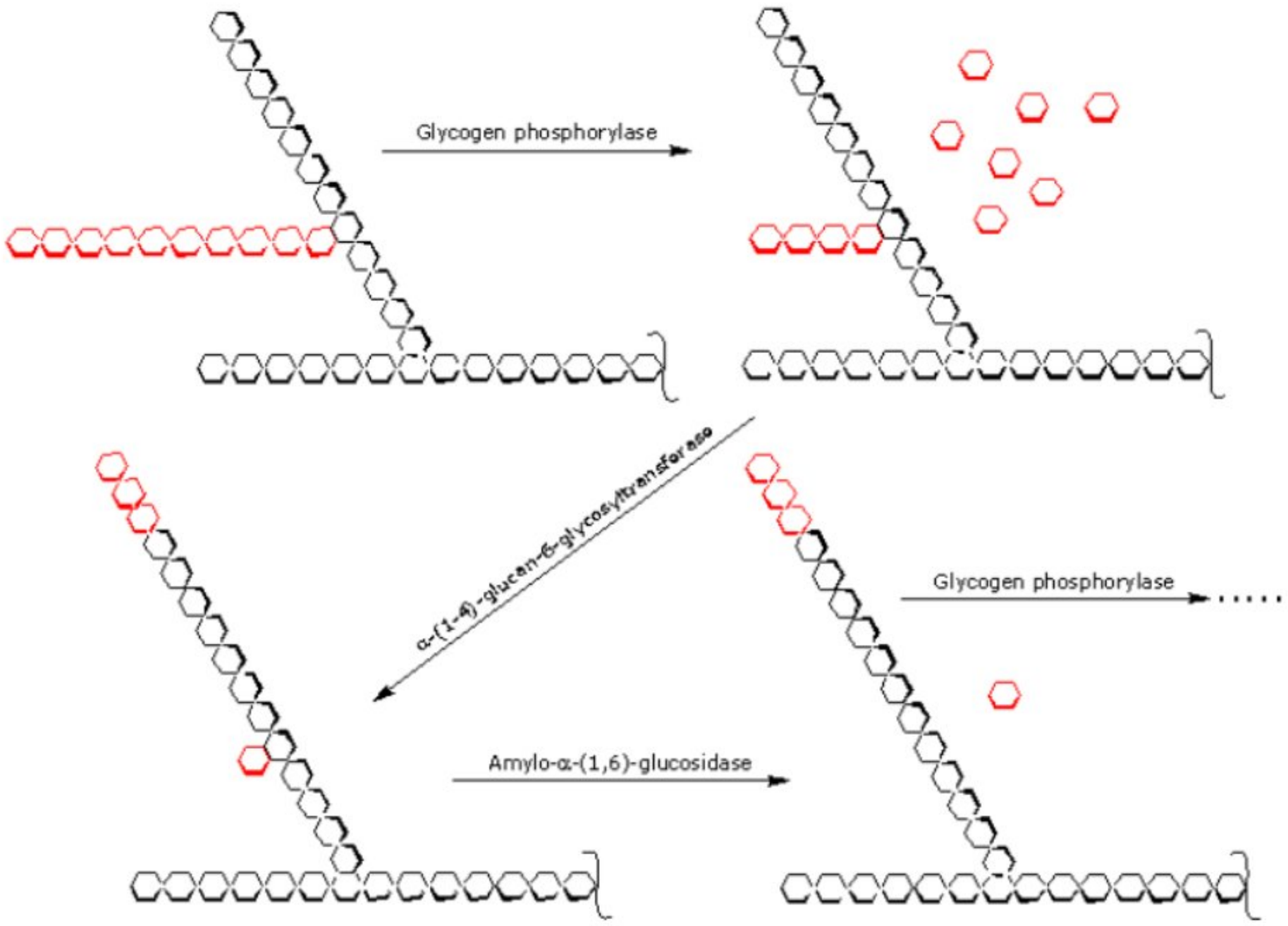


بناء الجلايكوجين (Glycogenesis)



إستحداث الجلايكوجين (Gluconeogenesis)



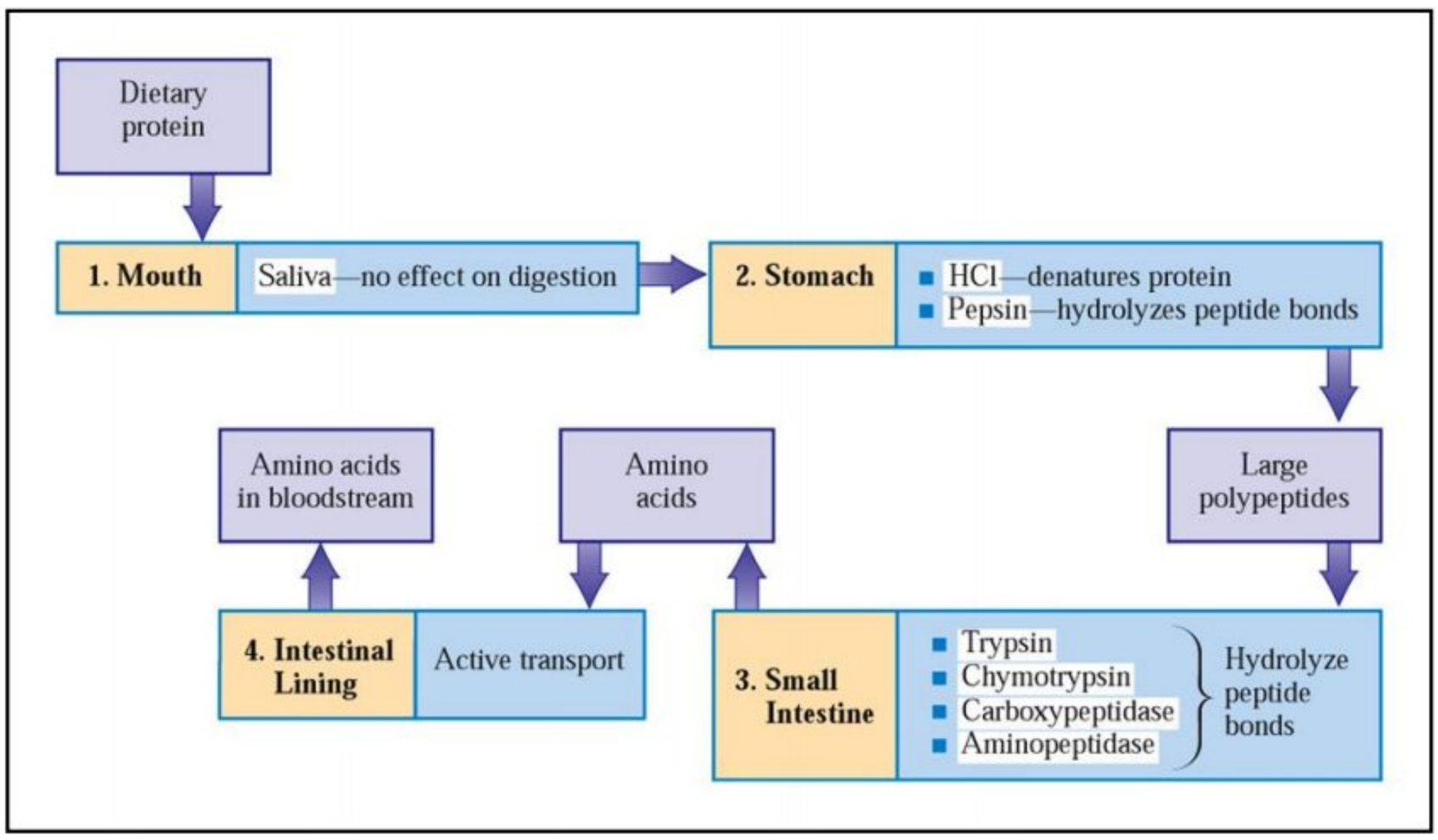


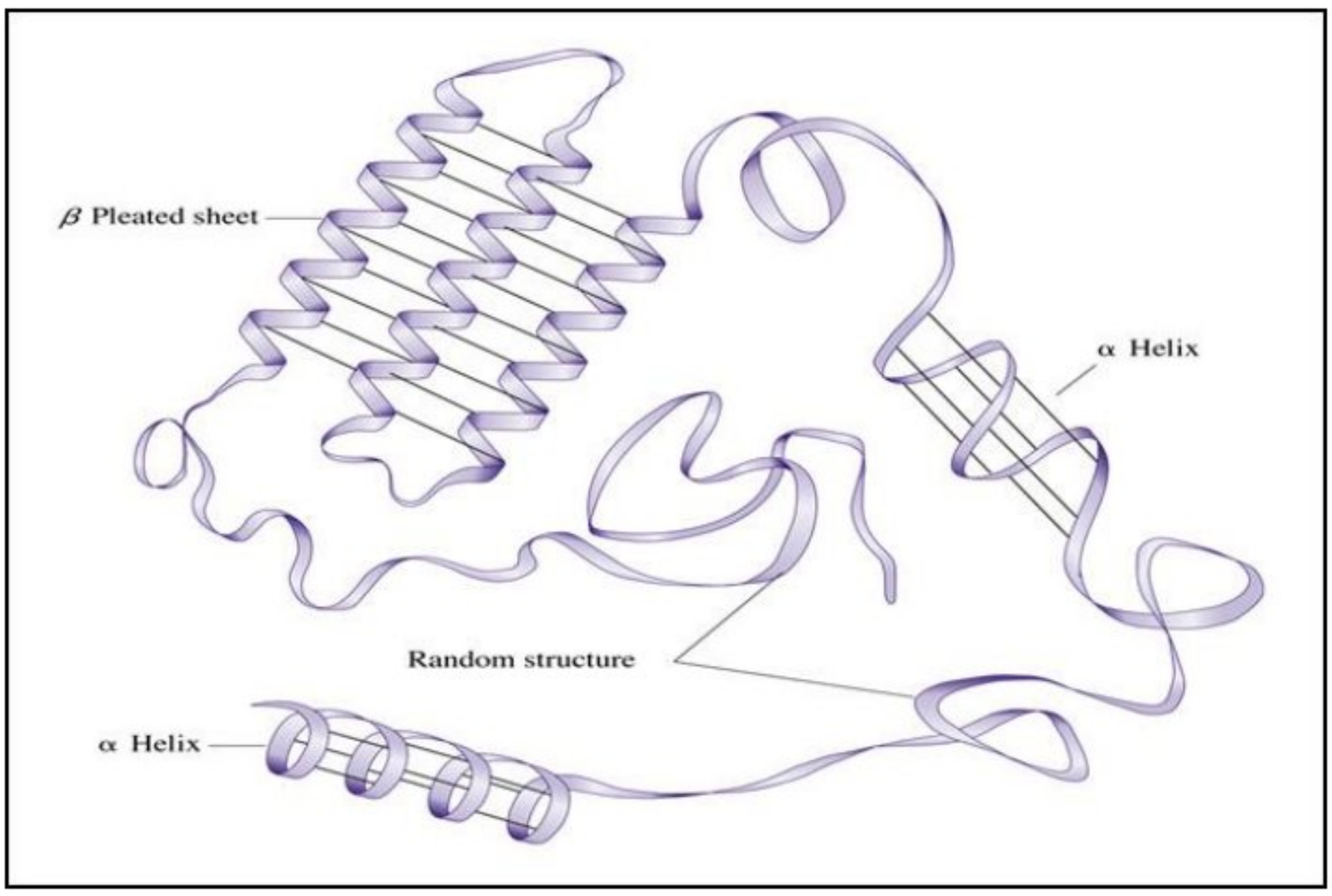
Proteins Metabolism

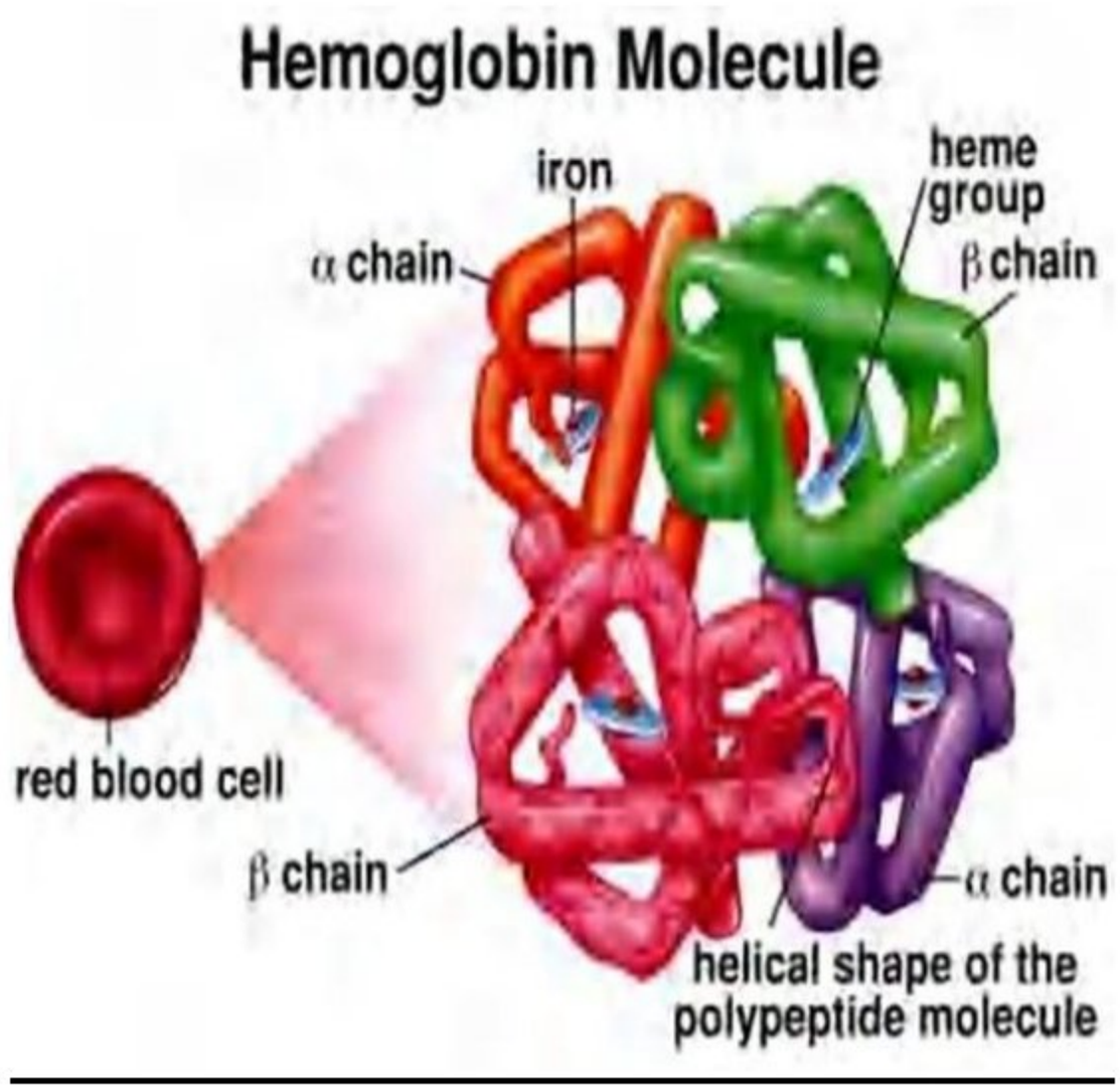
Protein Digestion

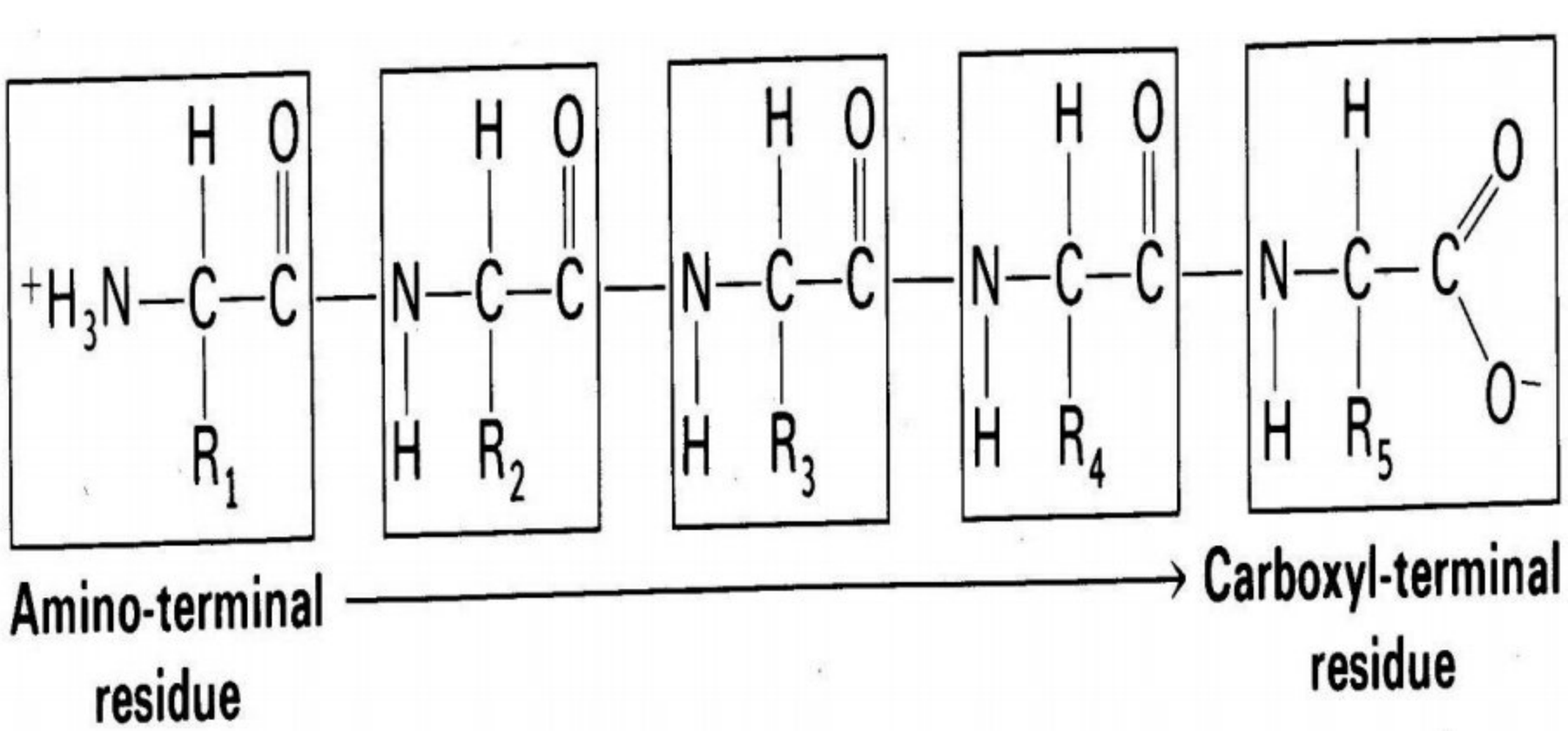
Protein breakdown begins in the **stomach**.

No protein hydrolyzing enzymes are found in saliva.









Hydrolysis (10% of peptide bonds) & **denaturization** by pepsin enzyme & HCl acid produce **short chain polypeptides** in the stomach.

Trypsin, chymotrypsin, & carboxypeptidase from Pancreatic juices, and **Aminopeptidase** from cells in the small intestine Brush Zone create "free" **amino acids**.

Free amino acids are absorbed thru intestinal wall via active transport.

Enter bloodstream and are brought to cells.

The total supply of free amino acids available is called: the **Amino Acid Pool**.

3 sources of "free" amino acids:

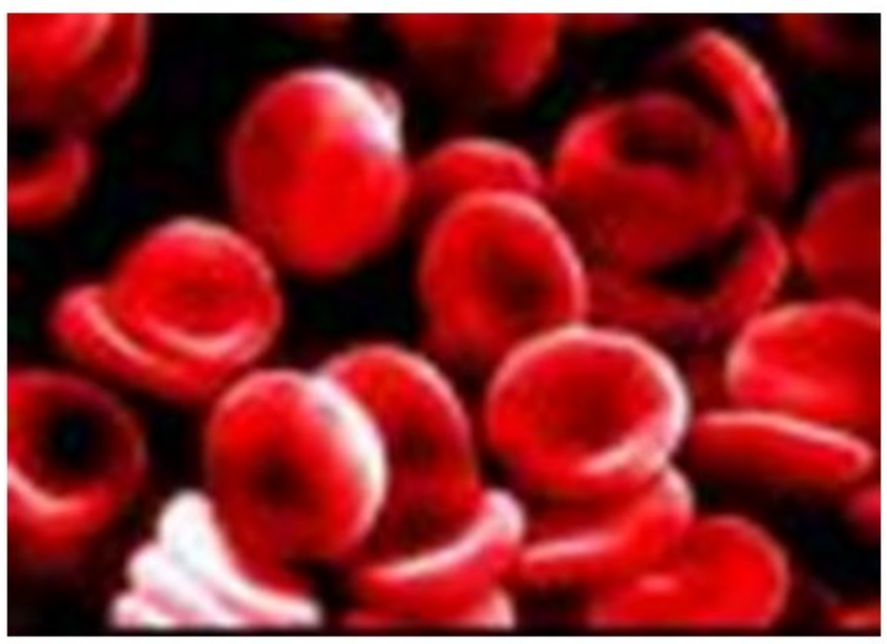
1. Dietary protein breakdown
2. Biosynthesis of amino acids in the Liver
3. Protein turnover (I prefer apple turnovers)

Protein turnover is the breakdown & re-synthesis of body protein:

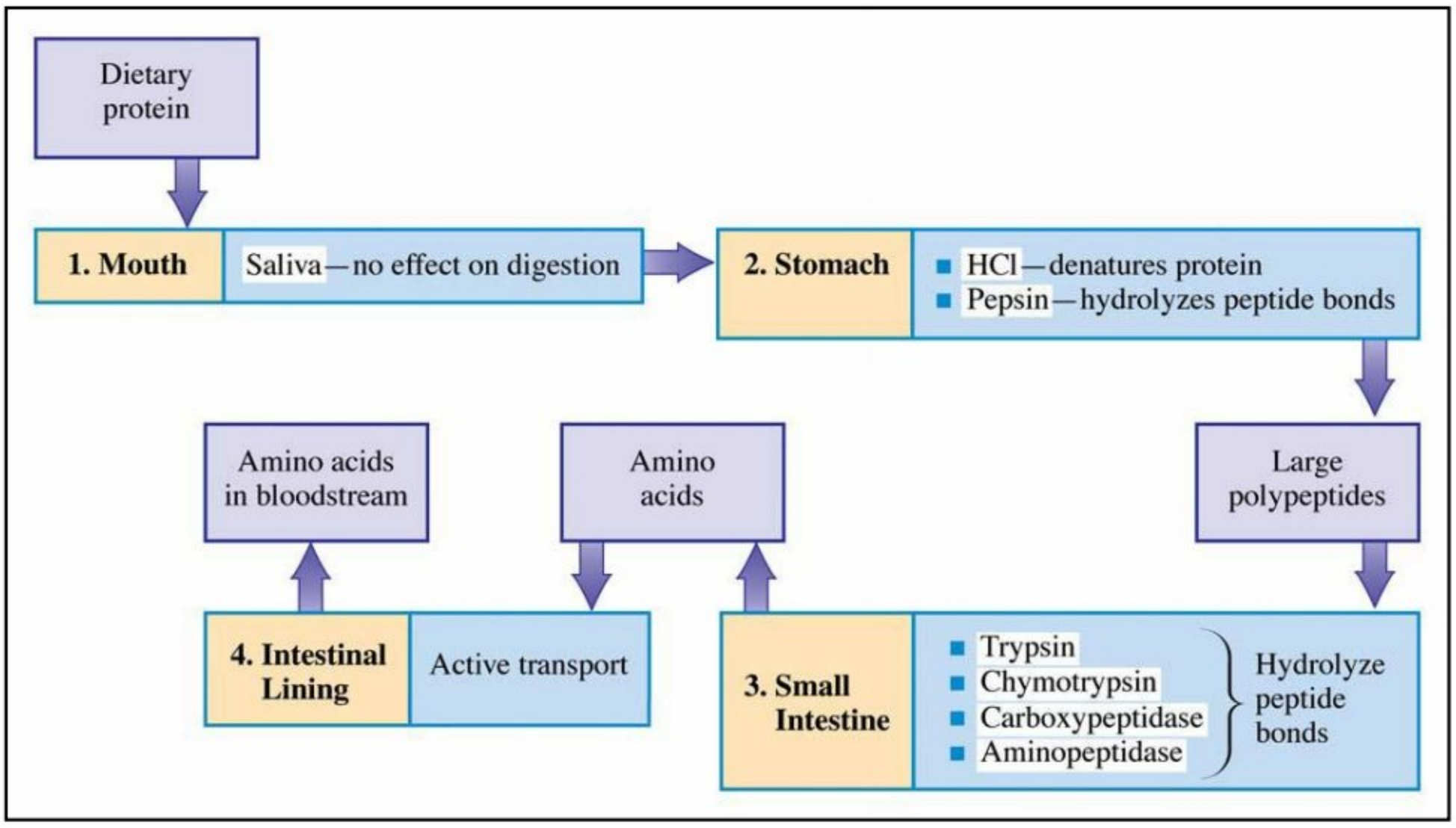
Old tissues

Damage

Recycling enzymes & hormones



Summary of protein digestion in the human body. Possible fates for amino acid degradation products.



Transamination and Oxidative Deamination:

Two steps in degrading amino acids

1) remove a-amino group

2) breakdown & process carbon skeleton

Release of an **amino group** is also two steps:

1) **Transamination**

2) **Oxidative deamination**

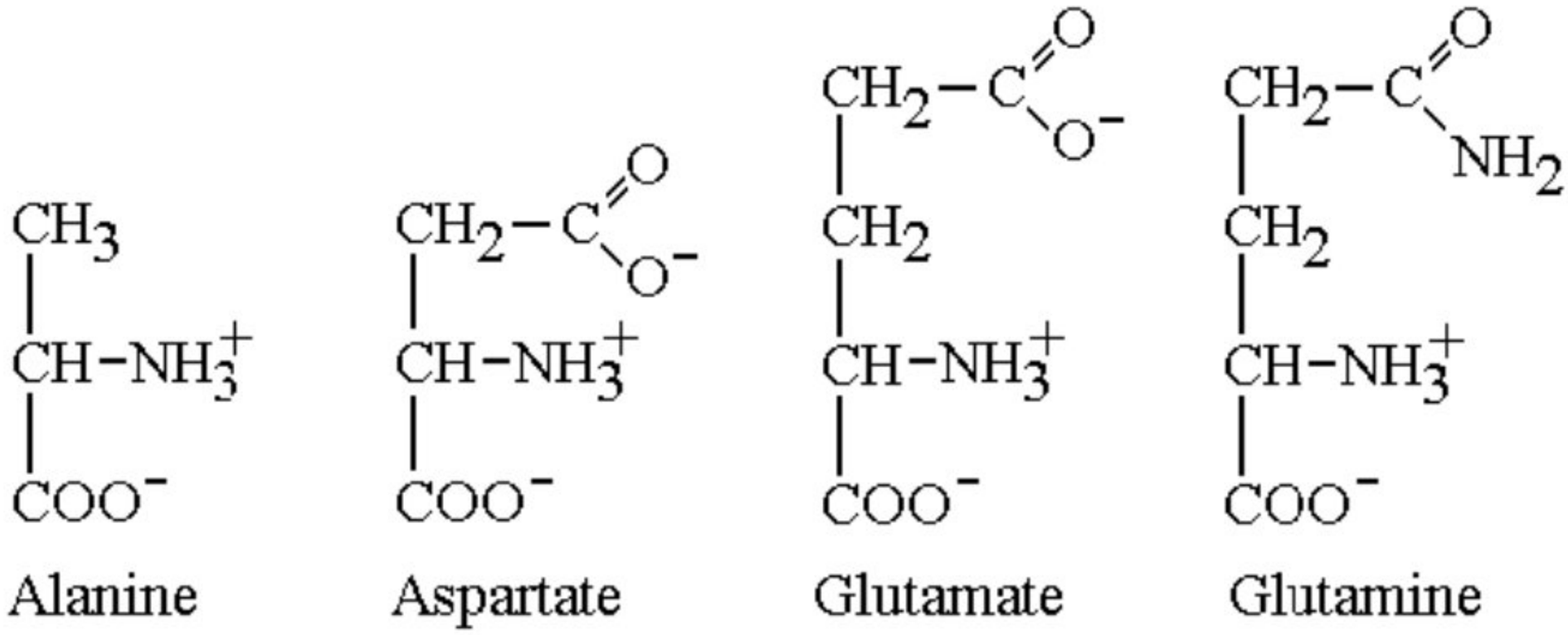
Central role of glutamate:

Amino acids:

Glutamate, **aspartate**, **alanine** & **glutamine**

present in higher concentrations in mammalian cells. Have metabolic functions as well as roles in proteins.

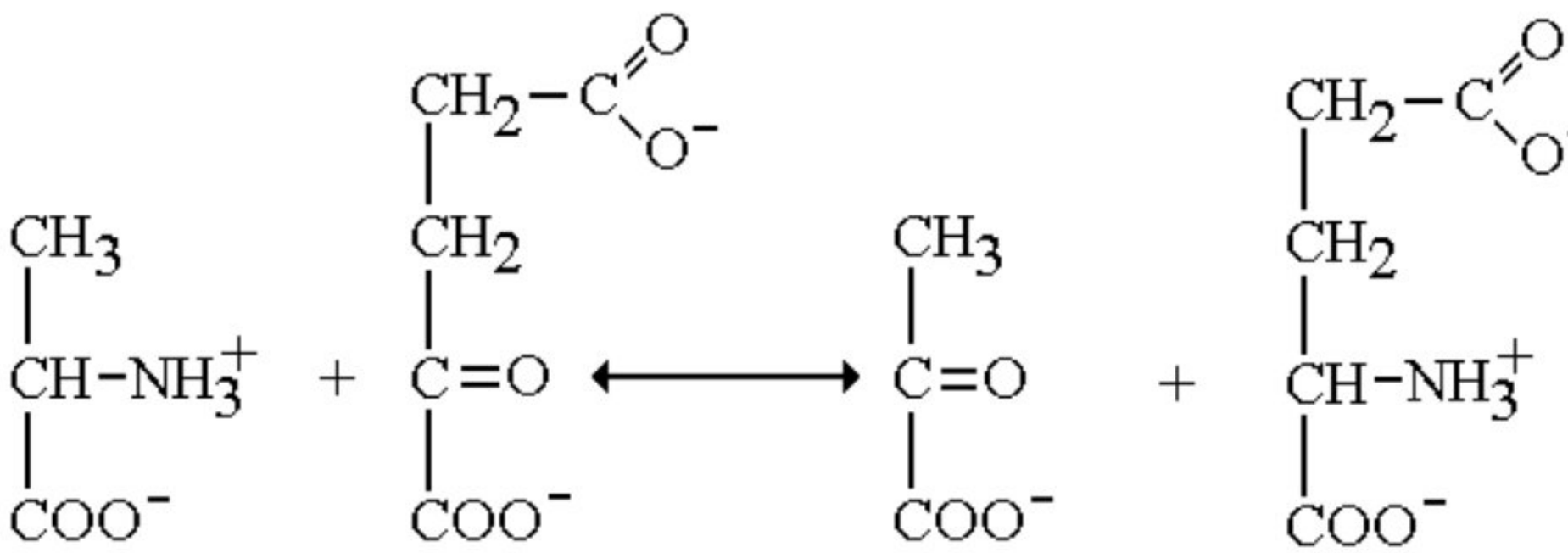
Glutamate is the most important, metabolically



Alanine Aspartate Glutamate Glutamine

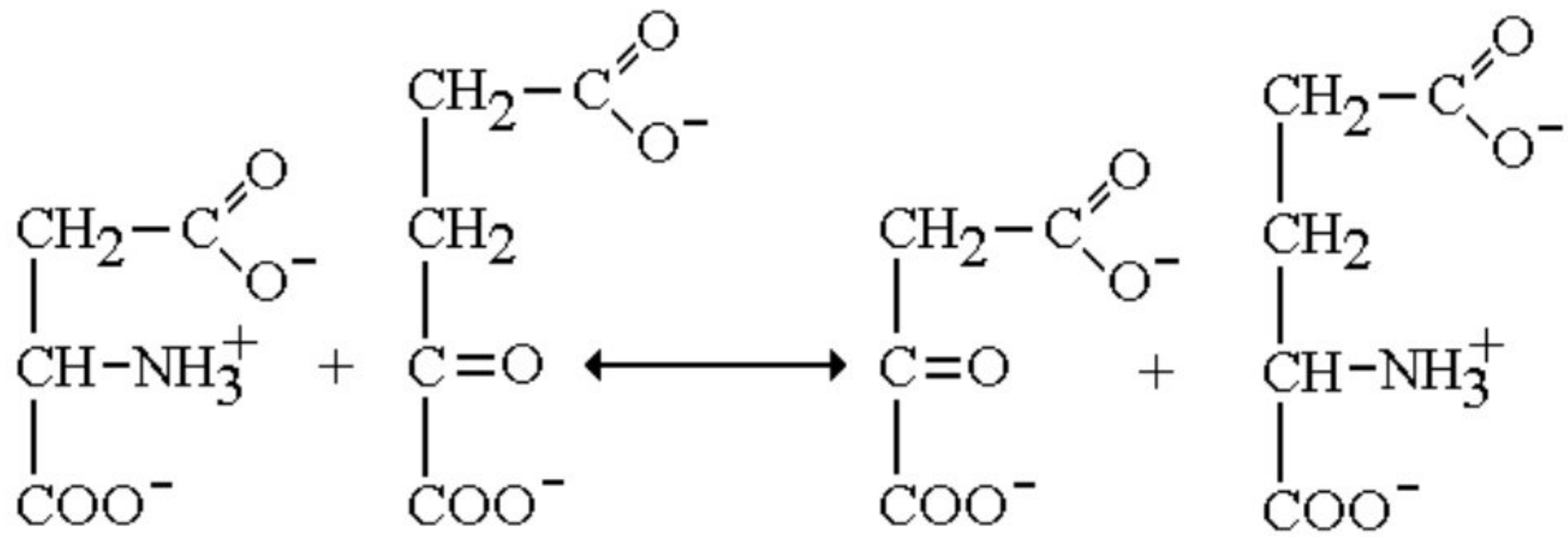
Some **transaminases** are used for diagnosing disorders:

enzyme **alanine aminotransferase**. Escapes in large amounts from dead or dying liver tissue. Measured in blood samples for diagnostic purposes.



Alanine Oxoglutarate Pyruvate Glutamate

Transaminase enzyme **aspartate aminotransferase** very active enzyme inside heart cells. Also escapes in large amounts from dead or dying heart tissues & enters bloodstream. Measured in blood for diagnosing myocardial infarction.



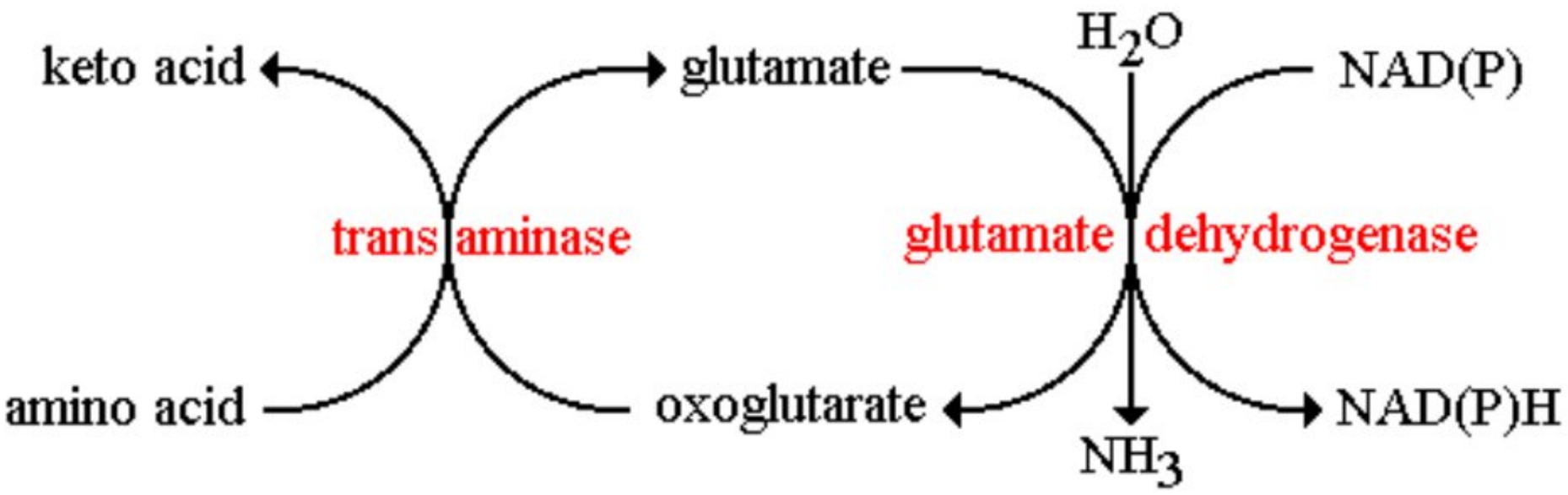
Aspartate Oxoglutarate Oxaloacetate Glutamate

Trans-deamination (sum it up)

Most **transaminases** share a common substrate and product (oxoglutarate and glutamate) with the enzyme **glutamate dehydrogenase**.

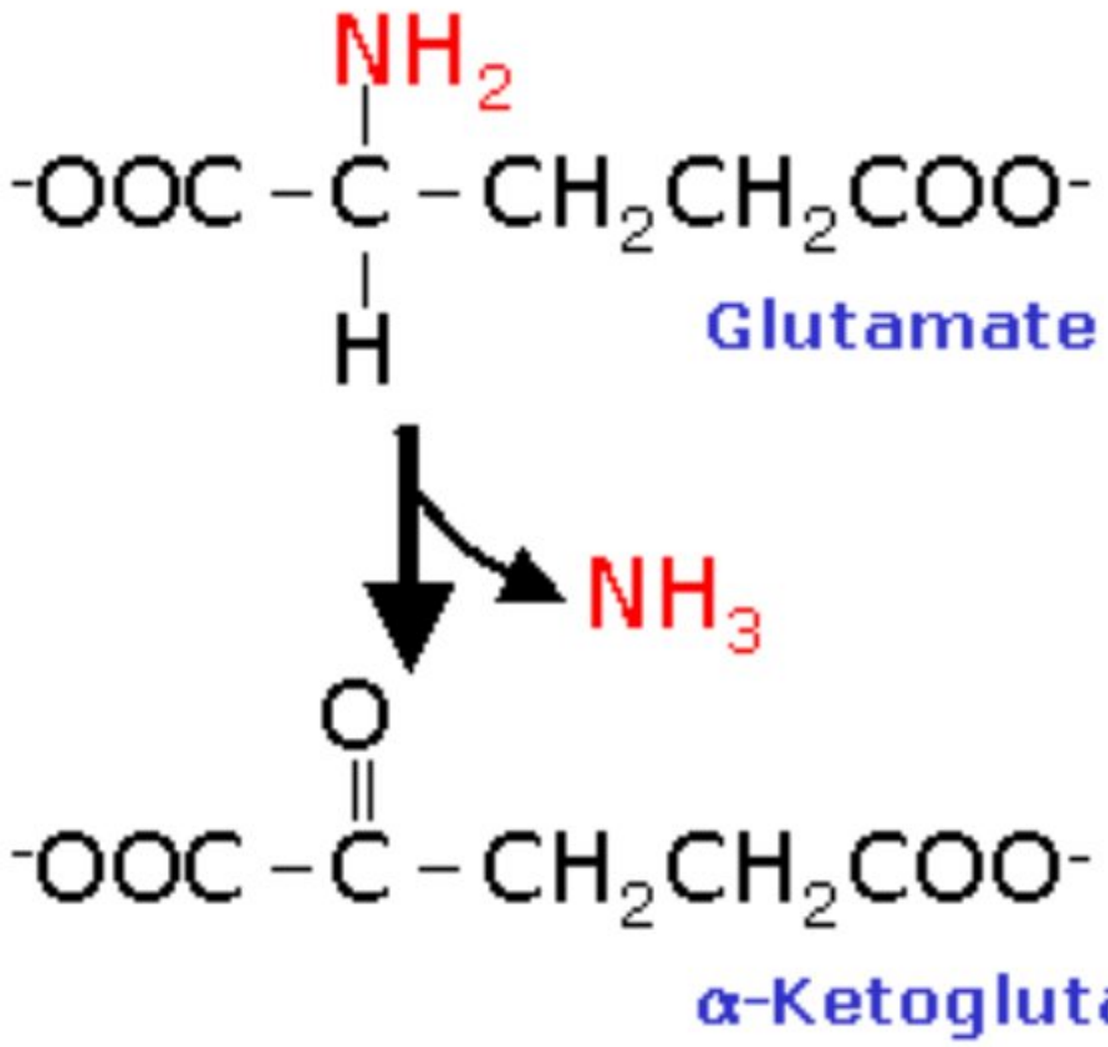
This permits a ***combined*** N excretion pathway for individual amino acids: "trans-deamination."

Glutamate has a central role in the overall control of nitrogen metabolism.



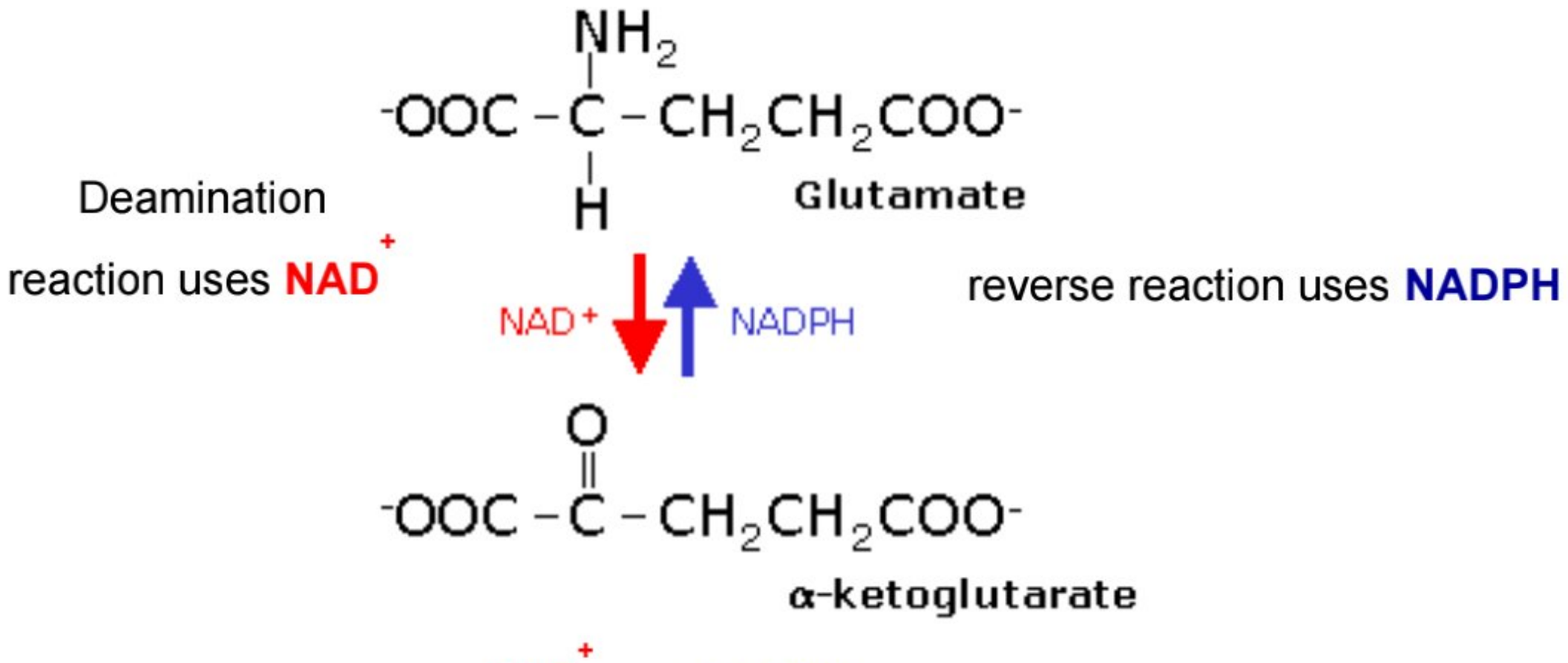
Oxidative Deamination

The **glutamate** produced from the transamination step is then deaminated by **oxidative deamination** using the enzyme **glutamate dehydrogenase**



Recycles back to a ketodiacid & releases ammonia

Glutamate dehydrogenase [GluDH] will reversibly convert **glutamate** to **a-ketoglutarate** and **a-ketoglutarate** to **glutamate**.



Uses ***both*** **NAD**$^+$ and **NADPH** – how to regulate it?

Urea cycle:

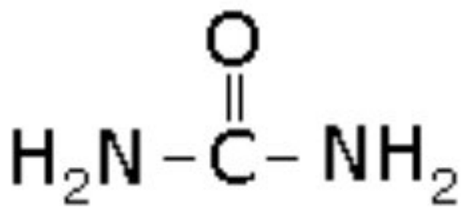
Ammonium salts (NH_4^+) are toxic compounds.

Oxidative deamination converting glutamate to a-ketoglutarate is an easily shifted equilibrium reaction.

Ammonium ions building up favors the synthesis of excessive amounts of glutamate, decreasing the Krebs cycle intermediate **a-ketoglutarate**.

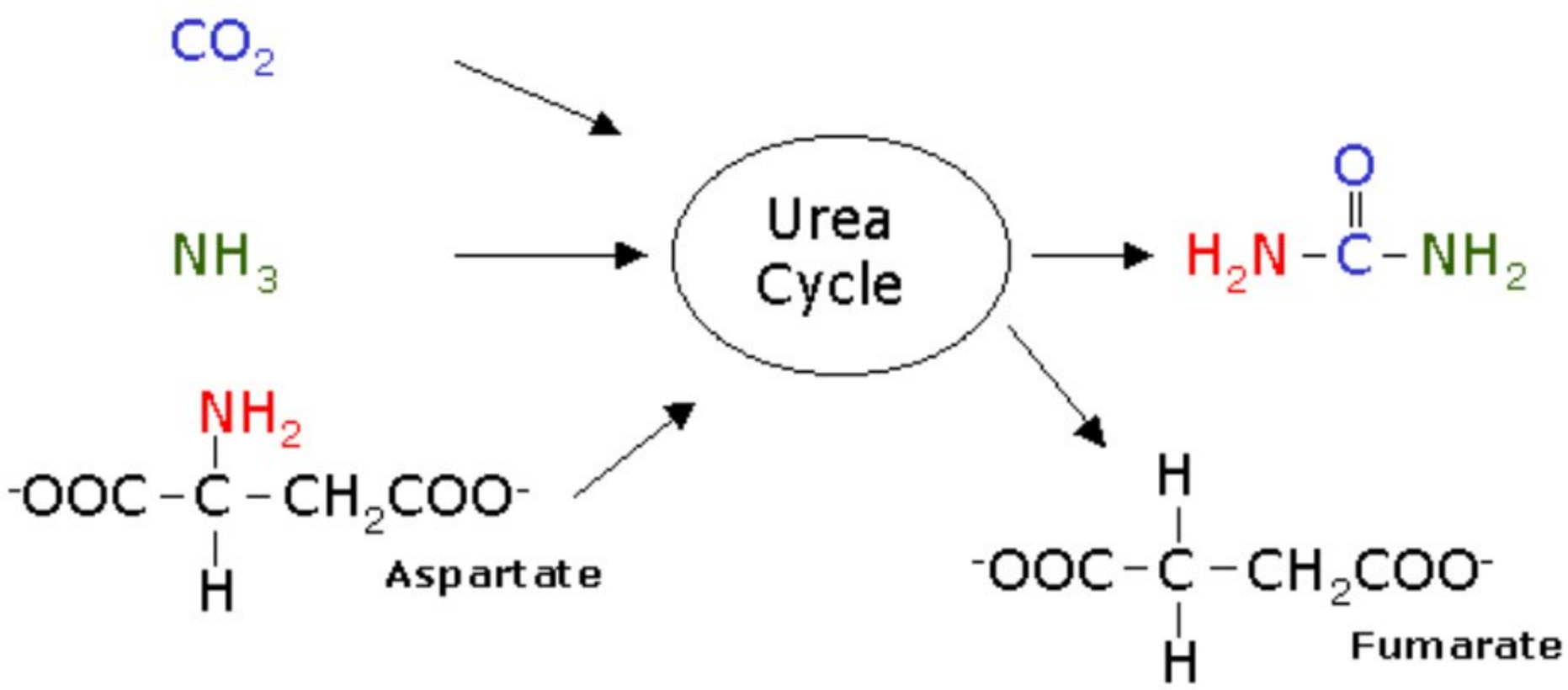
This in turn decreases **ATP production**, and that affects the nervous system.

The answer is Urea:

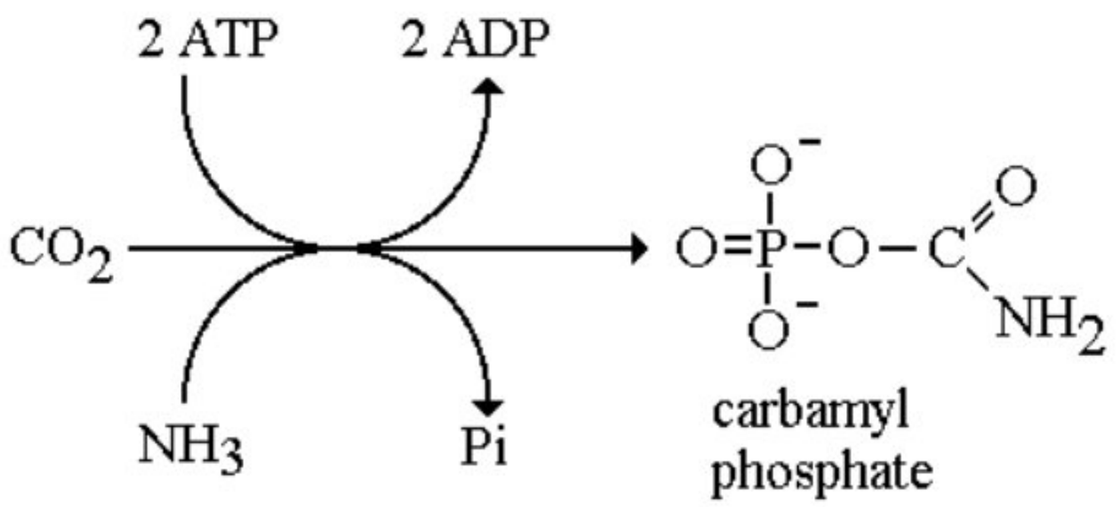


The **inputs** to the urea cycle are NH_3, CO_2 and aspartic acid and ATP.

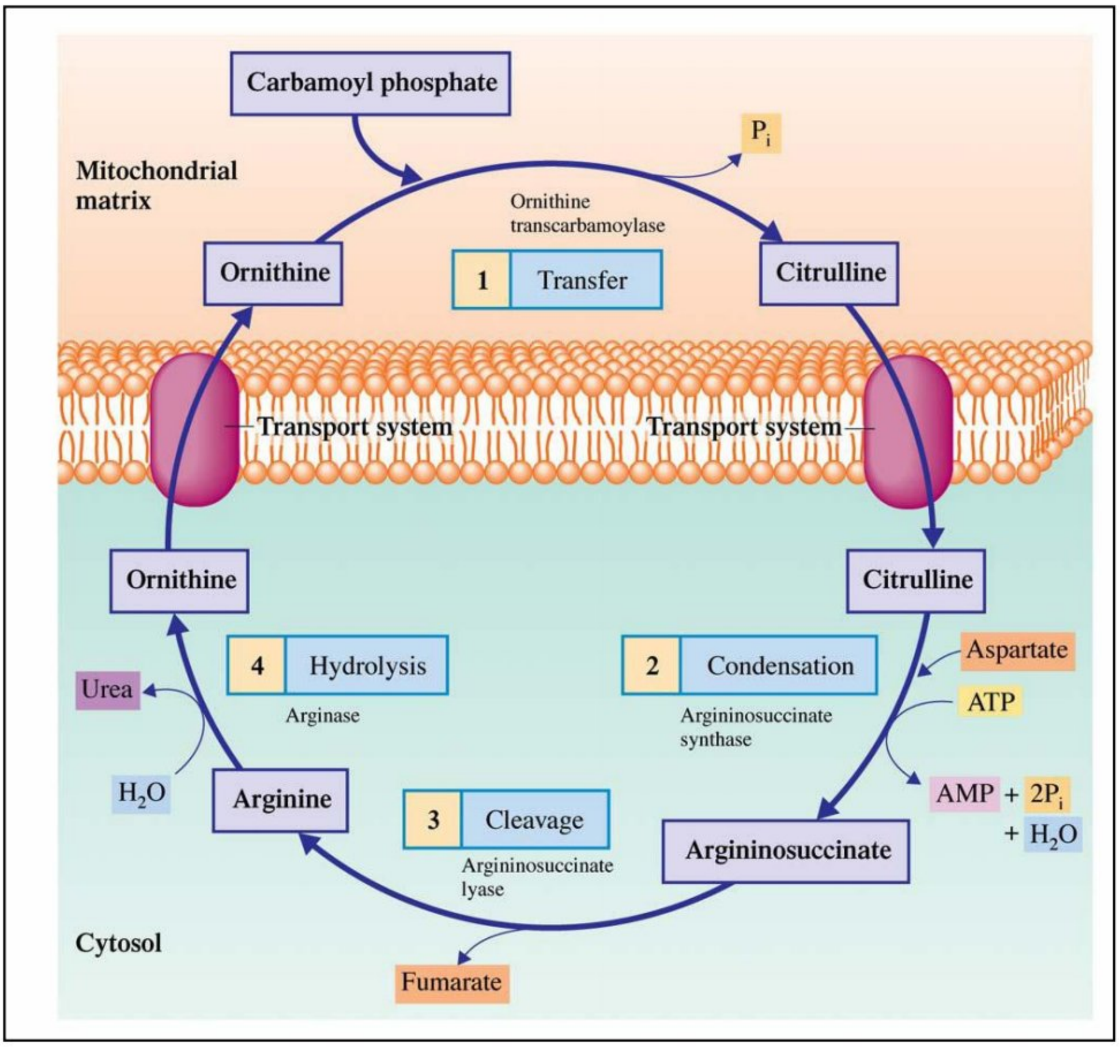
The **outputs** are urea, ADP and fumaric acid.



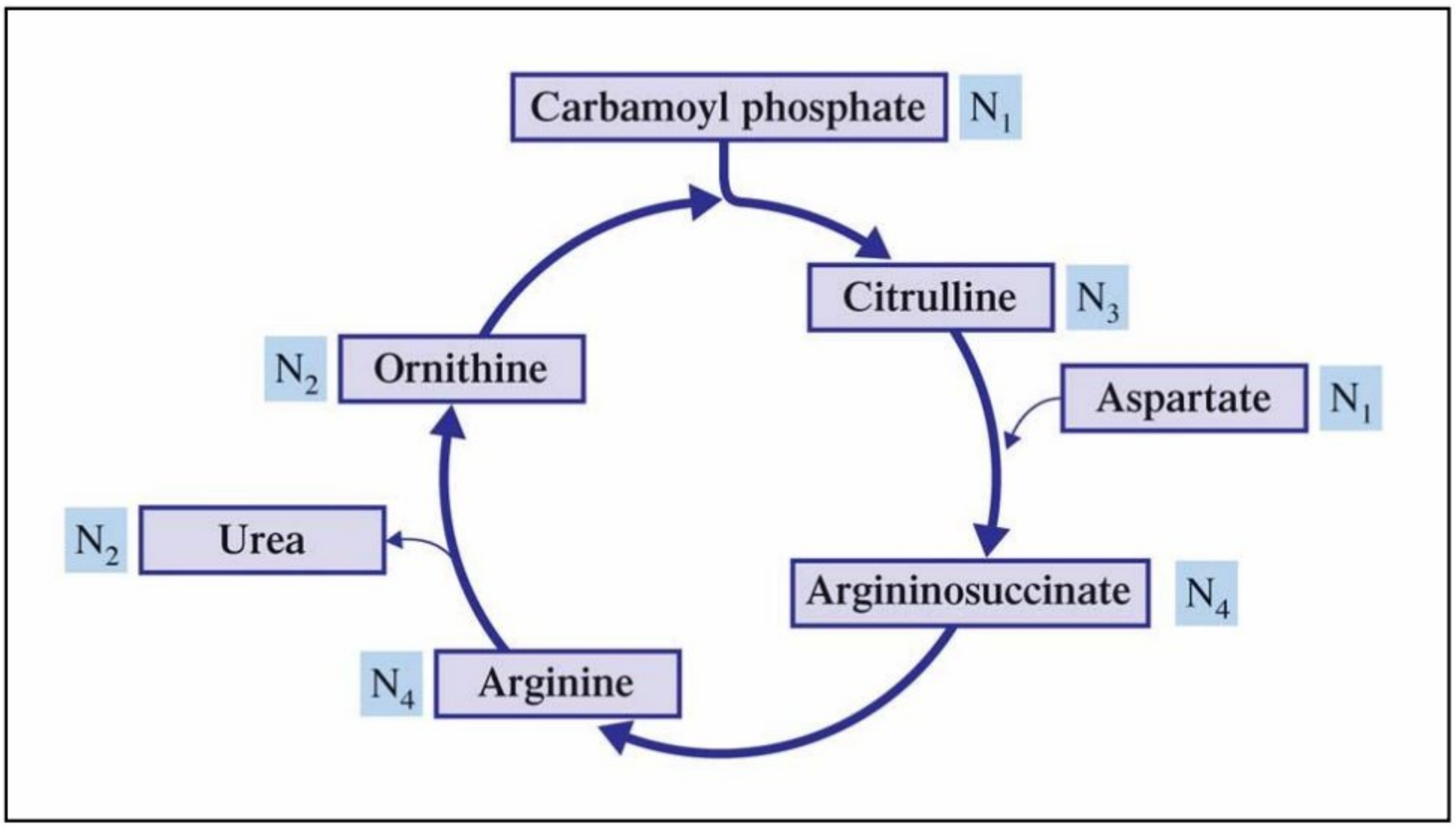
The carbonyl group of urea is derived from **CO_2** , **Ammonia** contributes one of the amine groups on urea



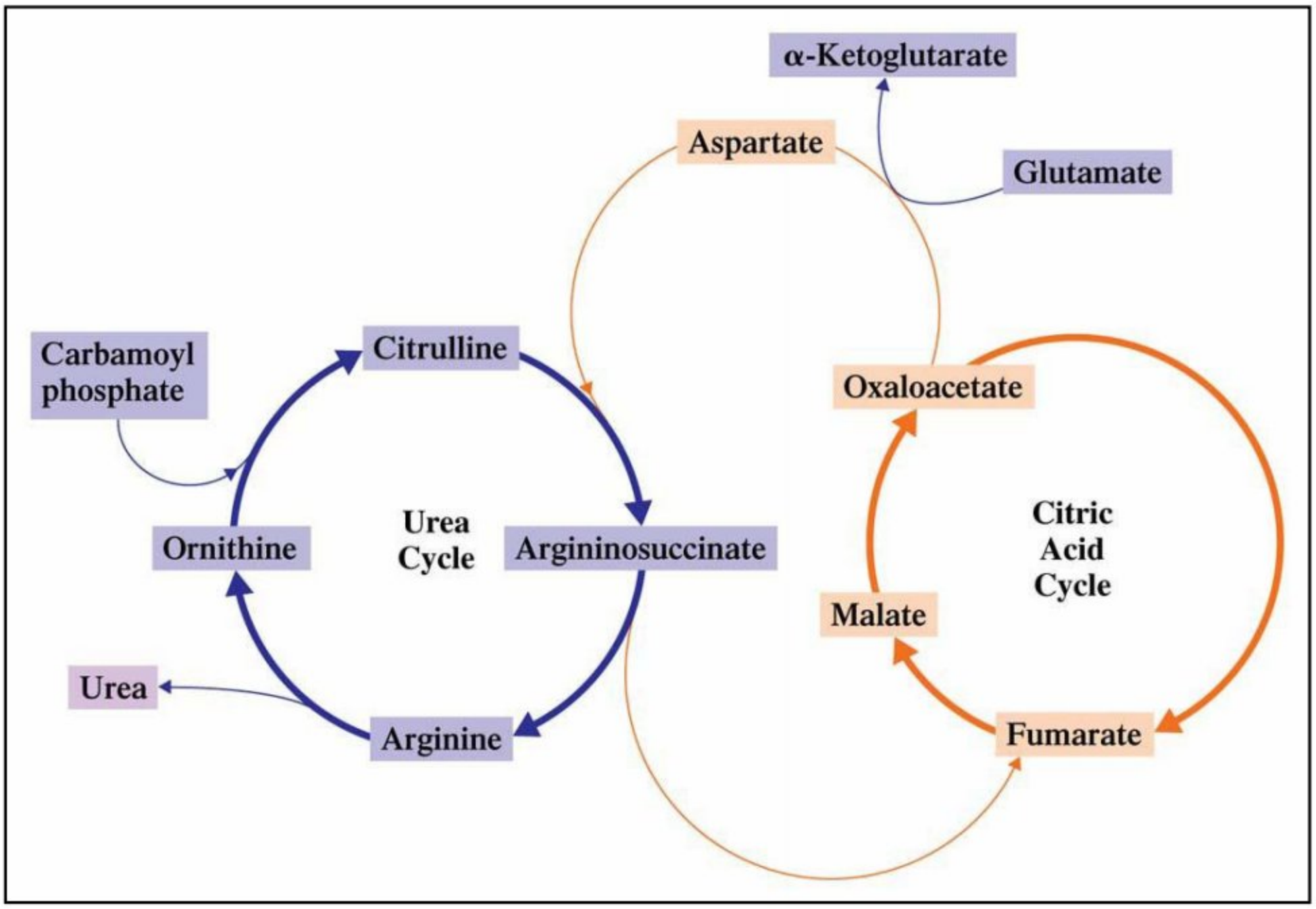
The **four-step** urea cycle in which **carbamoyl phosphate** is converted to **urea**.



The nitrogen content of the various compounds that participate in the urea cycle



Fumarate from the urea cycle enters the Krebs cycle. **Aspartate** produced from **oxaloacetate** of the Krebs cycle enters the urea cycle.



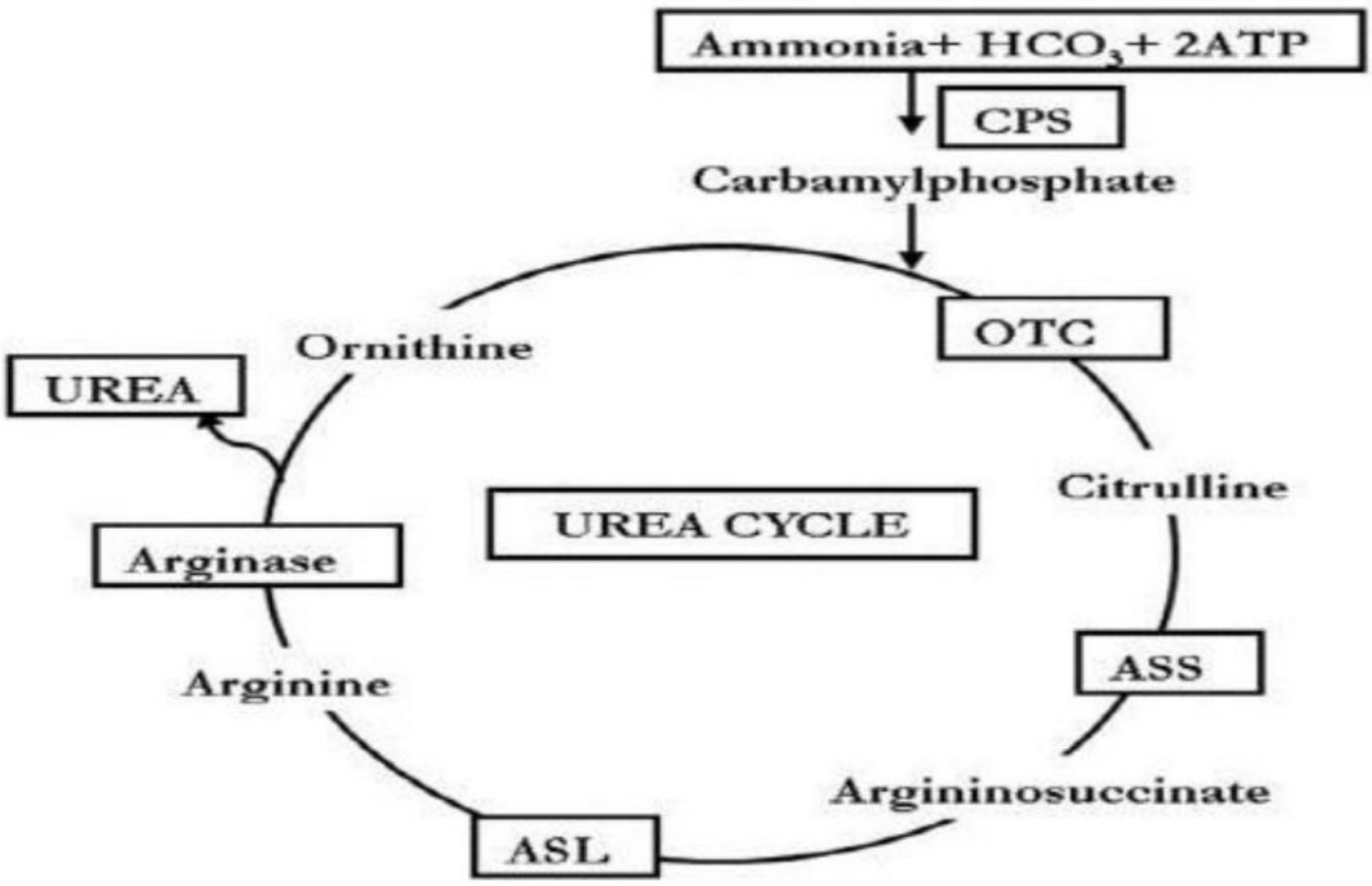
Oxaloacetate has 4 potential fates: transamination; conversion to glucose; formation of citrate; conversion to pyruvate

Summary:

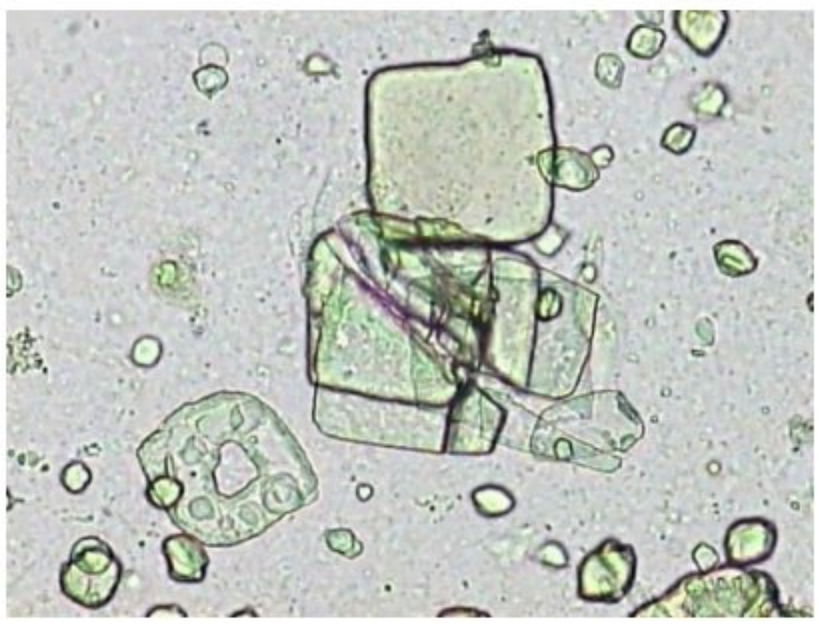
Transamination takes off amine groups from amino acids and forms **glutamate**
(ionized glutamic acid)

Amine groups form **ammonia** when removed in **deamination**
This combines with **CO_2** & **Aspartate**.

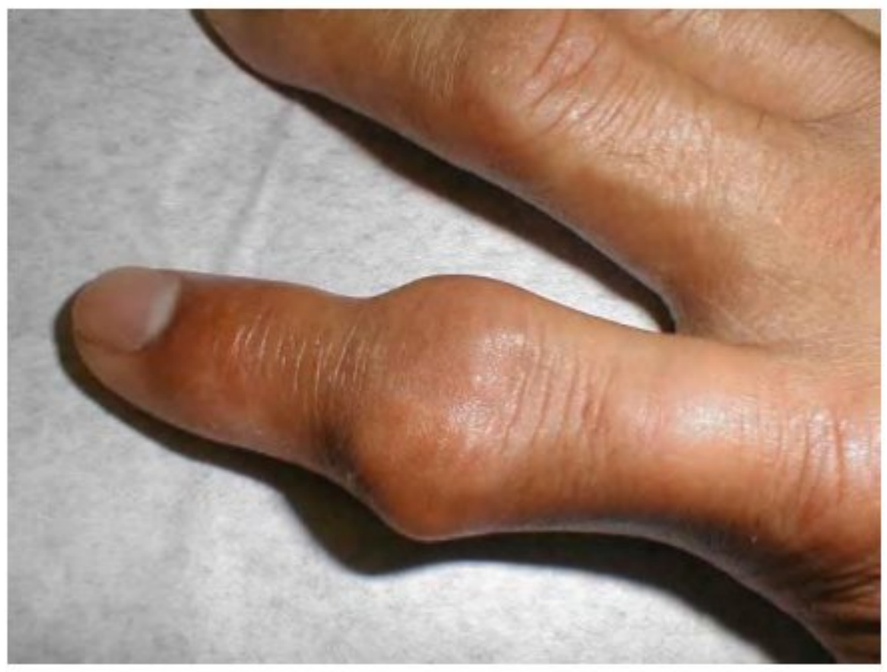
Forms **urea**, **Arginine**,
& **Fumarate**

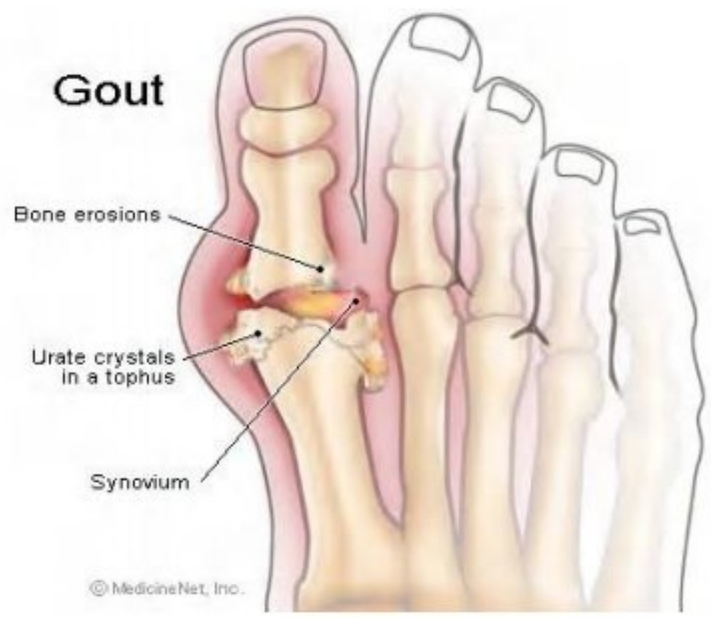


Reptiles & birds excrete **uric acid** – very ***insoluble*** purine compound – forms supersaturated solutions. Concentrated urine, supersaturated with uric acid, goes from cloaca into hindgut – uric acid crystalizes & water is reabsorbed.



In humans uric acid deposits crystals & causes gout





Processing Amino Acid Carbon Skeletons

Transamination or Oxidative deamination both produce a-keto acids

Degradation of these carbon skeletons may take several different pathways:

Amino acid C skeletons that degrade to form a Krebs cycle intermediate can then be used to make glucose via **gluconeogenesis**.

These are called **Glucogenic Amino Acids**.

Amino acid C skeletons that degrade to form **Acetoacetyl CoA** or **acetyl CoA** can form fatty acids or ketone bodies.

These are called **Ketogenic Amino Acids**.

Amino Acid Biosynthesis

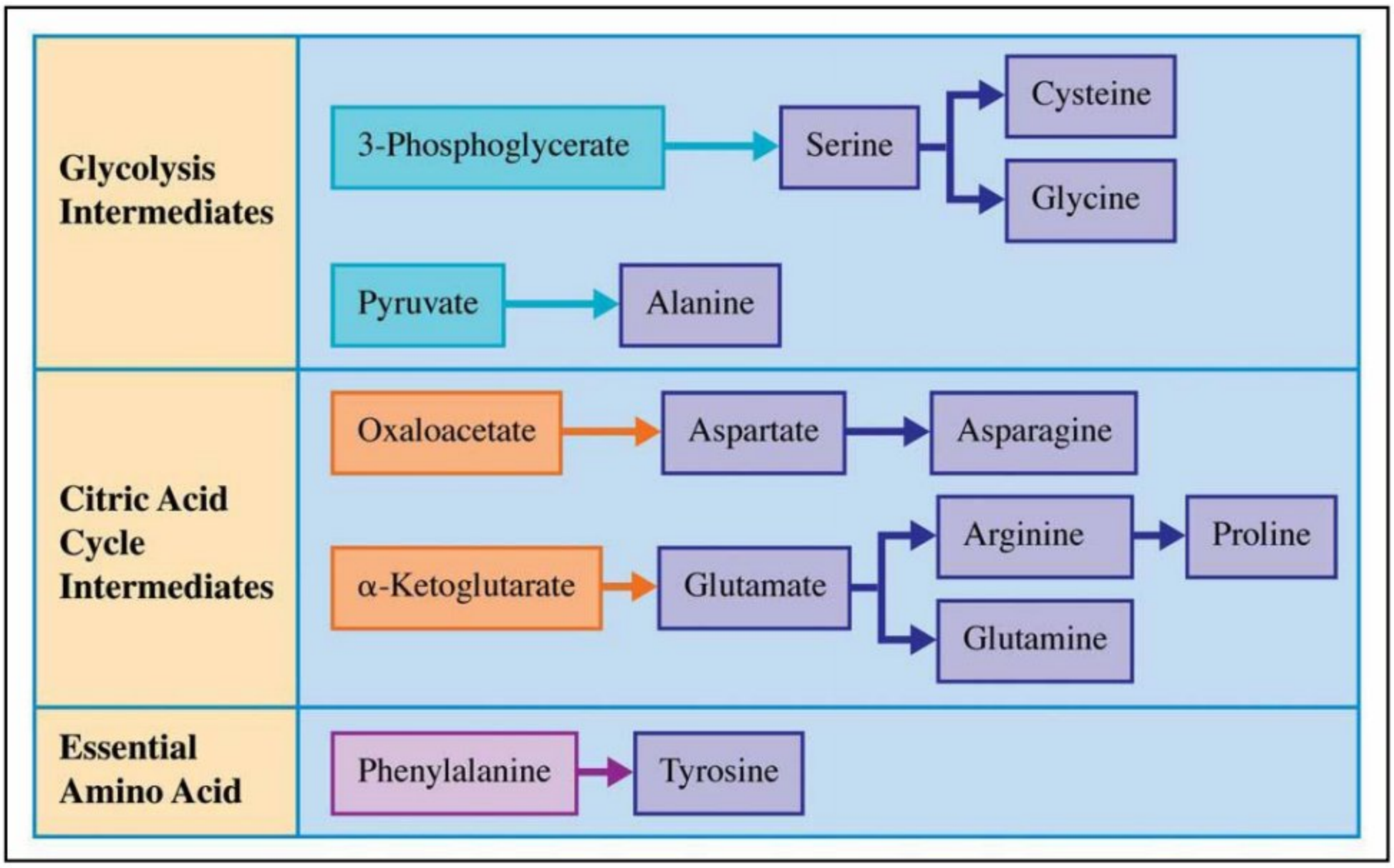
Essential amino acids can be made by plants & bacteria in 7 to 10 steps.

We obtain these amino acids by eating plants.11 Non-essential amino acids synthesized in 1 to 3 steps. Use glycolysis intermediates:

3-phosphoglycerate & pyruvate Krebs cycle intermediates:

Oxaloacetate & **a-ketoglutarate**.

Starting materials for biosynthesis of 11 **nonessential** amino acids: 1 step, 2 steps, or 3 steps



Alanine, aspartate, & glutamate use transamination

Phenylketonuria (PKU):

Defective phenylalanine hydroxylase – **phenylalanine** accumulates in body. Phenylalanine is transaminated to **phenylpyruvate**.

Accumulation of phenylpyruvate leads to severe mental retardation in infants. Persons suffering from phenylketonuria should not consume foods containing high levels of phenylalanine, such as aspartame.

Hemoglobin catabolism

Red blood cells contain oxygen carrying pigments of a conjugated protein: Protein part is ***Globin*** Non-protein prosthetic group is ***Heme***. **Heme** contains four pyrrole (**tetrapyrrole**) groups held together by an **iron** atom. Old red blood cells degraded in the spleen. Globin is hydrolyzed into amino acids. Iron atom stored in a protein (***ferritin***) **Tetrapyrrole** degraded to **bile pigments**.

Review: can you…

- Describe the steps in Protein digestion & absorption
- Explain how Amino Acids are utilized in the body
- Explain **Transamination** and **Oxidative De-amination**
- Describe **The Urea Cycle** – purpose and steps
- Describe how a.a. Carbon Skeletons are processed
- Define and explain Amino Acid Biosynthesis.
- Describe the chemical composition of urine.

Lipid Metabolism

Fatty acids (F.A.s) are taken up by cells.

They may serve as:

- precursors in synthesis of other compounds
- fuels for energy production
- substrates for ketone body synthesis.

Ketone bodies may be exported to other tissues: used for **energy production**. Some cells **synthesize fatty acids** for storage or export.

Energy

Fats are an important source of calories. Typically 30-40% of calories in American diet are from **fat**. Fat is the major form of **energy storage**.

Typical body fuel *reserves* are:

fat: **100,000 kcal.**

protein: **25,000 kcal**.

carbohydrate: **650 kcal**.

Provides 60% of energy needs for body at restTAG reserves would enable someone to survive starvation for ~30 days.

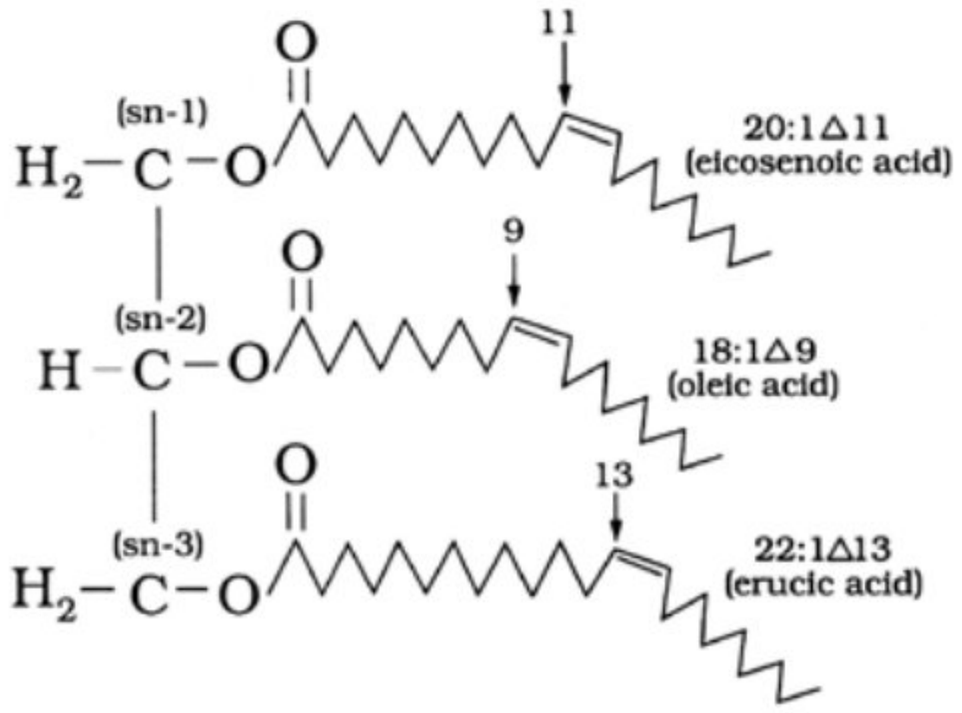
Digestion and Absorption of Lipids

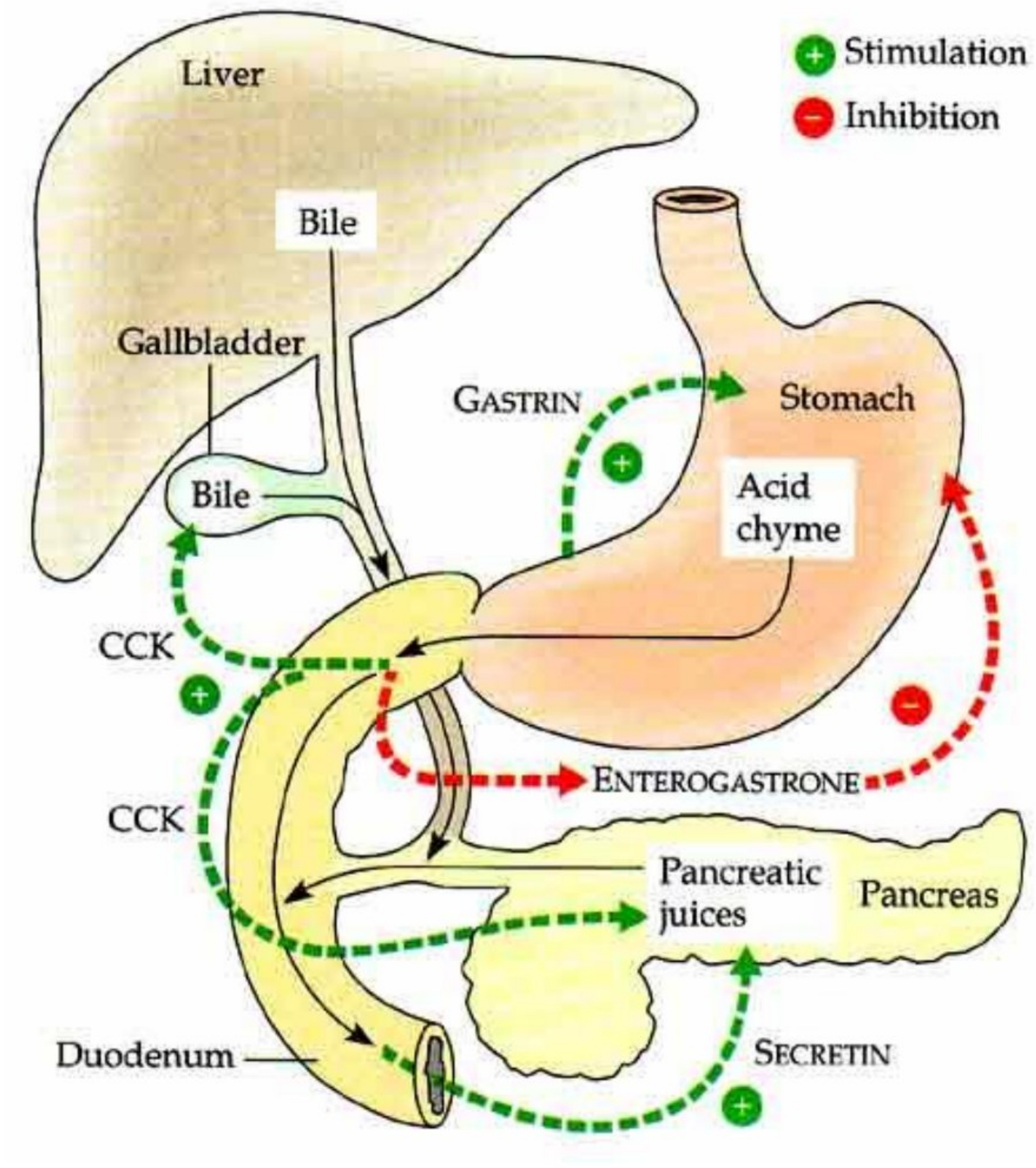
- 98% of ingested lipids are triacylglycerols (TAGs)
- Digestion in the Mouth: enzymes are **aqueous**-little effect on lipids
- Digestion in the Stomach:causes a large ***physical*** change-

  Churned into droplets:

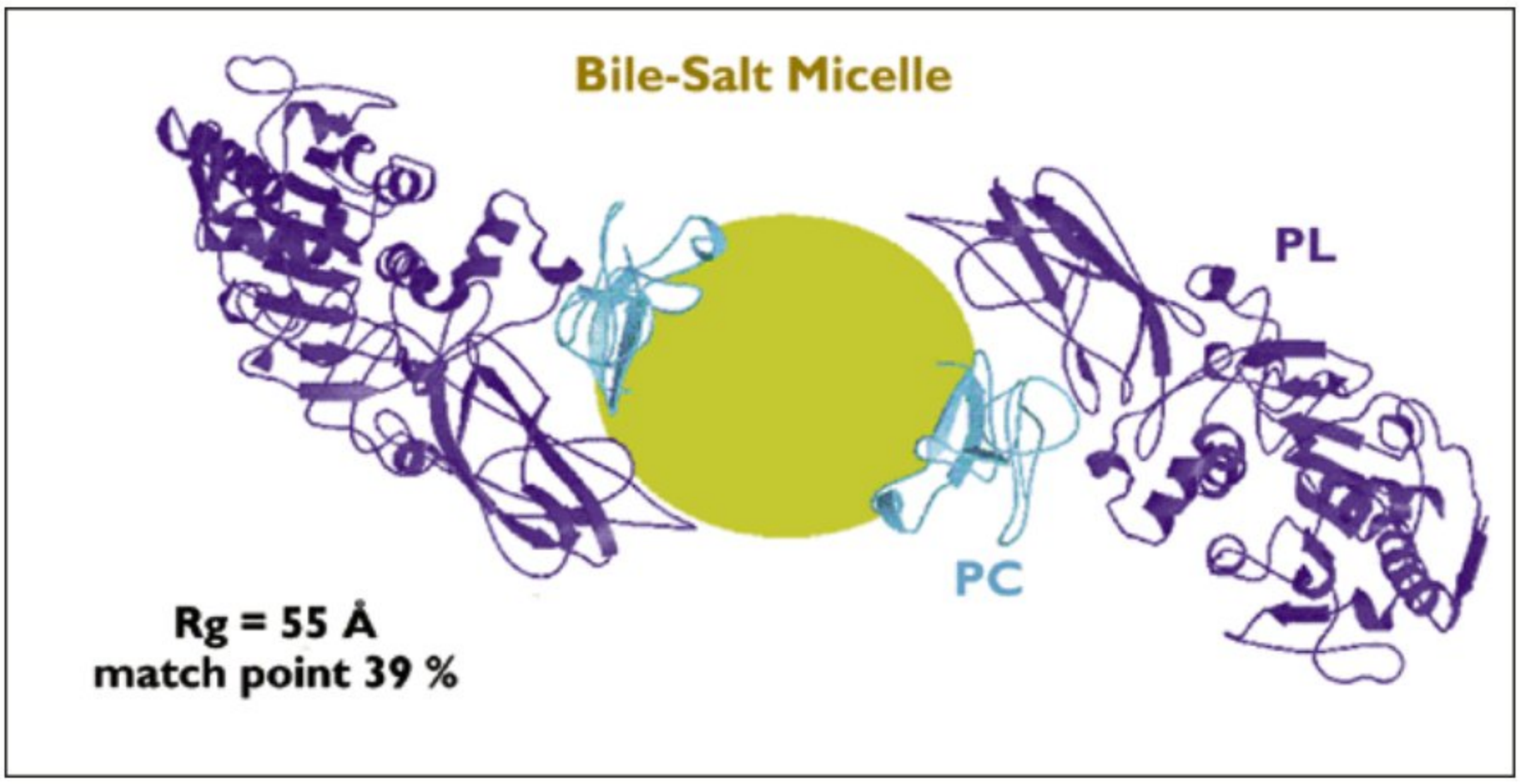
  "Chyme"

TRIACYLGLYCEROL



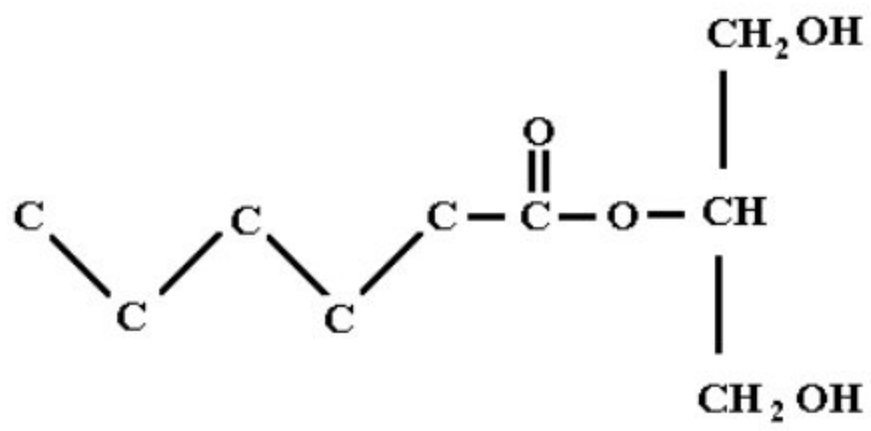


Gastric Lipase: Begins actual lipid digestion.~10% of TAGs are hydrolyzed in the **stomach**.Chyme stimulates **cholecystokinin** (CCK) to release **bile** from gallbladder.Bile is an emulsifier

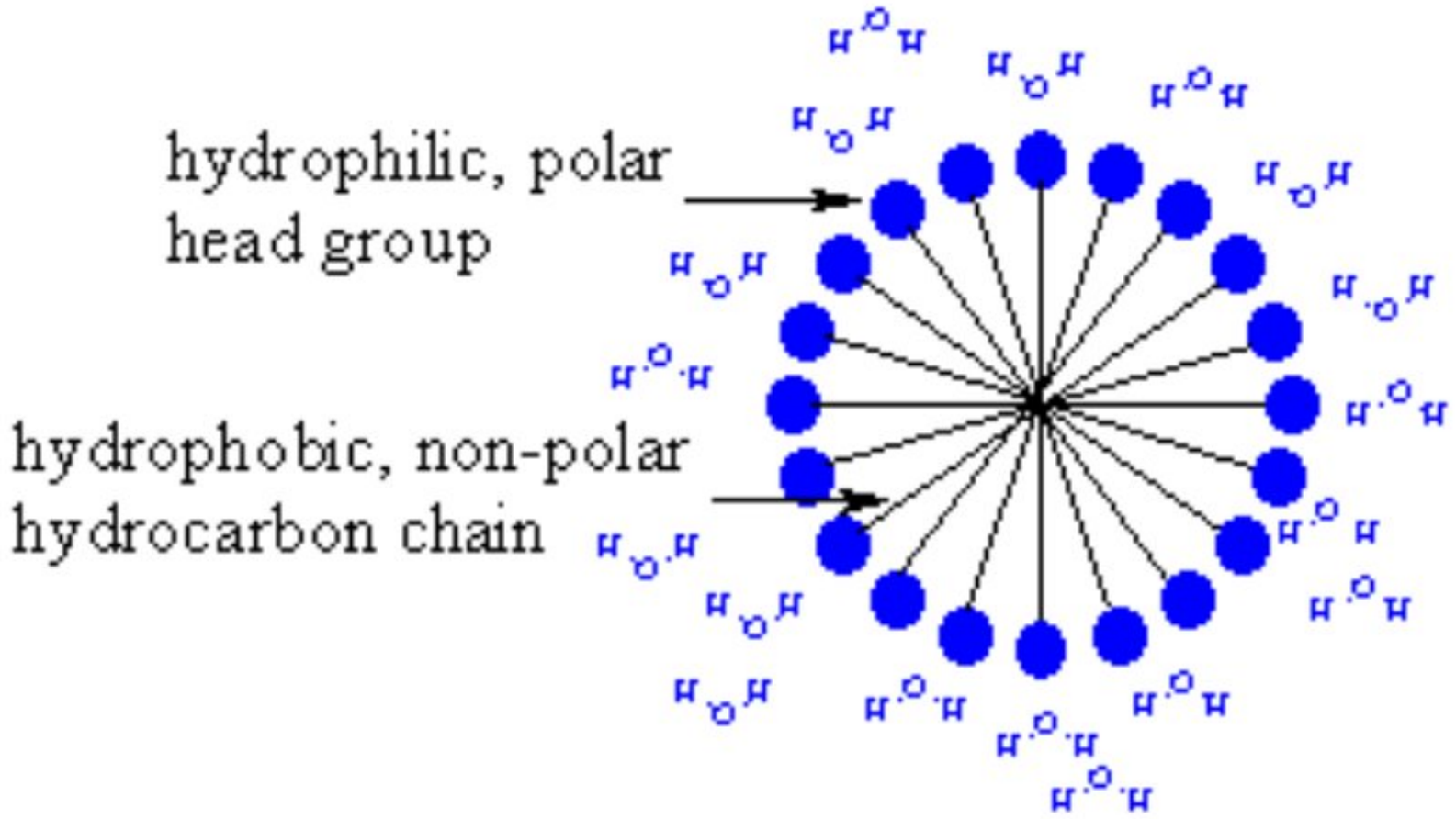


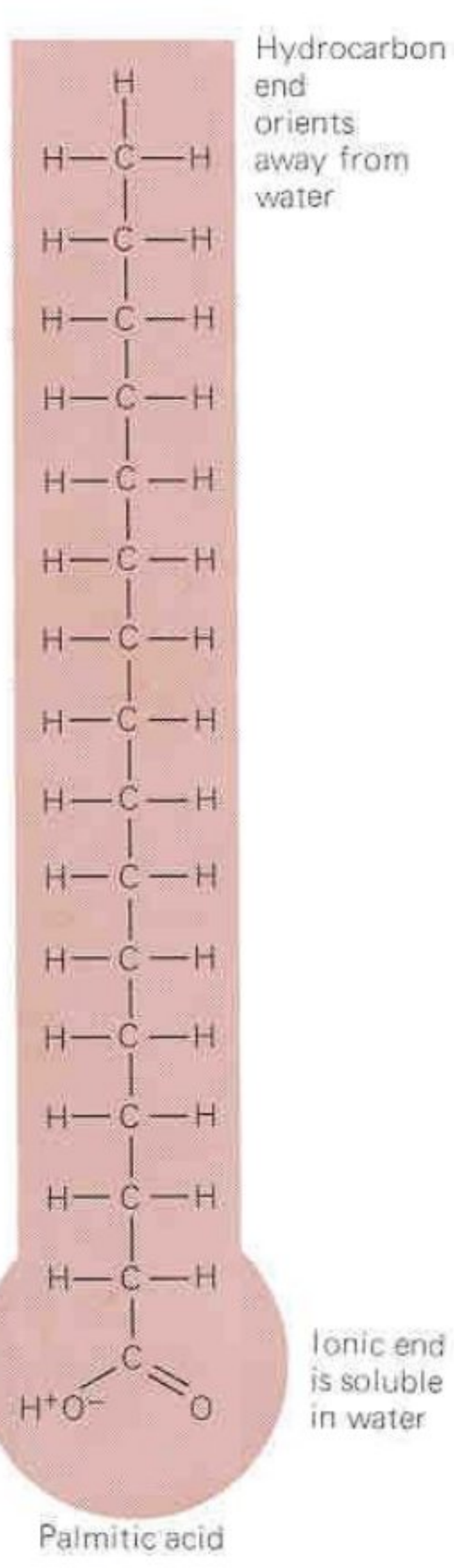
Pancreatic lipase (PL) hydrolyzes insoluble triglyceride by binding to the **bile-salt micelles**TAGs are ***partially*** hydrolyzed: 2 of the 3 F.A.s have ester linkages hydrolyzed and are released.

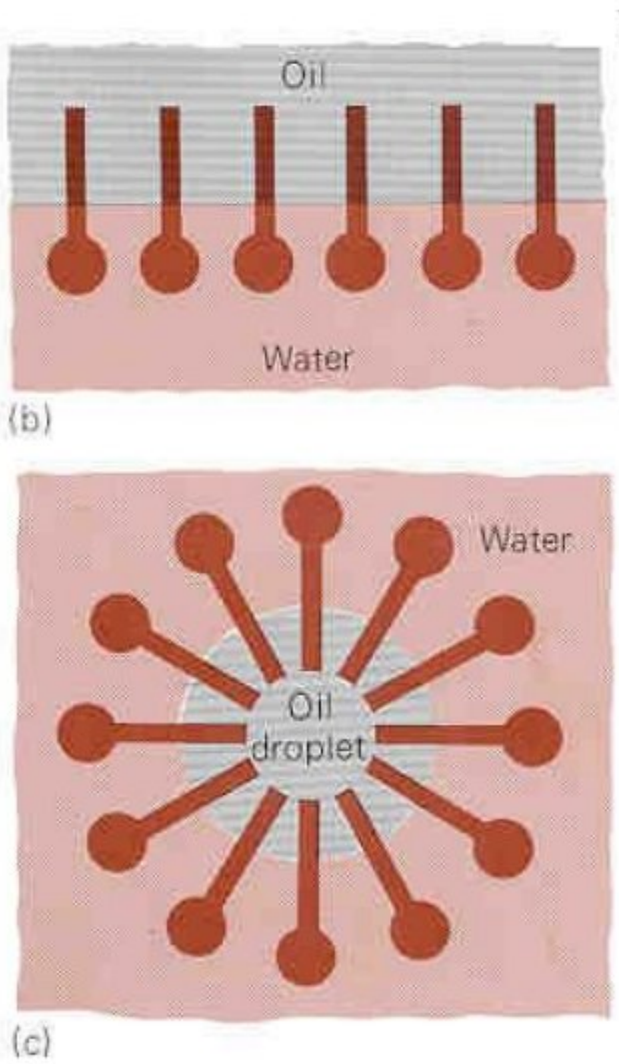
Monoacylglycerol remains = glycerol and 1 fatty acid



Oil droplets will form spherical **micelle** shapes.Bile salts aid this process clumping fatty acids and monacylglycerols.

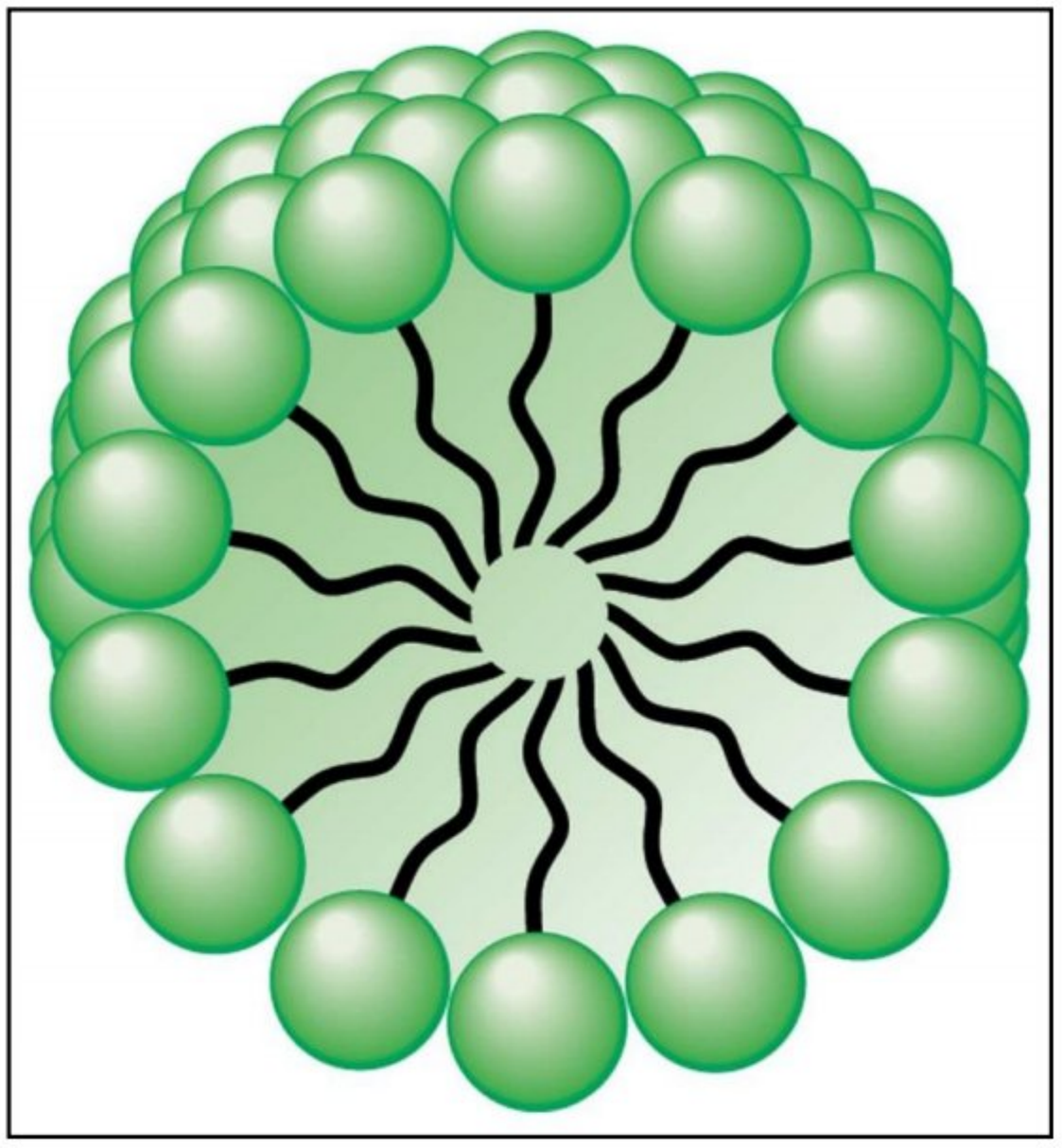






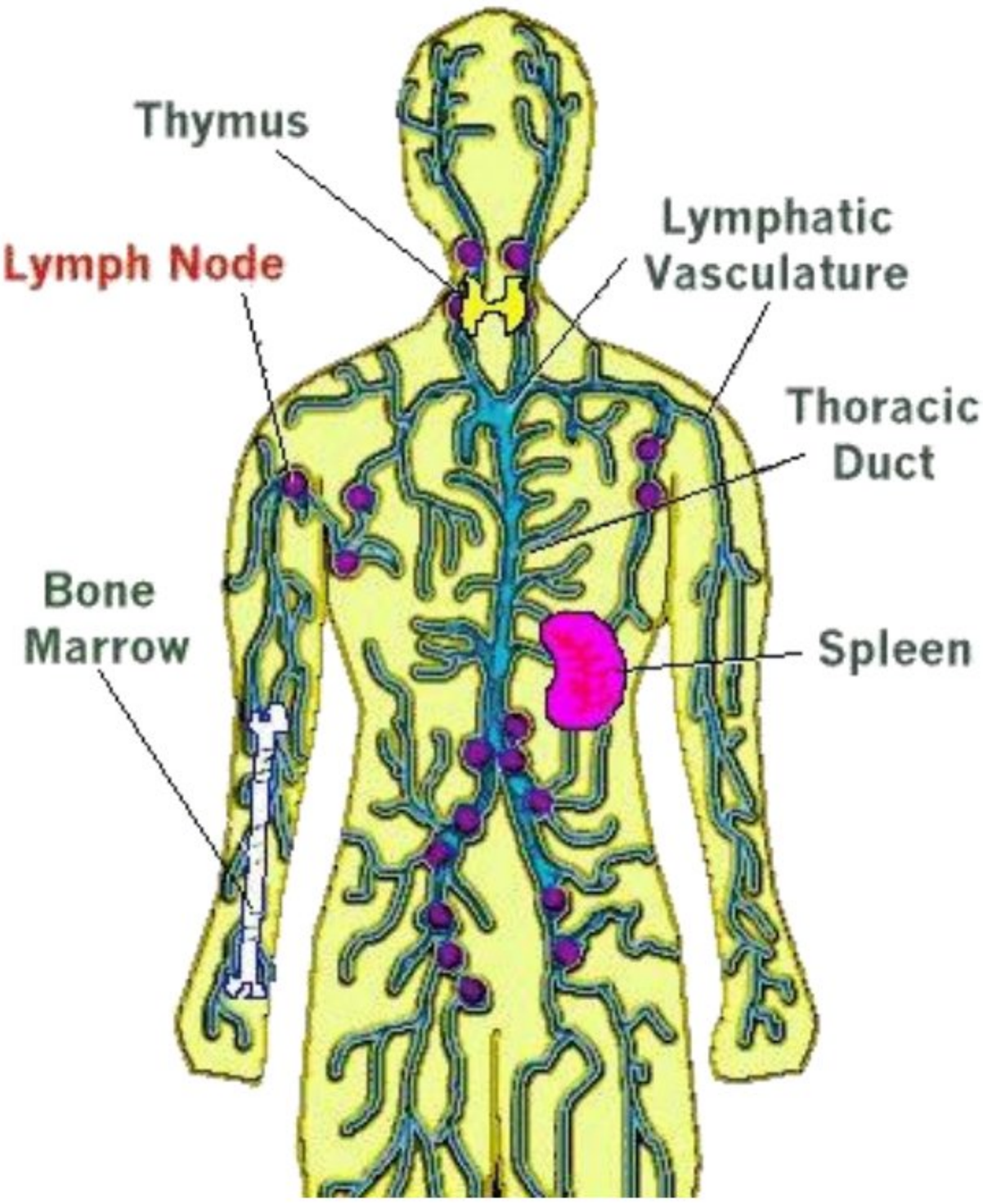
Fatty acid micelle: **hydrophobic** fatty acids & monoacylglycerols are in the interior. Bile salts on exterior.

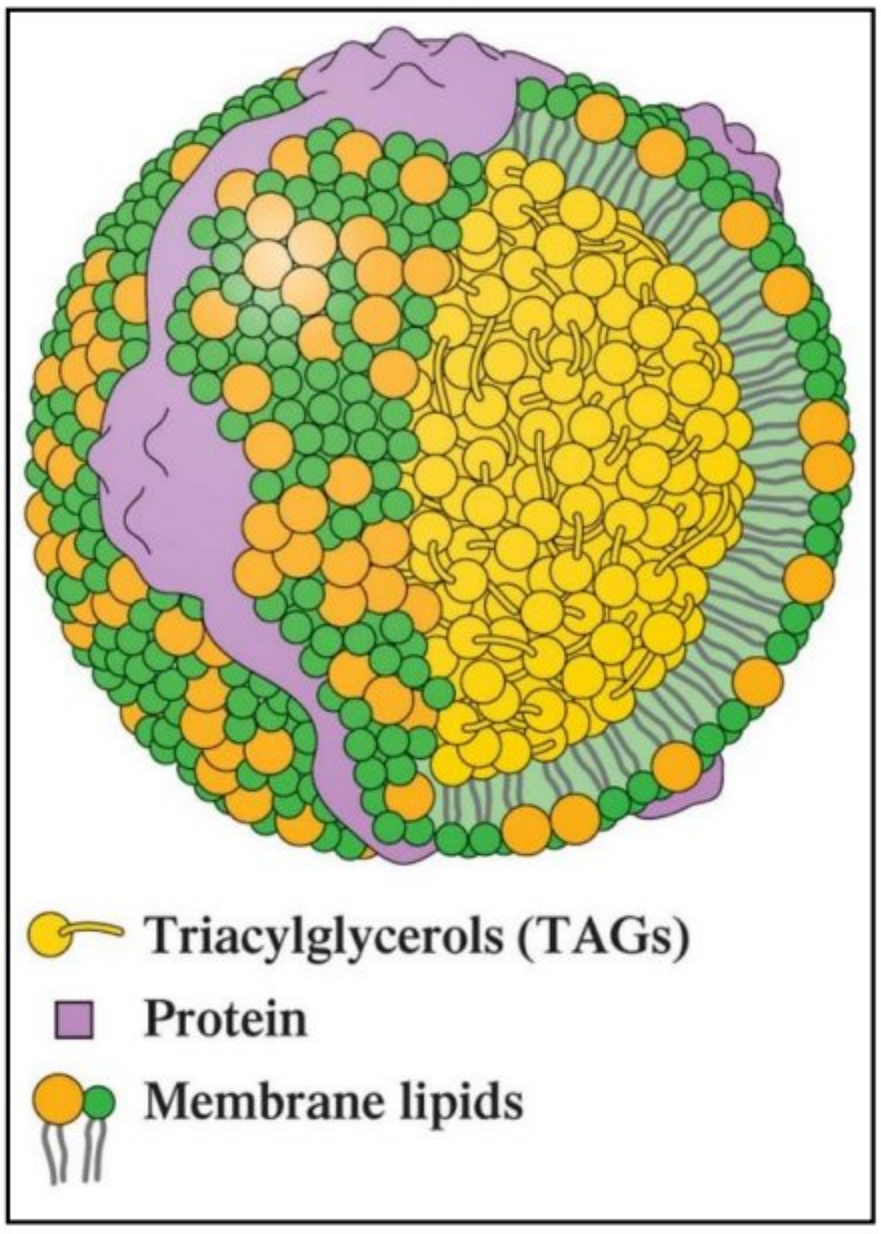
Micelles are small enough to penetrate membrane of intestinal cells.
Free fatty acids & monoacylglycerols are reformed into **triacylglycerols**.



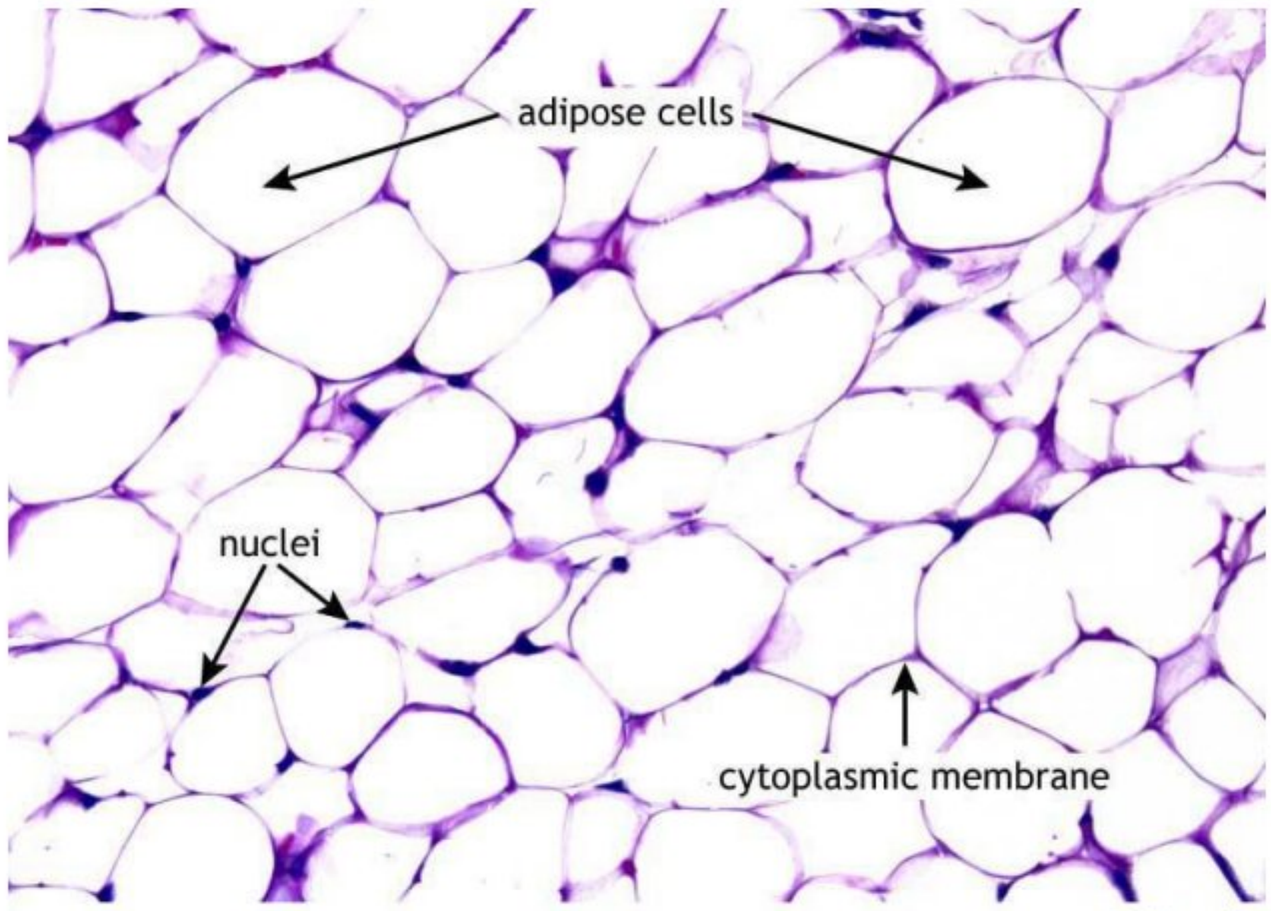
TAGs are combined with membrane & water soluble proteins to form a **chylomicron**, a lipoprotein.

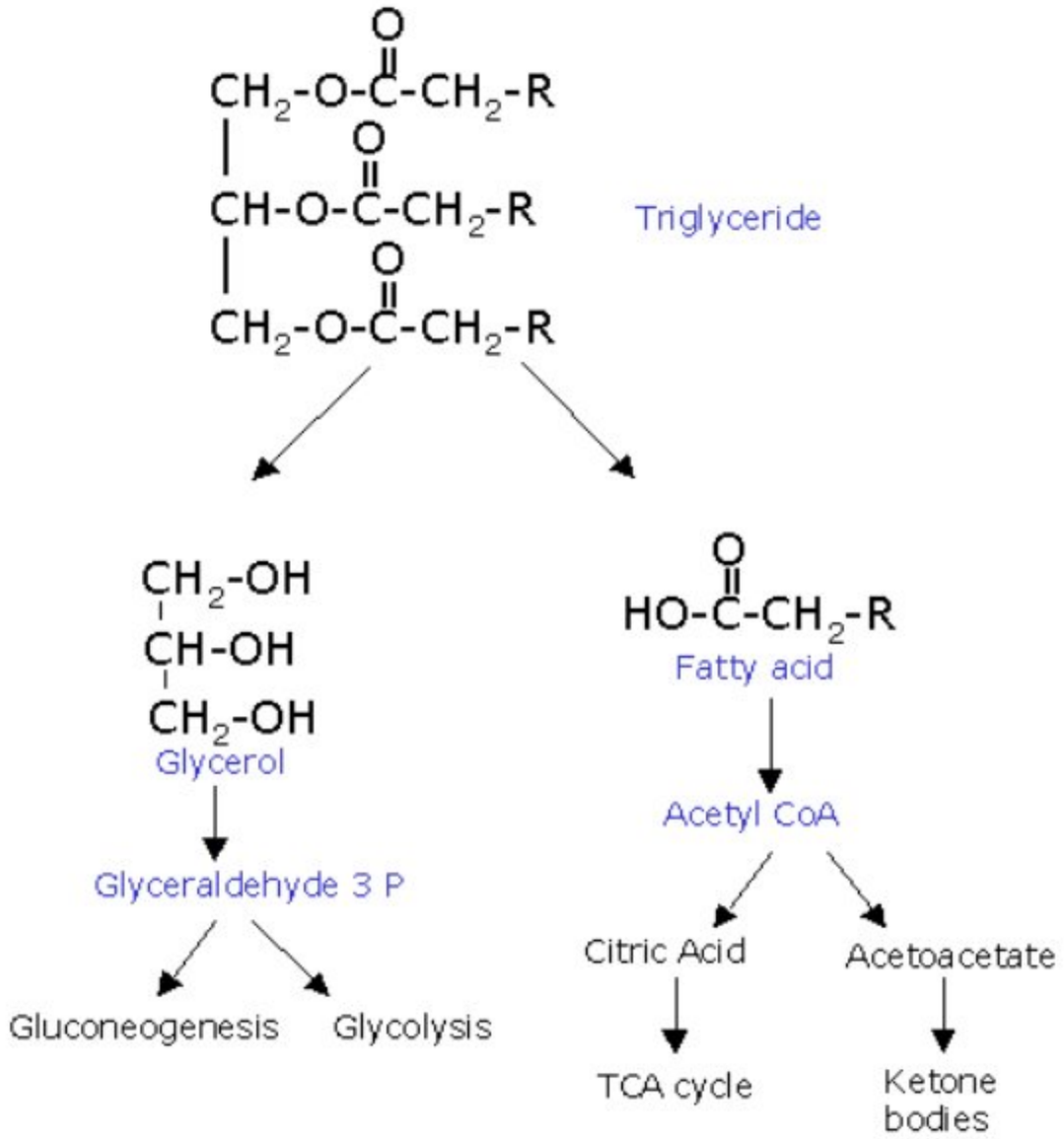
Chylomicrons carry TAGs from intestinal cells into bloodstream via the **lymph system**.



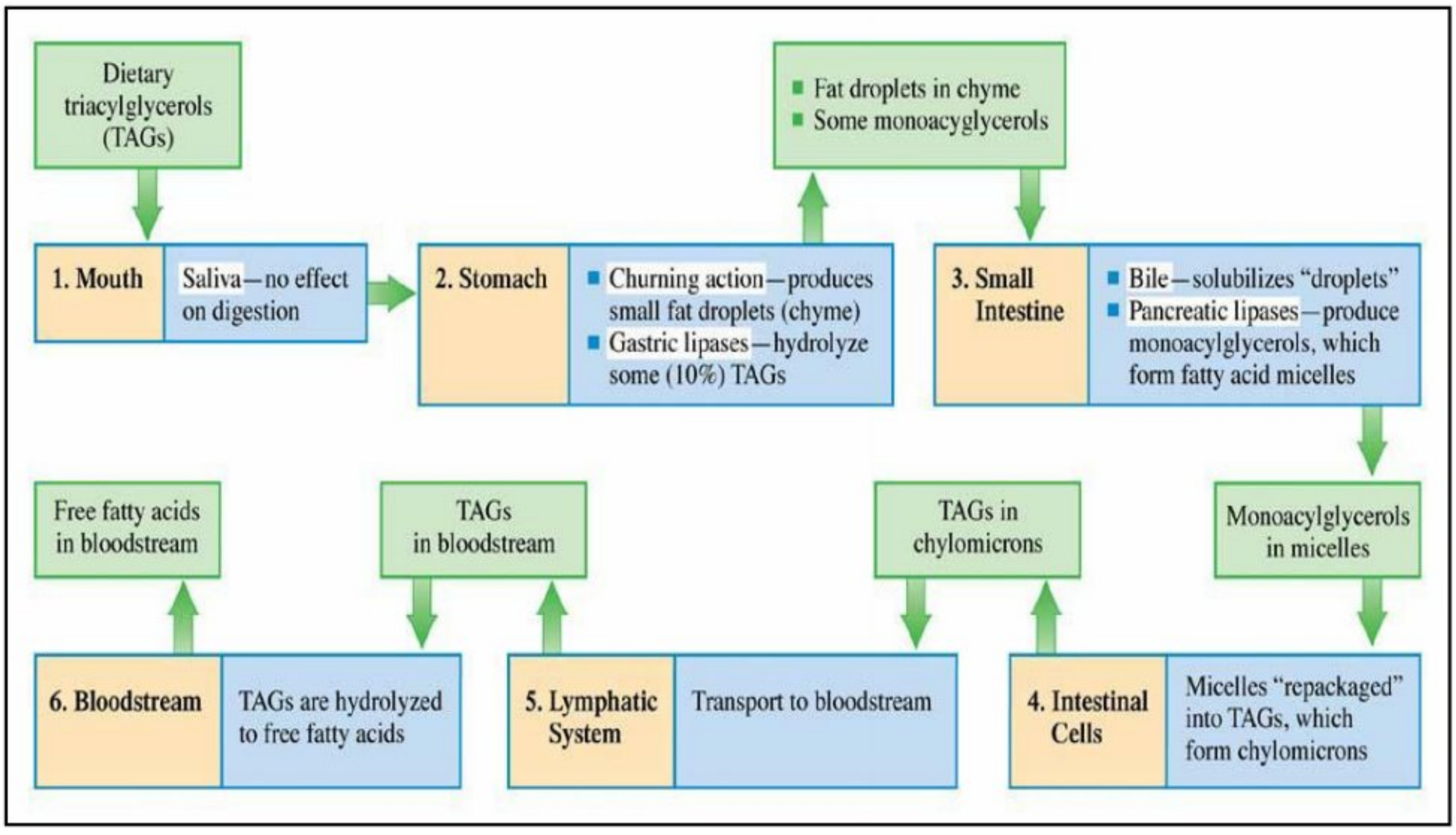


Triacylglycerols reach bloodstream & are hydrolyzed down to **glycerol** and **fatty acids**.These are absorbed by cells and processed further for energy by forming **acetyl CoA**. Or Stored as lipids in fat cells (adipose tissue.



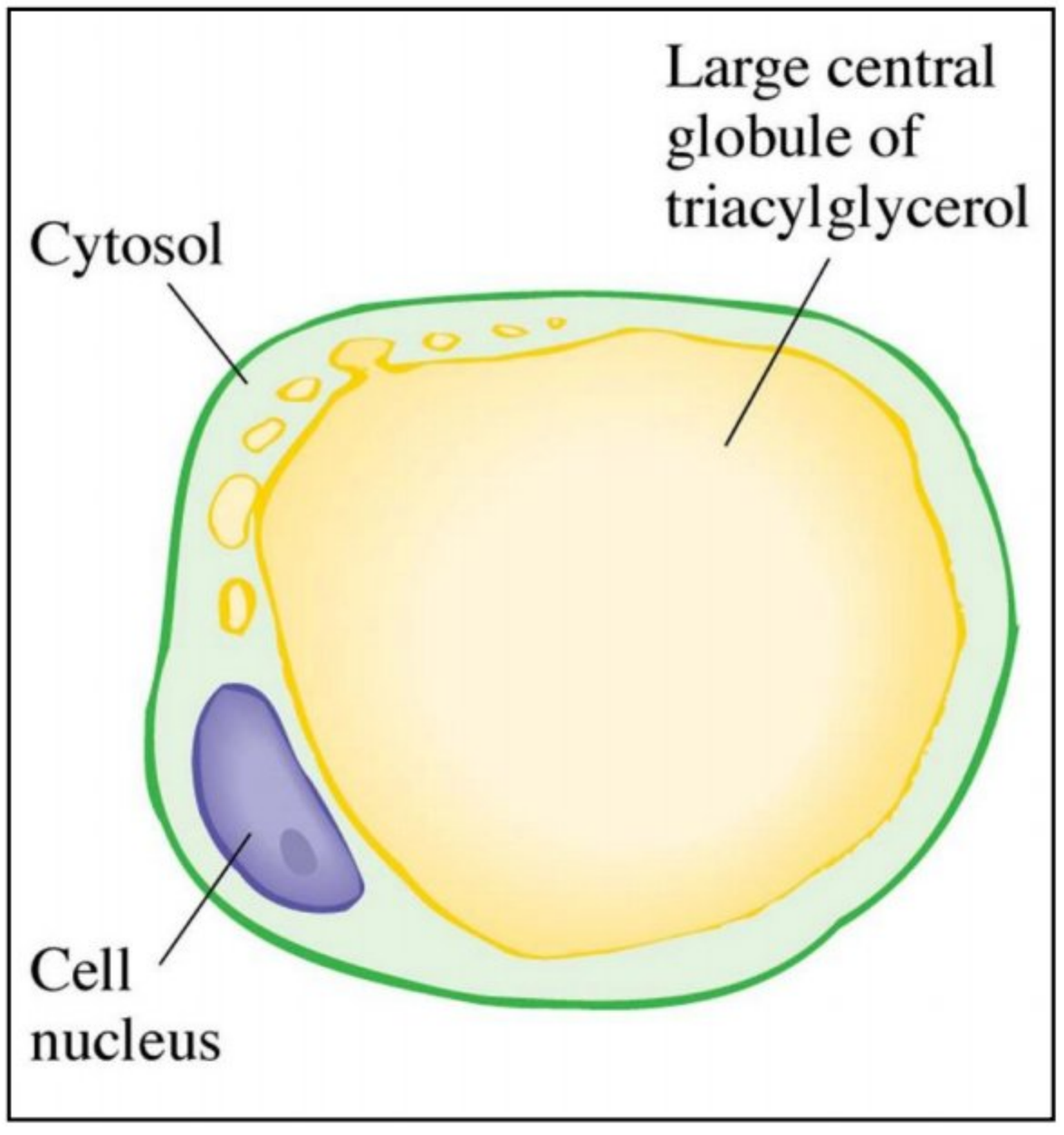


Summary of events that must occur before triacyglycerols (TAGs) can reach the bloodstream through the digestive process.



Triglyceride Storage & Mobilization

Storage of triacylglycerol is in **adipocytes** Fatty acids stored primarily as triacylglycerol. Triacylglycerol is **hydrolyzed** to release **fatty acids** when needed.



Hormonal control of lipolysis

The breakdown of triglycerides by lipases is under hormonal control.

Hormones involved are:

Epinephrine, glucagon, and insulin.

Epinephrine & glucagon:

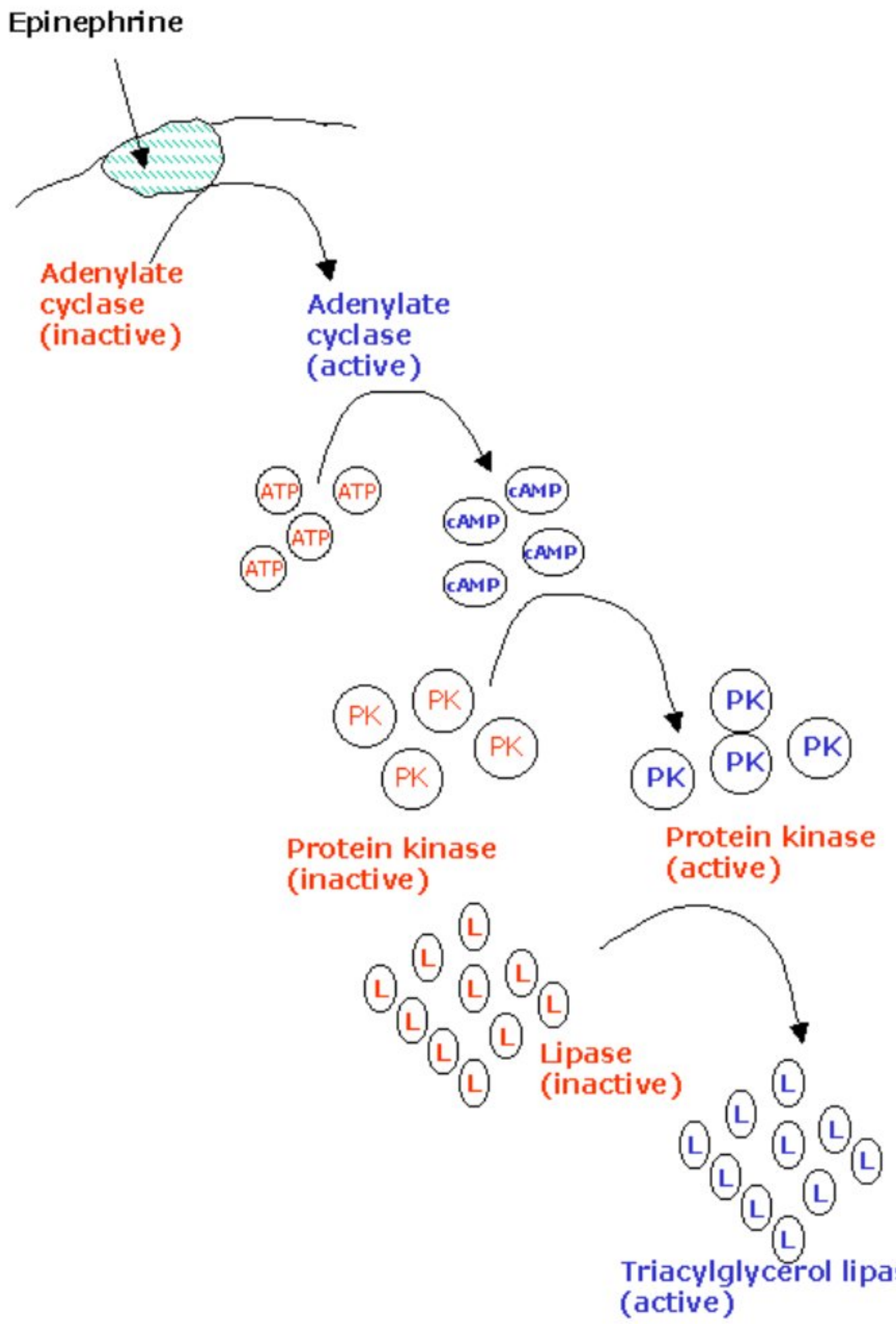
promote breakdown of fat (lipolysis)

Insulin:

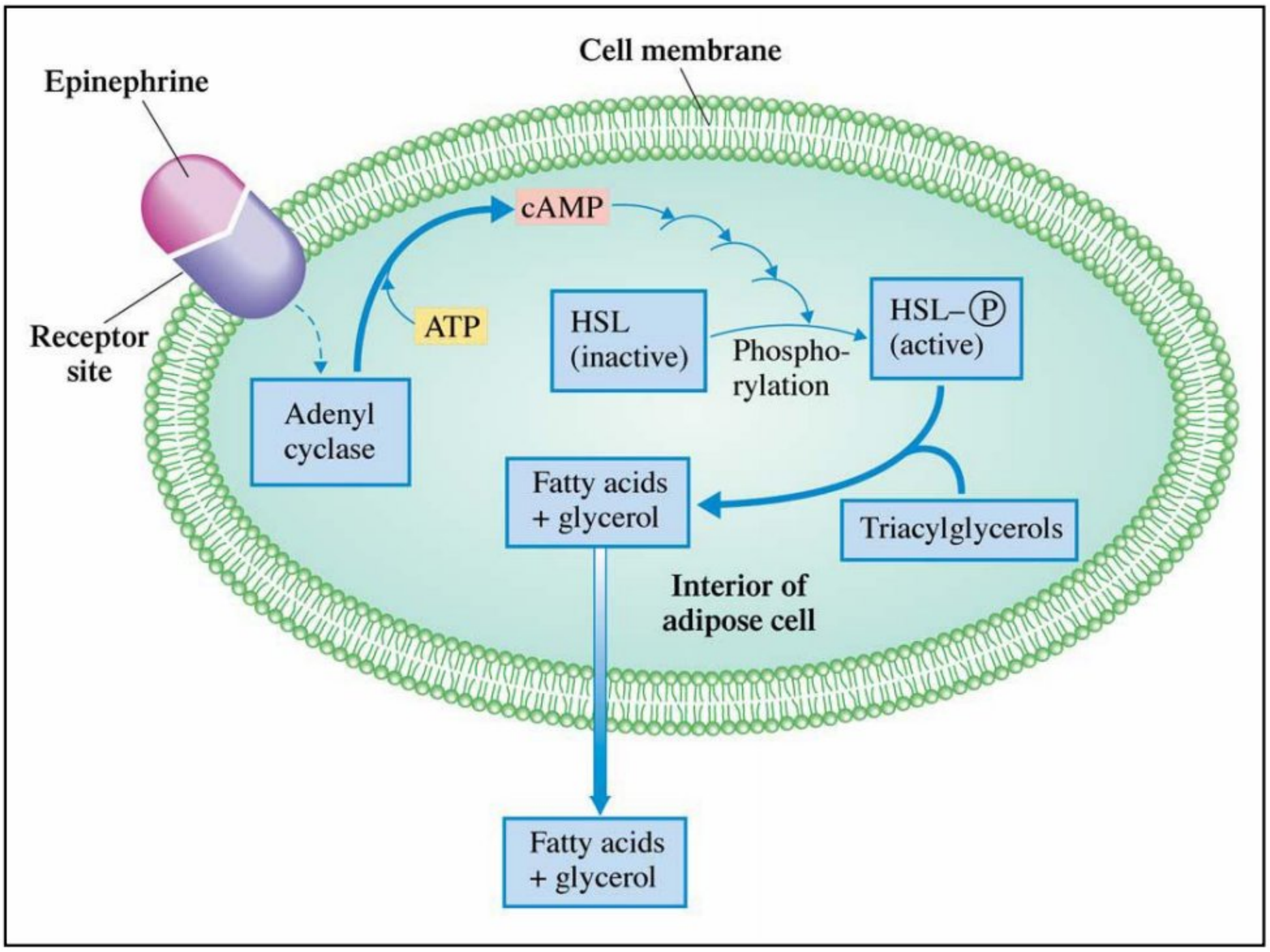
inhibits lipolysis.

Triacylglycerol Mobilization:

Hydrolyzing lipid reserves in adipose tissue for **energy**.Triggered by hormones~10% TAGs replaced in adipose tissue daily as they get used up for energy.



Hydrolysis of stored triacylglycerols in adipose tissue is triggered by hormones that stimulate cAMP production within adipose cells.

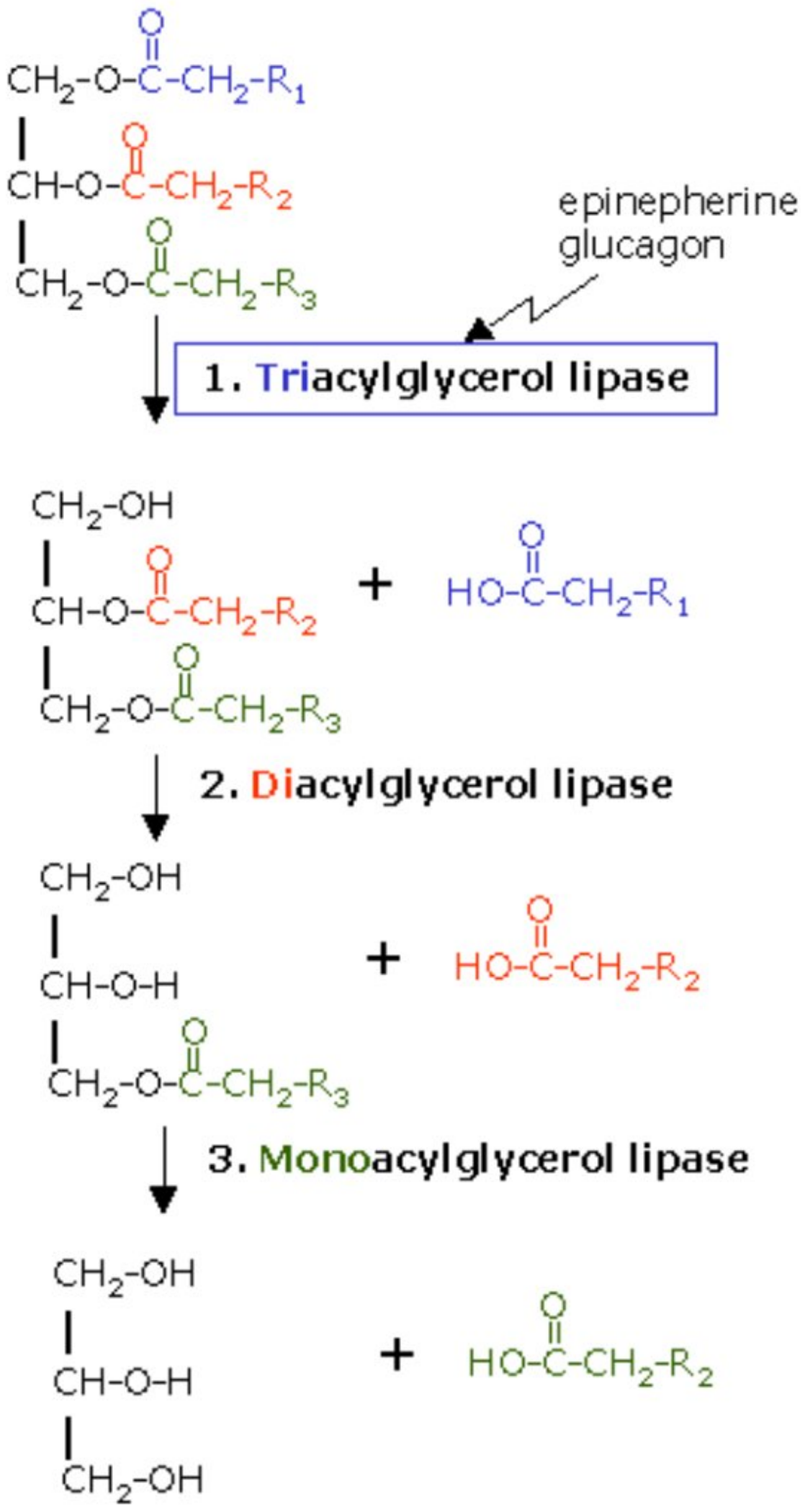


rd

Third time is a charm! TAGs hydrolyzed a 3 time to form fatty acids.

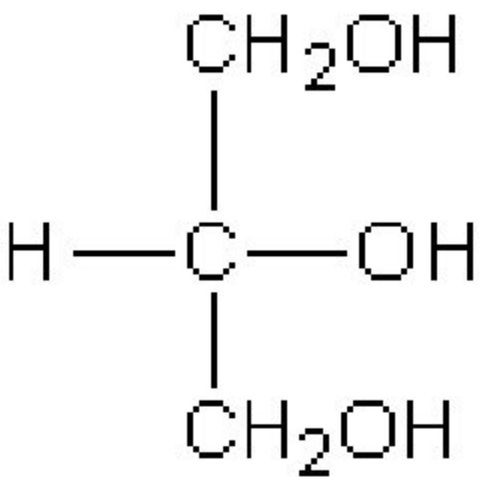
Triacylglycerol lipase **Di**acyclglycerol lipase **Mono**acylglycerol lipase

Only triacylglycerol lipase is activated by epinephrine.

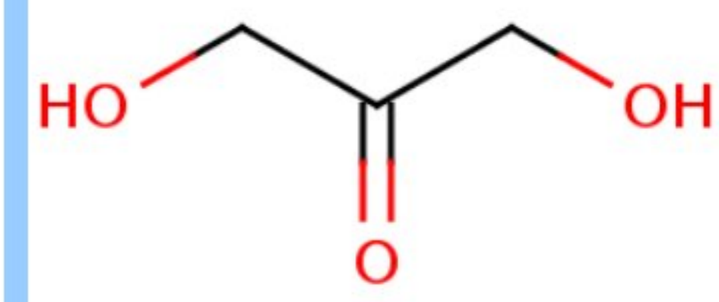


One glycerol formed for each TAG hydrolyzed. Enter bloodstream & go to liver or kidneys for processing. Converted in 2 steps to

Dihydroxyacetone phosphate

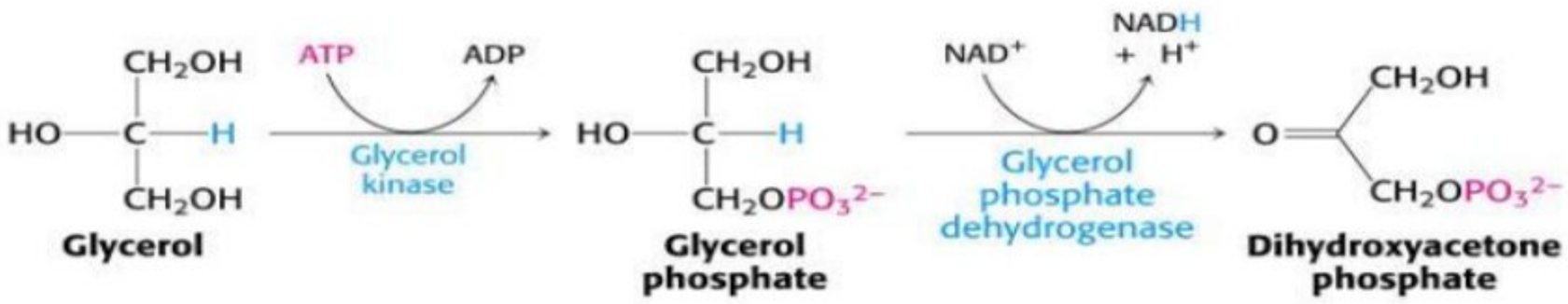


glycerol



Where will the phosphate be attached?

Uses up one ATP.Reduces one NAD^+ to NADH



Primary hydroxyl group is phosphorylated

Dihydroxyacetone phosphate

is an intermediate for both

Glycolysis:

converted to Pyruvate, then to Acetyl CoA, & eventually to CO_2,

releasing its energy.

Gluconeogenesis:

creates Glucose from **non-carbohydrate** source

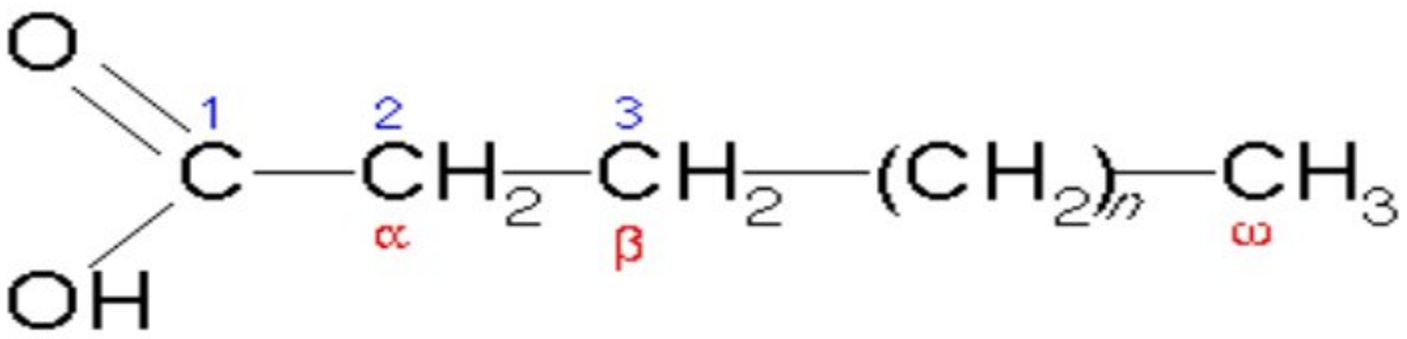
Lipid metabolism & carbohydrate metabolism

are connected.

Fatty acids can also be broken down for energy. What kind of reaction is needed?

Oxidation!

Quick review first on fatty acid numbers & letters:



Fatty acid numbering system

Review Important fatty acids:

Name	# Carbons: (saturation)
Palmitate	16:0
Stearate	18:0
Palmitoleate	16:1 - cis at C9
Oleate	18:1 - cis at C9
Linoleate	18:2 - cis at C9 and C12
Linolenate	18:3 - cis at C9, C12 & C15

Lipid Metabolism

Lipid nomenclature

•Oxidation of Fatty acids

•β-oxidation

•Ketone Bodies

Lipid nomenclature

Fatty acids

•triacylglycerols: know structure

•phospholipids

•waxes

•sphingolipids

•Glycosphingolipids

•Isoprenoids

•Steriods

•Nomenclature

•saturated: palmitate, stearate, no double bonds

•unsaturated: palmitoleate, Oleate: double bond at cis9 position

•polyunsaturated

•Melting points: saturated vsunsaturated

Oxidation of Fatty acids

•Know equation for palmitate: $C_{16}H_{32}O + O_2$ ---> $CO_2 + H_2O$

•Comparison of glucose with palmitatefor ATP production and energy yield

•Mobilization of Triacylglycerols from adipose tissue

–hormonal control: glucagon, epinephrine

–lipases

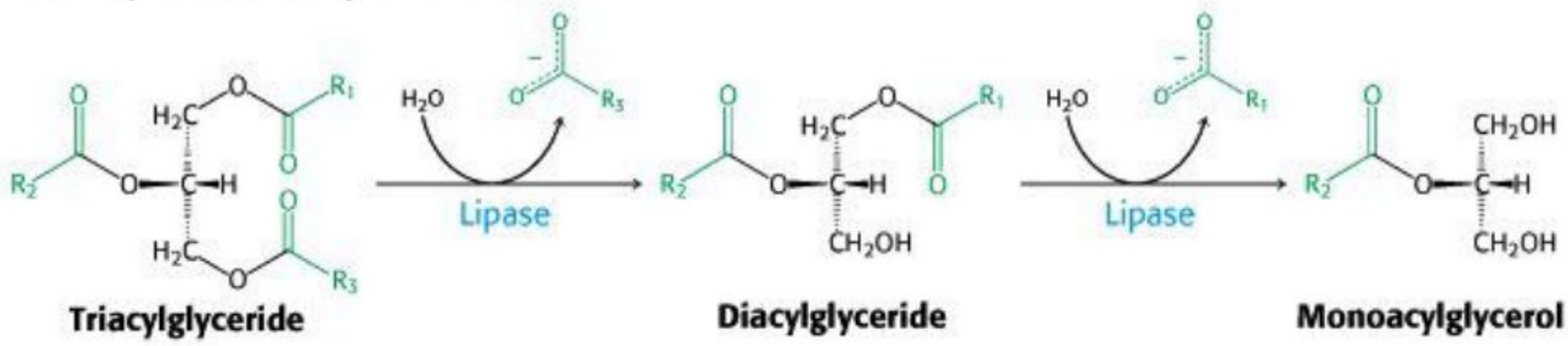
–transport by lipoproteins

–fate of glycerol

•transport into cytoplasm of cell

Digestion of lipid in diet

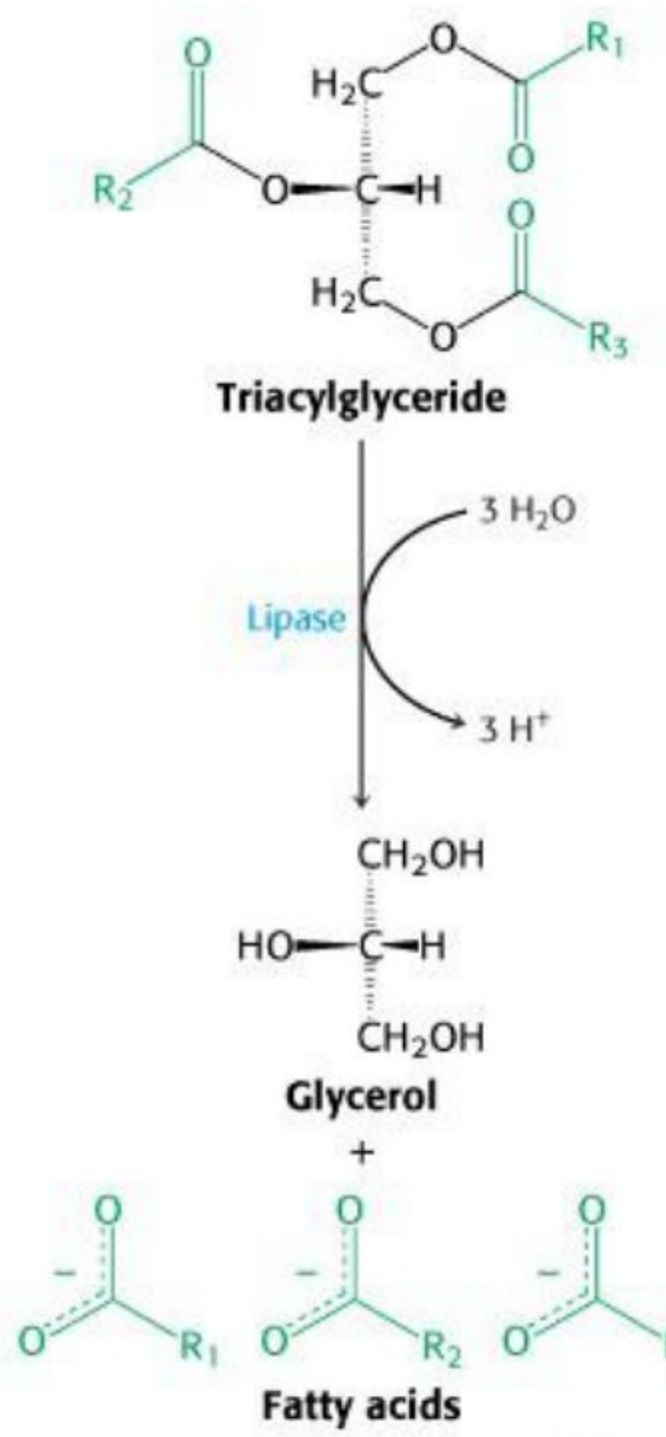
•Triacylglycerolsfrom diet
•broken down in small intestine
•lipases
•bile salts
•transport to adipose tissue

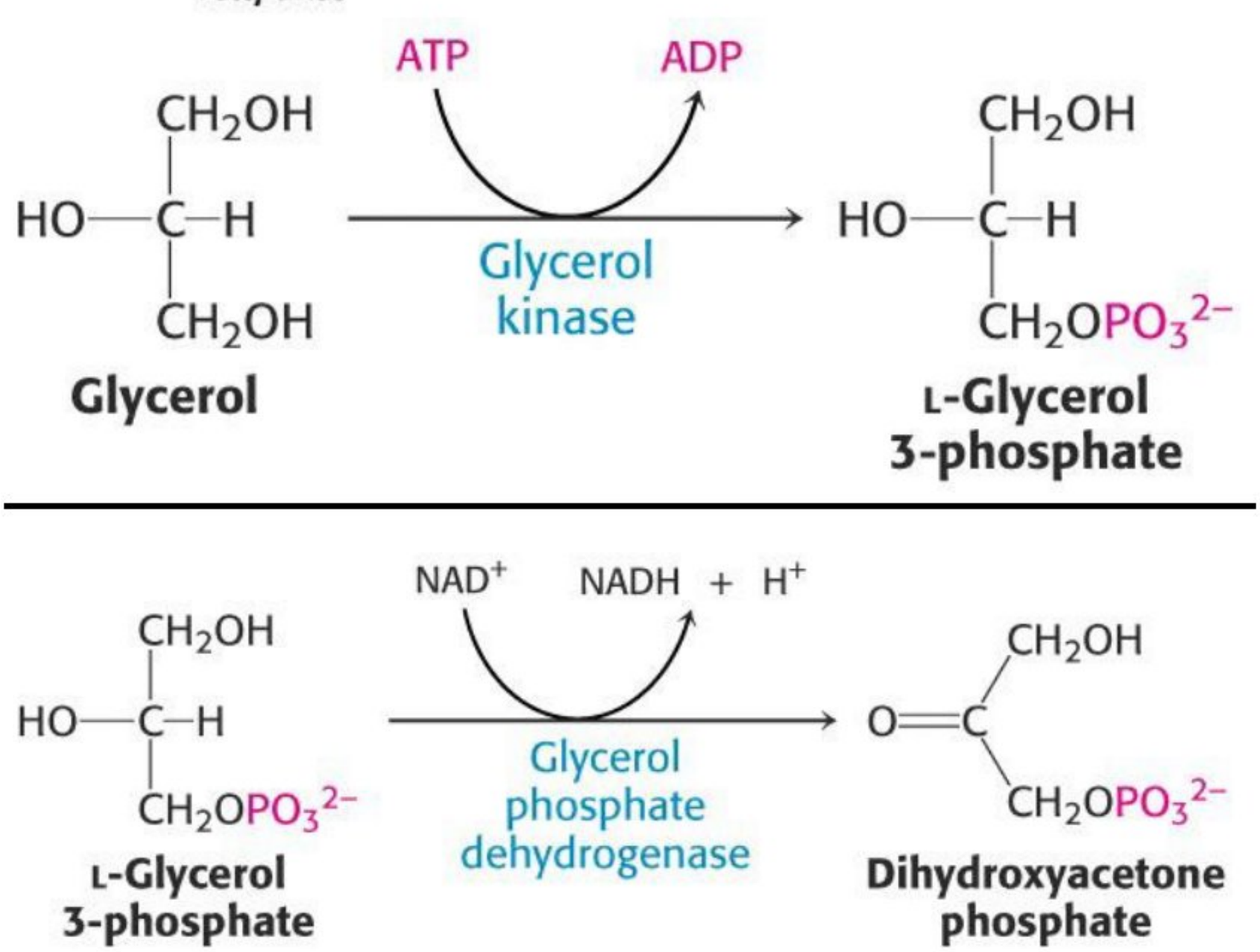


Mobilization of Triacylglycerols

–hormonal control of lipolysis: glucagon, epinephrine
–lipases
–transport by lipoproteins
–transport into cytoplasm of cell
–Insulin inhibits lipolysis

Breakdown of triacylglycerides

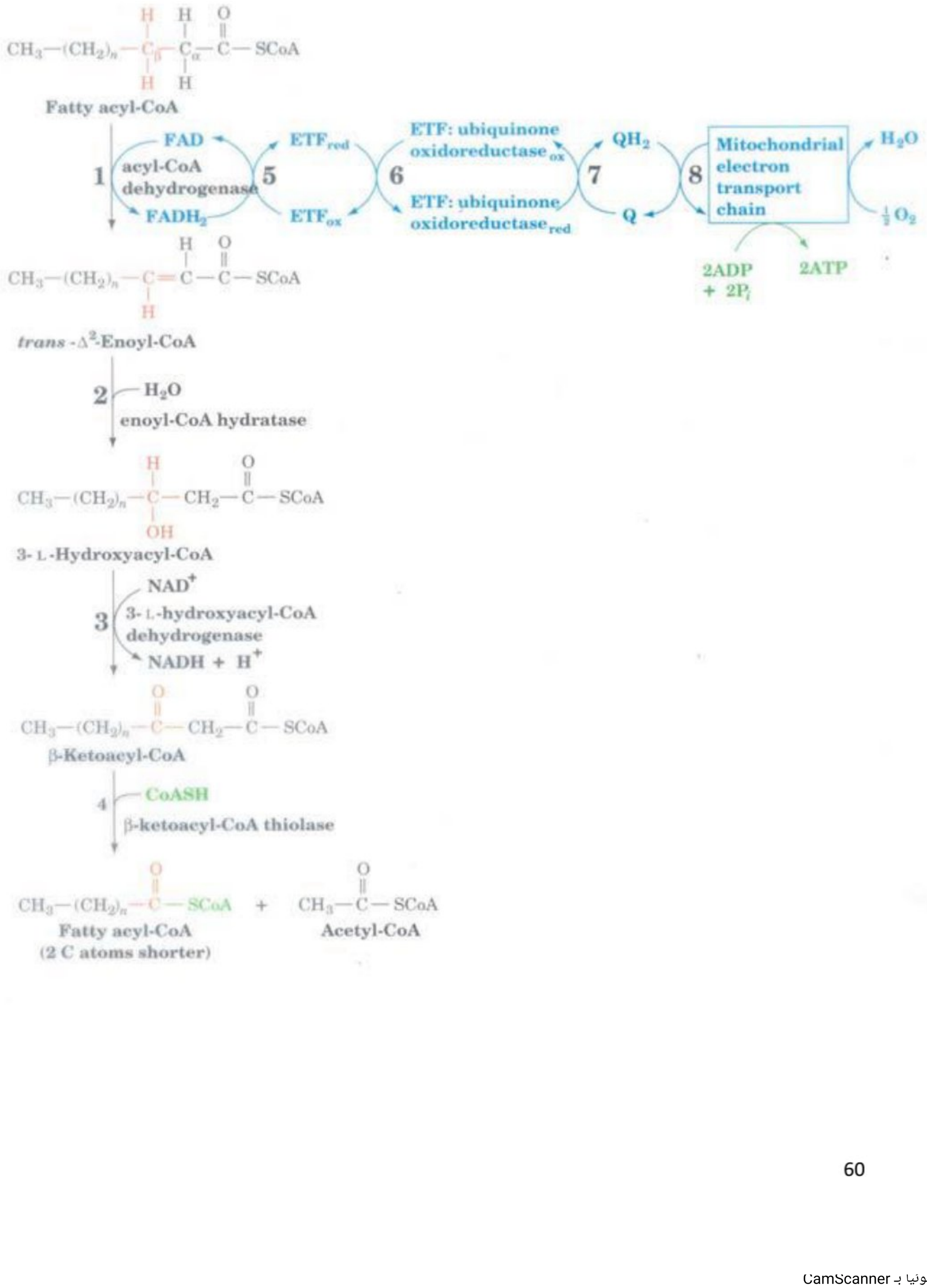




fate of glycerol

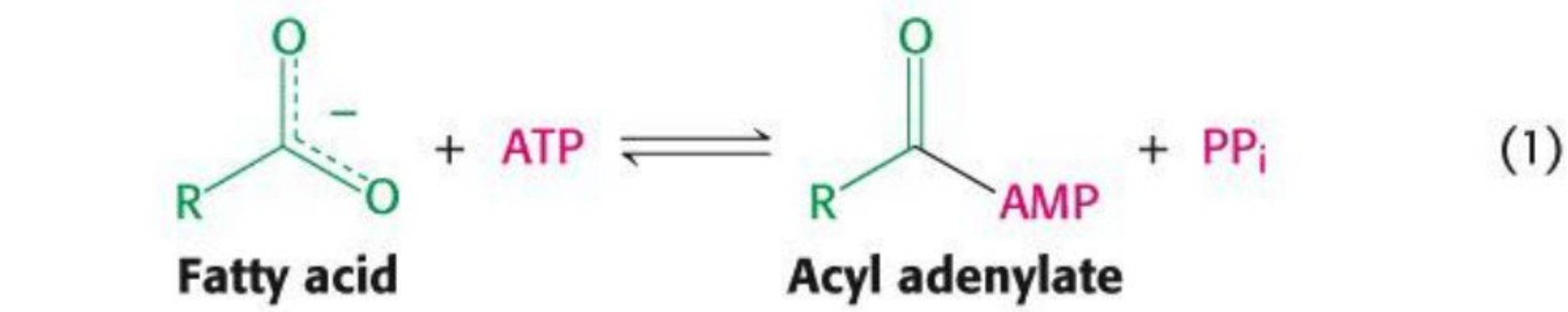
β-oxidation

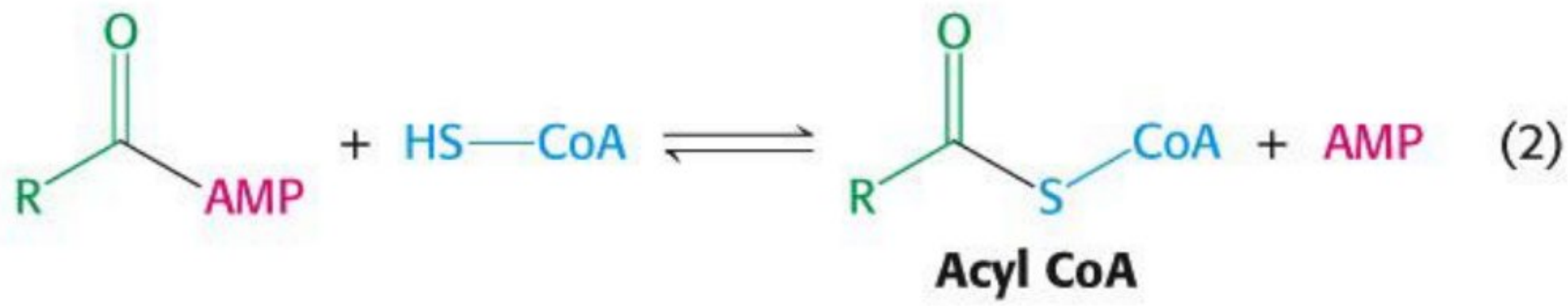
- occurs in mitochondria
- uses FAD and NAD
- produces acetyl CoA



acylCoA synthetase

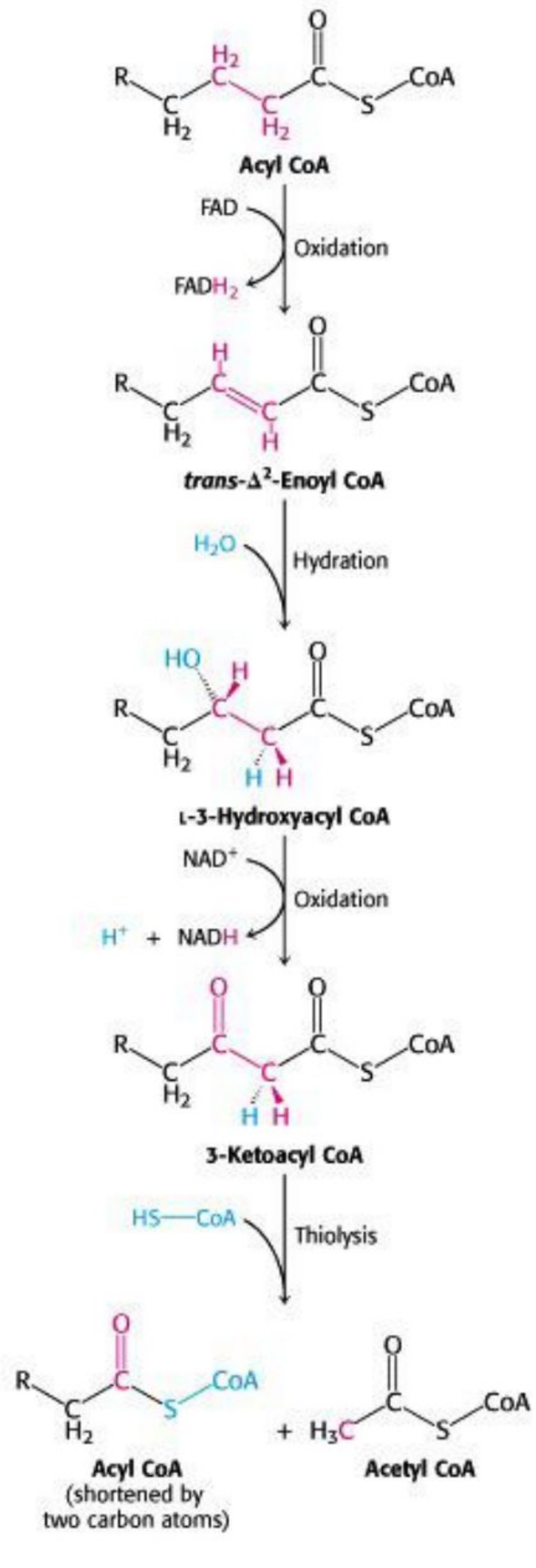
•two step reaction
•ATP + FA ---> AMP-FA
•AMP-FA + CoASH------> FA-CoA + AMP





β-oxidation

AcylCoA dehydrogenase
•enoyl-CoA hydratase
•L-hydroxyacyldehydrogenase
•ketoacyl-CoA thiolase
•Repeat steps



Summary of Reactions

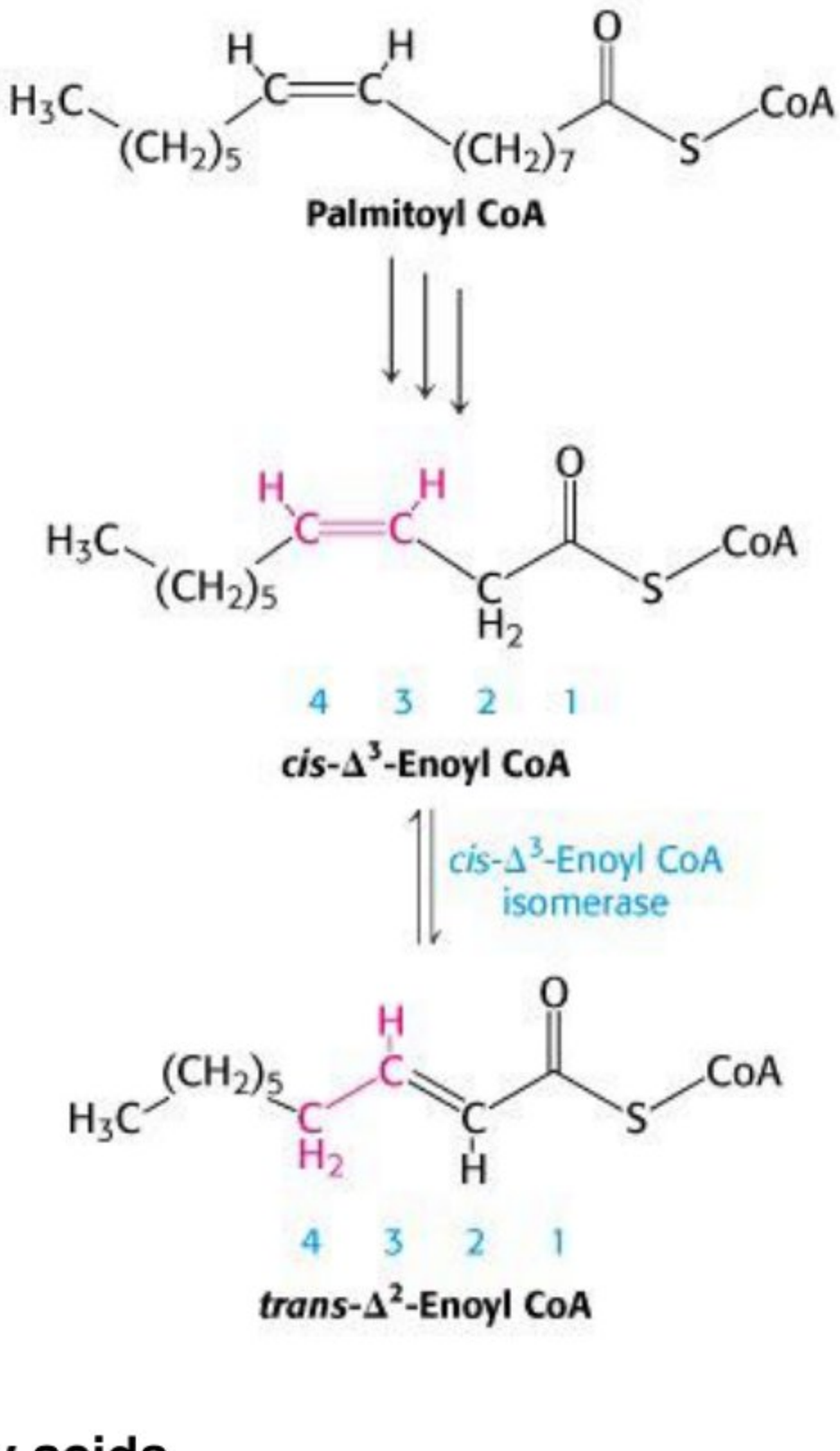
TABLE 22.1 **Principal reactions in fatty acid oxidation**

Step	Reaction	Enzyme
1	Fatty acid + CoA + ATP $\rightleftharpoons$ acyl CoA + AMP + PP_i	Acyl CoA synthetase [also called fatty acid thiokinase and fatty acid:CoA ligase (AMP)]
2	Carnitine + acyl CoA $\rightleftharpoons$ acyl carnitine + CoA	Carnitine acyltransferase (also called carnitine palmitoyl transferase)
3	Acyl CoA + E-FAD $\longrightarrow$ *trans*-Δ^2-enoyl CoA + E-$FADH_2$	Acyl CoA dehydrogenases (several isozymes having different chain-length specificity)
4	*trans*-Δ^2-Enoyl CoA + H_2O $\rightleftharpoons$ L-3-hydroxyacyl CoA	Enoyl CoA hydratase (also called crotonase or 3-hydroxyacyl CoA hydrolyase)
5	L-3-Hydroxyacyl CoA + NAD^+ $\rightleftharpoons$ 3-ketoacyl CoA + NADH + H^+	L-3-Hydroxyacyl CoA dehydrogenase
6	3-Ketoacyl CoA + CoA $\rightleftharpoons$ acetyl CoA + acyl CoA (shortened by C_2)	β-Ketothiolase (also called thiolase)

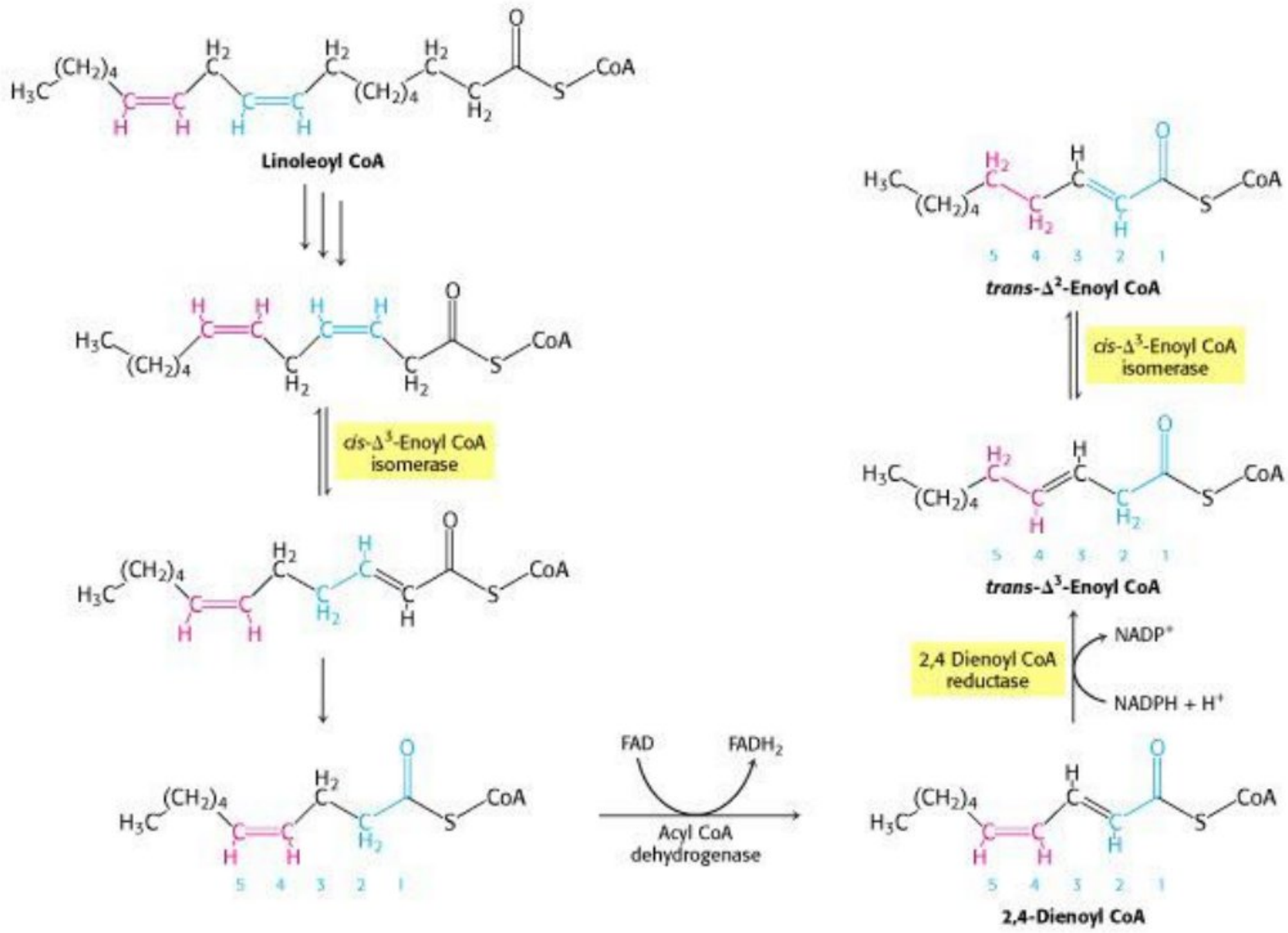
Energy production

- NADH and FADH from B-oxidation
- TCA cycle from acetyl CoA
- Total net yield is minus 2 ATP from activation

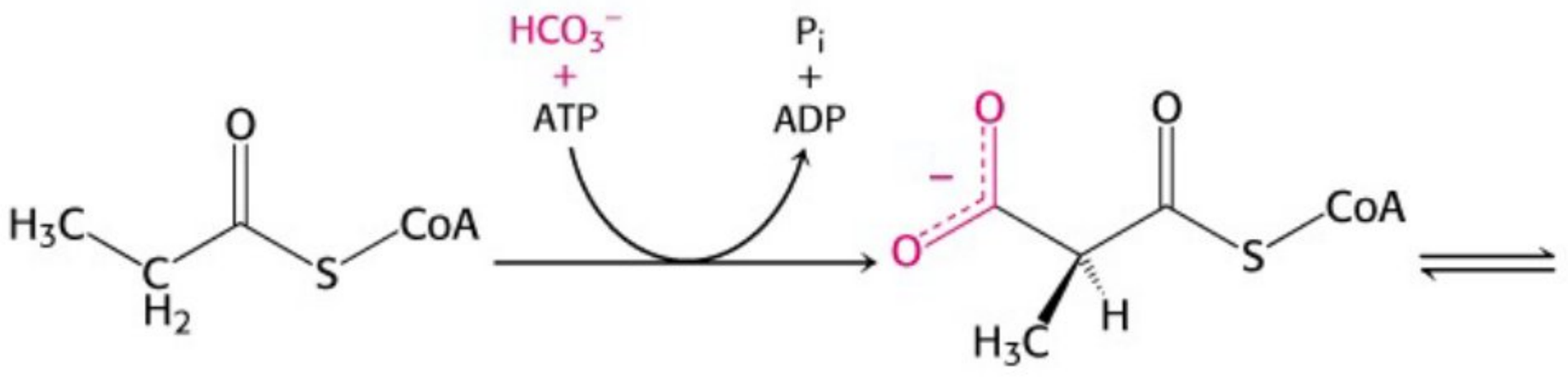
Oxidation of Unsaturated Fatty acids



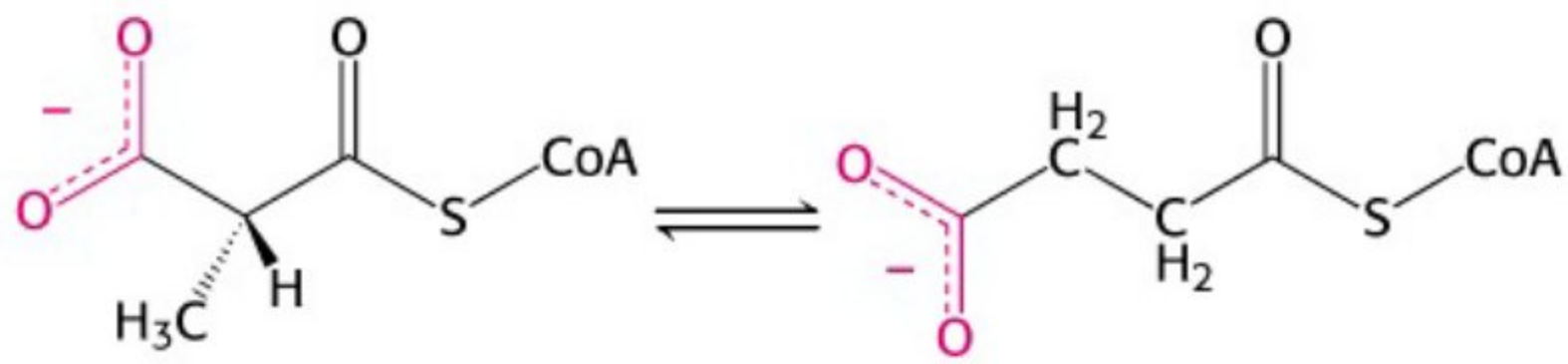
Unsaturated Fatty acids



Oxidation of odd chain fatty acids



Propionyl CoA **D-Methylmalonyl CoA**

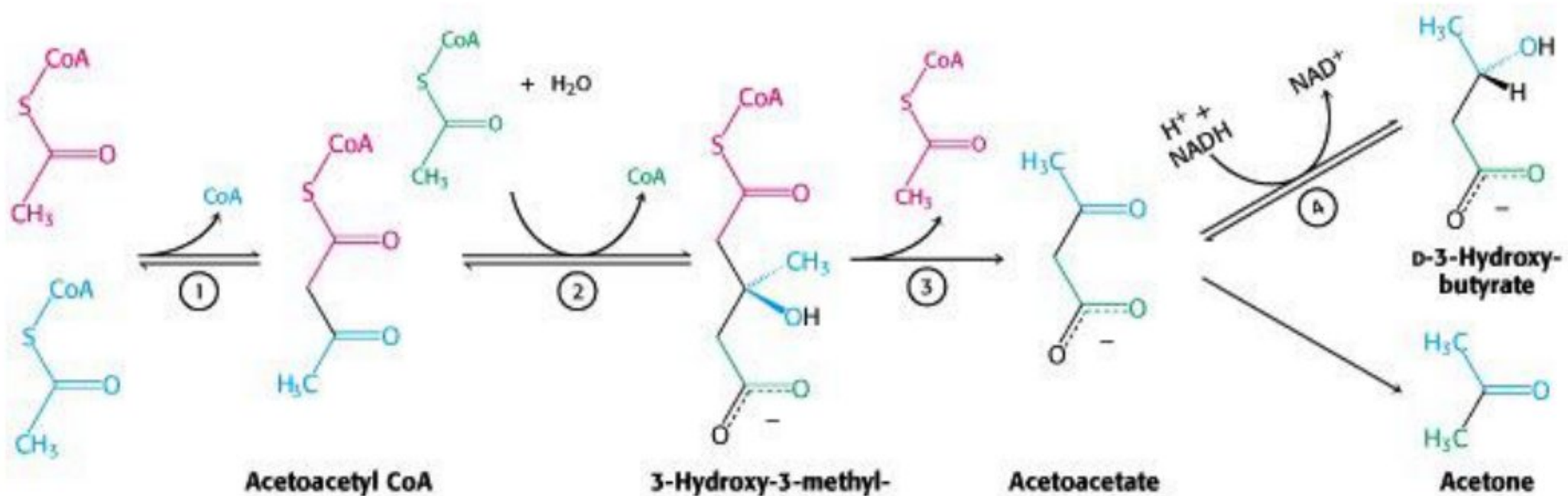


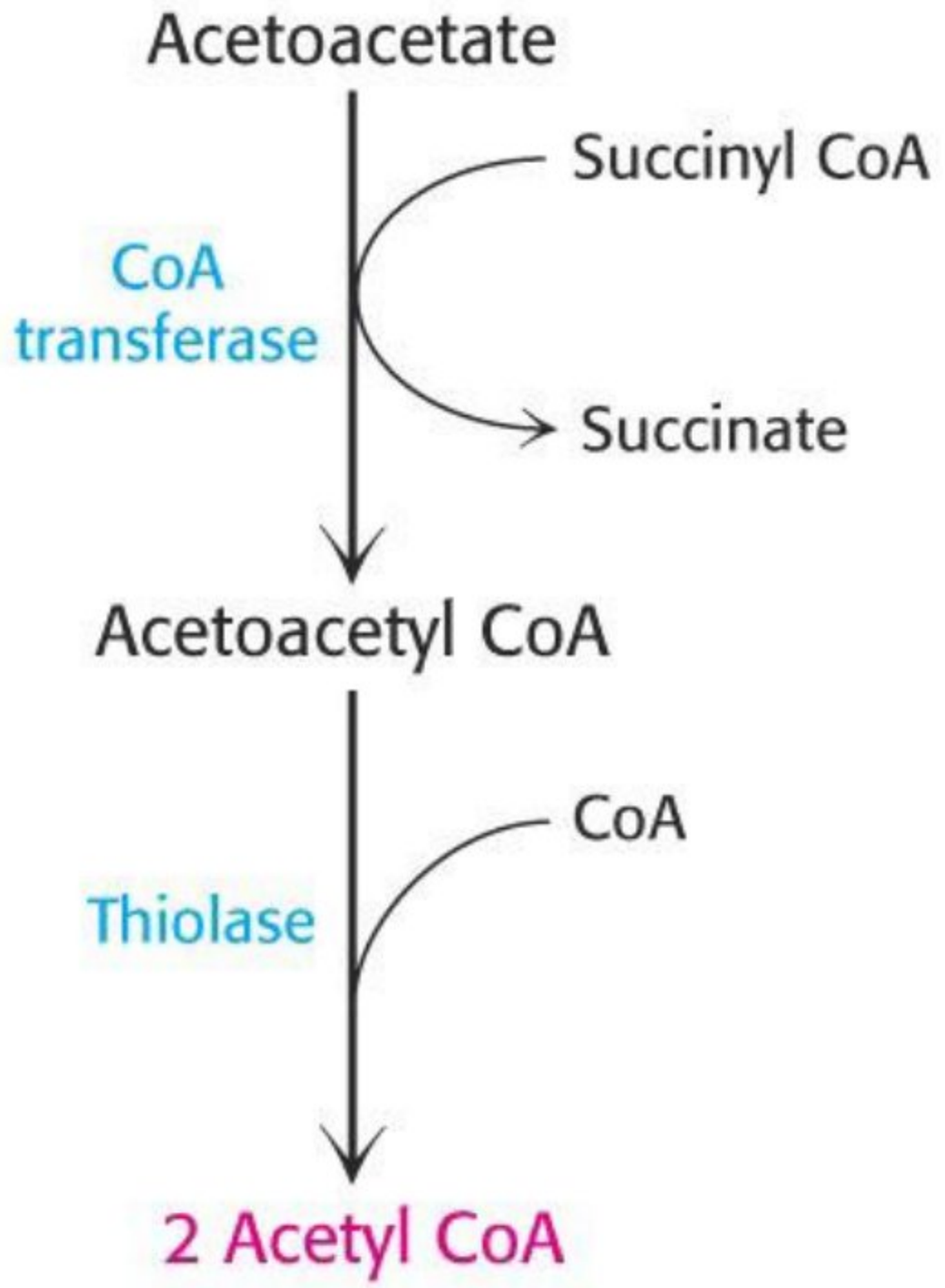
L-Methylmalonyl CoA **Succinyl CoA**

•form propionylCoA

•produce succinylCoA

Ketone Bodies





- Acetoacetate
- Acetone
- B-hyroxybutyrate
- HMG CoA synthase

Referances

Available online

1-BIOCHEMISTRY IN PERSPECTIVE

2-METABOLISM OF CARBOHYDRATES, LIPIDS, PROTEINS AND NUCLEIC ACIDS, Course Team

Prof. Anthony, I. O. Ologhobo(Course Writer)-UI

Prof. Jokthan,G.E. (Programme Leader)-NOUN

Dr. Salisu, B. Abdu (Course Editor)-ABU, Zaria

Dr. Ahmed A. Njidda (Course Coordinator)-NOUN ISBN: 978-978-970-183-4,

SOUTH VALLY UNIVERSITY

FACULTY OF SCIENCE
AT QENA

Chemotherapy

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كلية العلوم – قسم الكيمياء
العام الجامعي
٢٠٢٣

المحتوي :-

Chemotherapy

Paul ehrlich (1907 s) is the first scientist who introduced the term " chemotherapy “ . The higher plants made the earliest druge discovered , herbal remedies have been important throughout human history , crude plant product such as opium and belladonna have been valuable for centuries.

This field has changed when the antibiotics were discovered and change into drug biosynthesis.

In recent year the introduction of new synthesis pharmaceuticals has outpaced that of natural product . furthermore ,the isolated and purified active material superseded preparation of the parent crud drug.

These factors led to de-emphasis on chemotherapy in the pharmacy curriculum and often to its combination with medicinal chemistry.

Classification of drug on the basis of their origin

1-Drug from natural origin: Herbal or plant or mineral origin, some drug substances are of marine origin.

2-Drug from chemical as well as natural origin: Derived from partial herbal and partial chemical synthesis Chemical, example steroidal drugs

3-Drug derived from **chemical synthesis**.

4-Drug derived from animal origin: For example, hormones, and enzymes.

5-Drug derived from microbial origin: **Antibiotics**

6-Drug derived by biotechnology genetic-engineering, hybridoma technique for example

7-Drug derived from radioactive substances

A sampling of classes of medicine includes

1-Antipyretics: reducing fever (pyrexia/pyresis)

2-Analgesics: reducing pain (pain killers)

3-Antimalarial drugs: treating malaria

4-Antibiotics: inhibiting germ growth

5-Antiseptics : prevention of germ growth near burns, cuts

Definition of medicinal chemistry

Medicinal chemistry is the science which deals with the synthesis, chemistry of mode of action, chemical assay of drug substance.

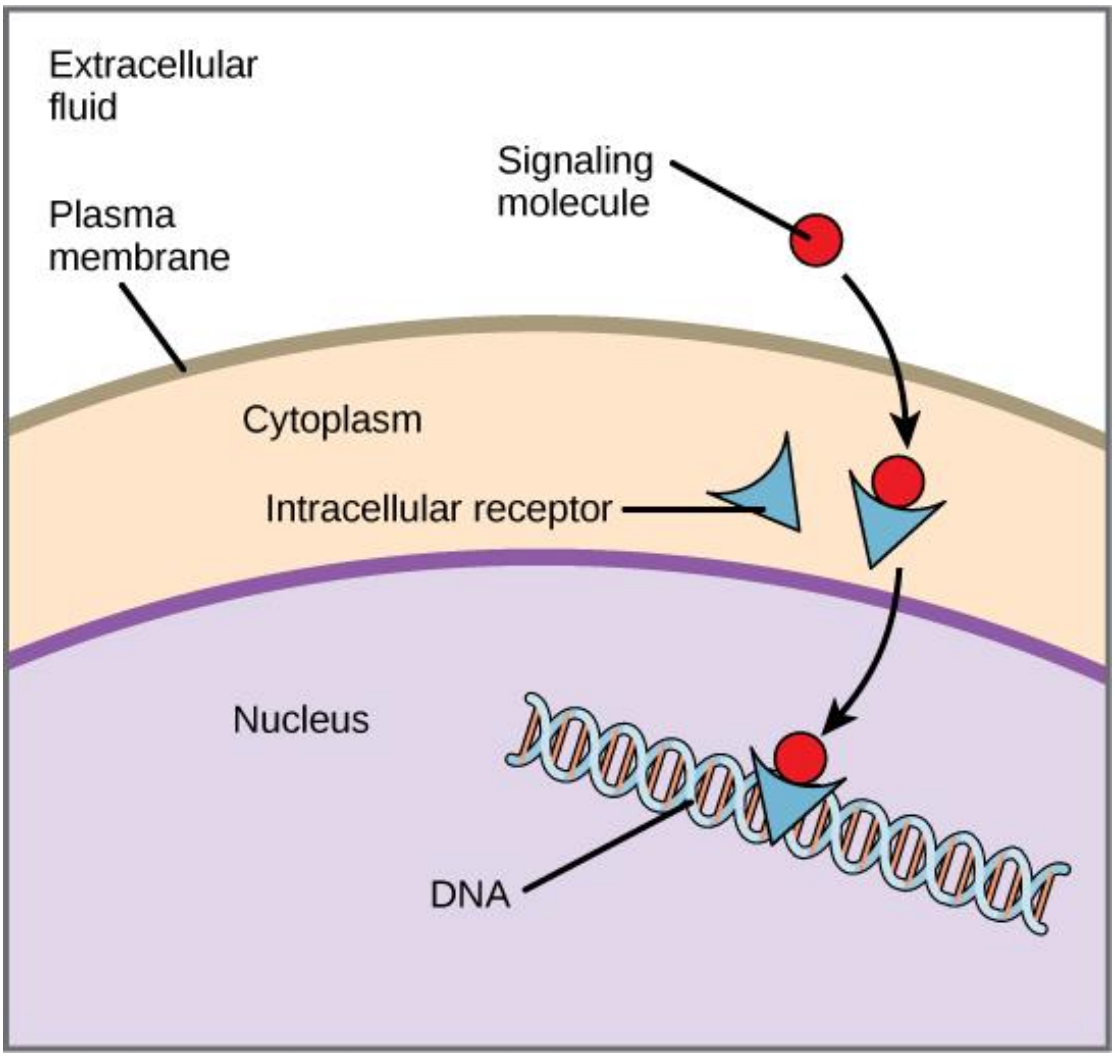
Definition of drug

Drug is any substance presented for treating, curing or preventing disease in human beings or in animals. It may also be used for making a medical diagnosis or for restoring, correcting, or modifying physiological functions.

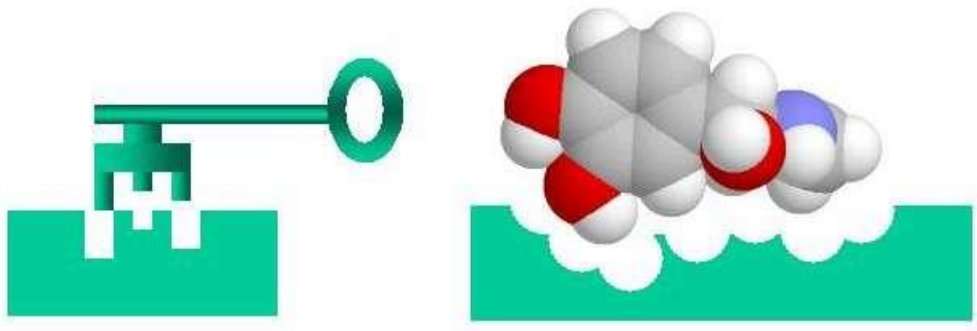



Definition of receptor

Receptor: It is a membrane bound or intracellular macromolecular protein which is capable of binding the specific functional groups of the drug with body.



LOCK & KEY" model of RECEPTORS



Four types of binding takes place between the receptor and the drug molecule

1. Van der Waals forces
2. Hydrogen bonding
3. Ionic interaction
4. Dipole- dipole bonding
5. Covalent bonding

1. Van der Waals Attraction

■weakest intermolecular force (0.5-1.0 kcal/mole)

■electrostatic

■occurs between nonpolar groups (e.g. hydrocarbons)

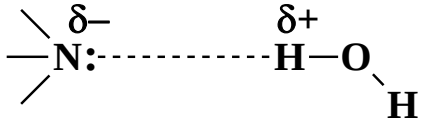
■highly distance and temperature dependent

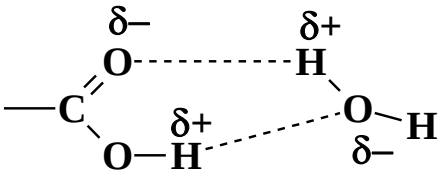
2. Dipole-Dipole Bonding

■stronger (1.0 to 10 kcal/mole)

■occurs electrostatically between electron deficient and electron excessive /ric atoms (dipoles)

■hydrogen bonding is a specific example of this bonding and serves as a prime contributor to hydrophilicity



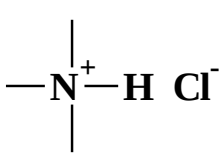


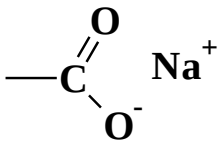
3.Ionic Bonding

■electrostatic attraction between cations and anions

■common in inorganic compounds and salts of organic molecules

■relatively strong (5 kcal/mole)





4.Ion-Dipole Bonding

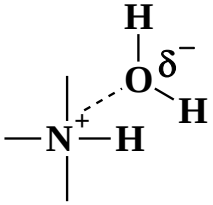
■electrostatic between a cation/anion and a dipole

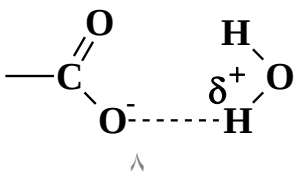
■relatively strong (1-5 kcal/mole)

■low temperature and distance dependence

■important attraction between OMAs**(organic medicinal agents**) and H2O

- **hydrophilic.....water loving**
- **lipophobic.....lipid hating**
- **lipophilic.....lipid loving**
- **hydrophobic.....water hating**

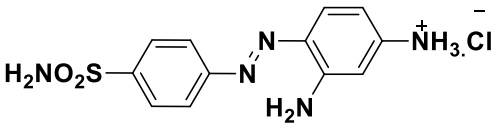




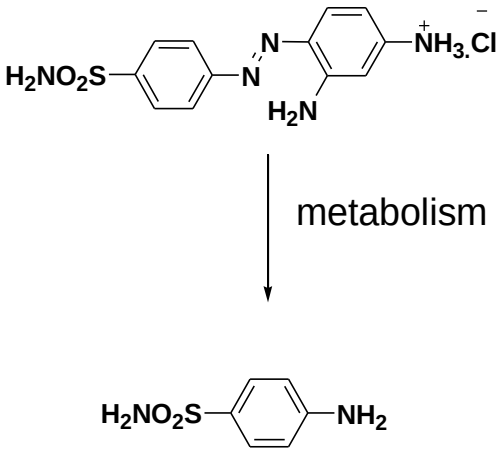
Sulpha drugs

Sulfonamides:-

The sulfonamide are synthetic ,not of natural origin which called " antimicrobials " and not antibiotics. They were the first antibacterial drugs that were not overtly toxic to human.

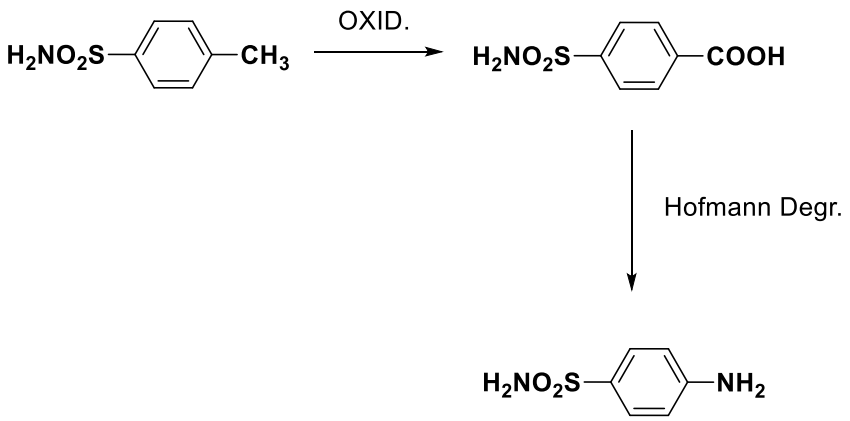


Prontosil which is 2,4-diamino-4-sulphamyl azobenzen hydrochloride was the first sulpha drug to be used in medicine ,it is red dye and metabolized in the body to p-aminobenzene sulphonamide.



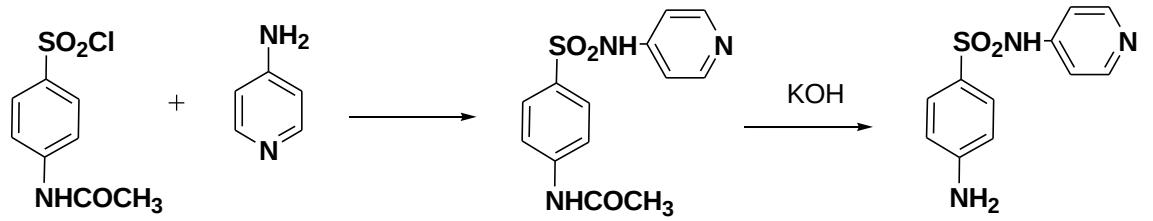
Synthesis of sulphanilamides derivative :-

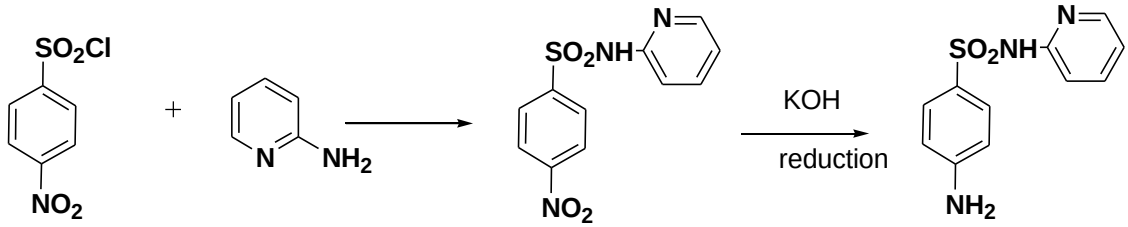
Oxidation of p-toluenesulphonamide to p-sulphamidobenzoic acid fallowed by Hoffmann degradation.



Sulpha pyridine

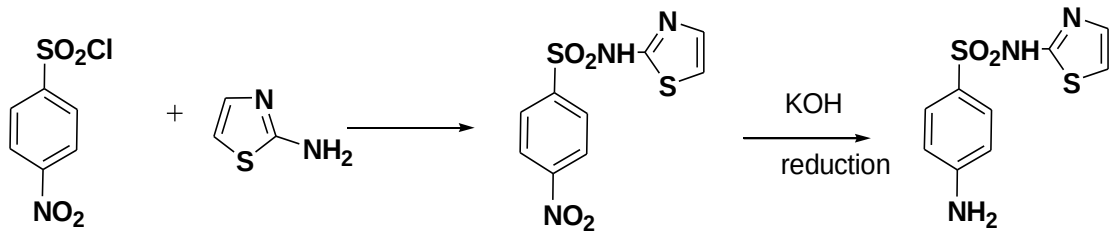
Used to treatment the cocci pneumonia ,but it high toxicity in men ,it is rarely used any longer.





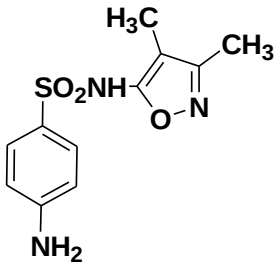
Sulpha thiazole

2-thiazolyl sulponilamide is more patent than sulphapyridine and less toxic ,it most highly bacteriostatic drug which has a permanent place in the pharma.



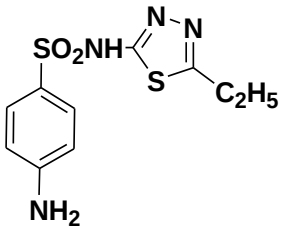
Sulphaisoxazole

Is soluble over a wide pH range ,which have highest bacteriostatic activity and rapid excretion through the kidney.



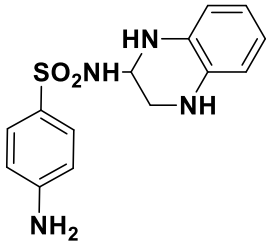
Sulphathiadiazole :-

2-sulphanilamide-5-ethyl-1,3,4-thiadizole is highly soluble and rapidly excretion from the kidney in urine so it consider the most suitable for urinary tract infection.



Sulphaquinoxaline :-

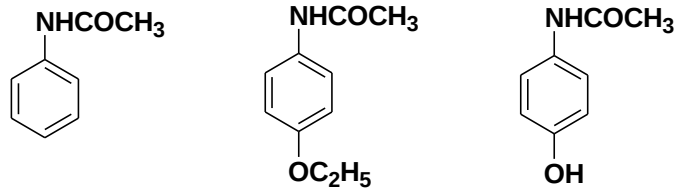
It is widely used in the treatment of coccidiasis infection caused by Eimeria tenella in chickens pheasants.



Antipyretic and analgesics

Aniline and p-aminophenol derivative :-

They have analgesic activity comparable to that of aspirin but don't have anti-inflammatory activity e.g. acetanilide , paracetamol and phenacetin .



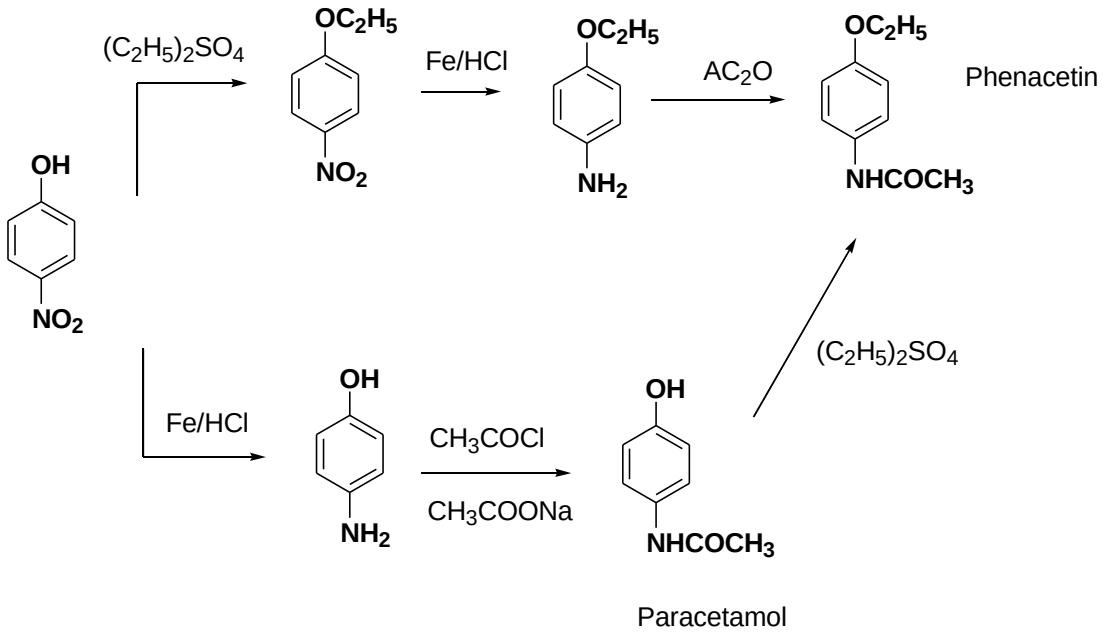
acetanilide phenacetine paracetamol

Acetanilide was introduced into therapy in 1886 as antipyretic-analgesic but it found later too toxic.

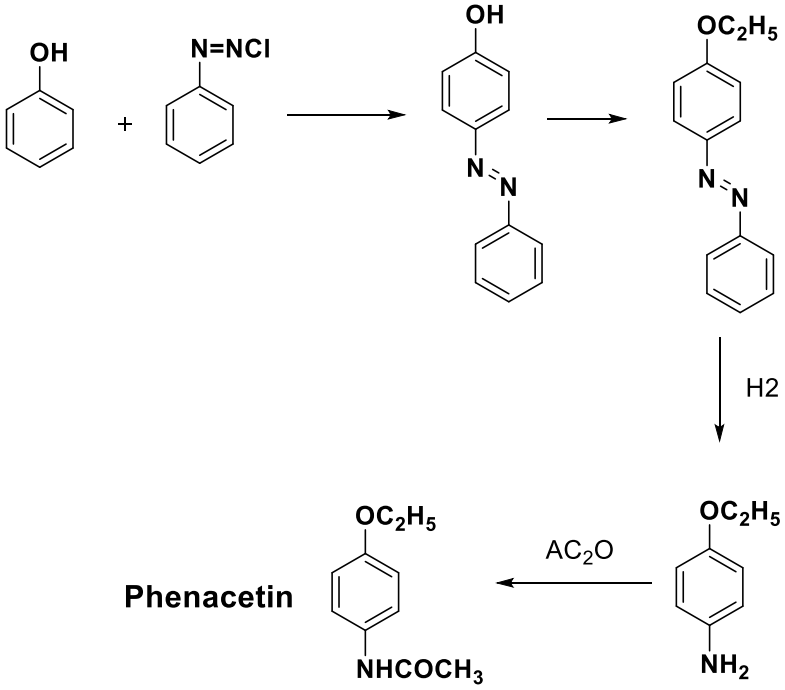
Phenacetin was introduced in the following year and it was widely used but recently it found nephrotoxicity.

Paracetamol is subseguently introduced in 1893 and it remains the only popular agent for this group.

Synthesis of paracetamol

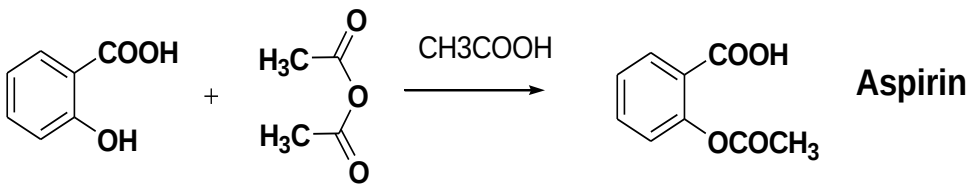


Industrial method for phenacetine



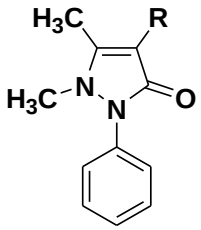
Salicylic acid derivatives

The major chemical classes of salicylates used in medicine are the ester ,the most common one is aspirin .

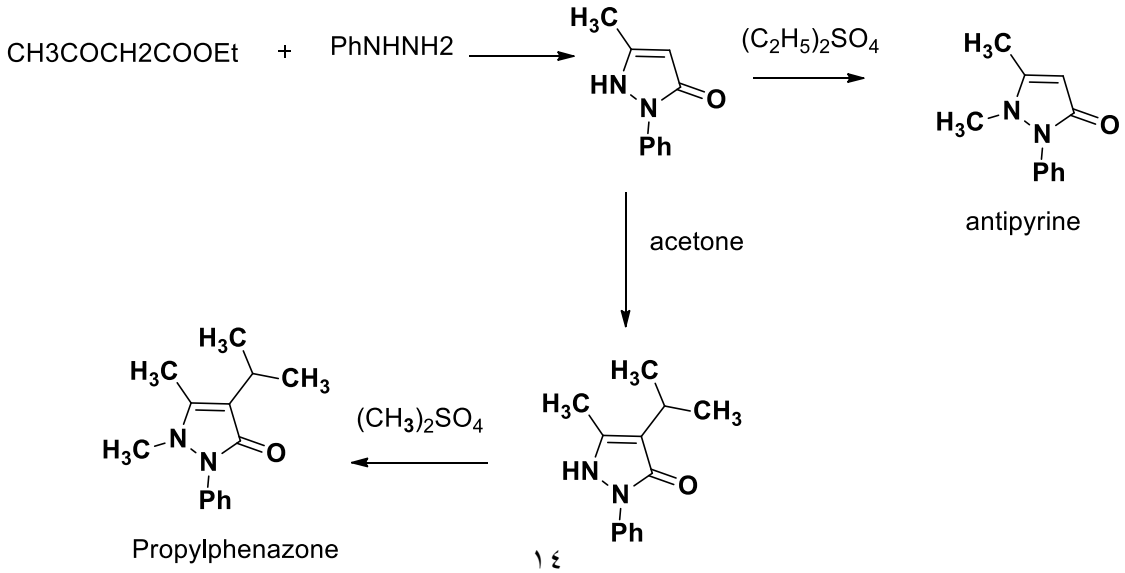


3-pyrazolone derivatives

Antipyrine(phenazone) and propylphenazone have analgesic, antipyretic and antirhumatic activities similar to those of aspirine and used for the same purpose.



Synthesis of antipyrine



Aryl and hetroarylacetic acid derivative

(aryl alkanoic acid derivative)

This class of compounds represents the largest group of NSAIDS (Nonsteroidal anti-inflammatory drugs). They have the following general chemical structure .

Ar-CH(R)-COOH

(R = H,CH3,alkyl ….)

(Ar = Aryl or heteroaryl)

- The main type of NSAID include
- ibuprofen.
- naproxen.
- diclofenac.

Ketoprofene (Propionic acid derivatives)

- mefenamic acid.
- etoricoxib.
- indomethacin.
- high-dose aspirin (low-dose aspirin is not normally considered to be an NSAID)

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines that are widely used to relieve pain, reduce inflammation, and bring down a high temperature.

They're often used to relieve symptoms of headaches, painful periods, sprains and strains, colds and flu, arthritis, and other causes of long-term pain.

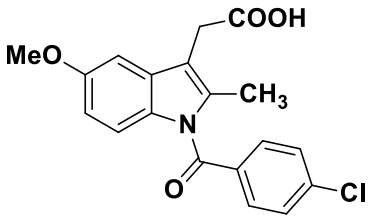
Although NSAIDs are commonly used, they're not suitable for everyone and can sometimes cause troublesome side effects.

Indoleacetic acid derivative

1- indomethacin

Indemethacin is one of the most potent non-steroidal anti-inflammatory agents.

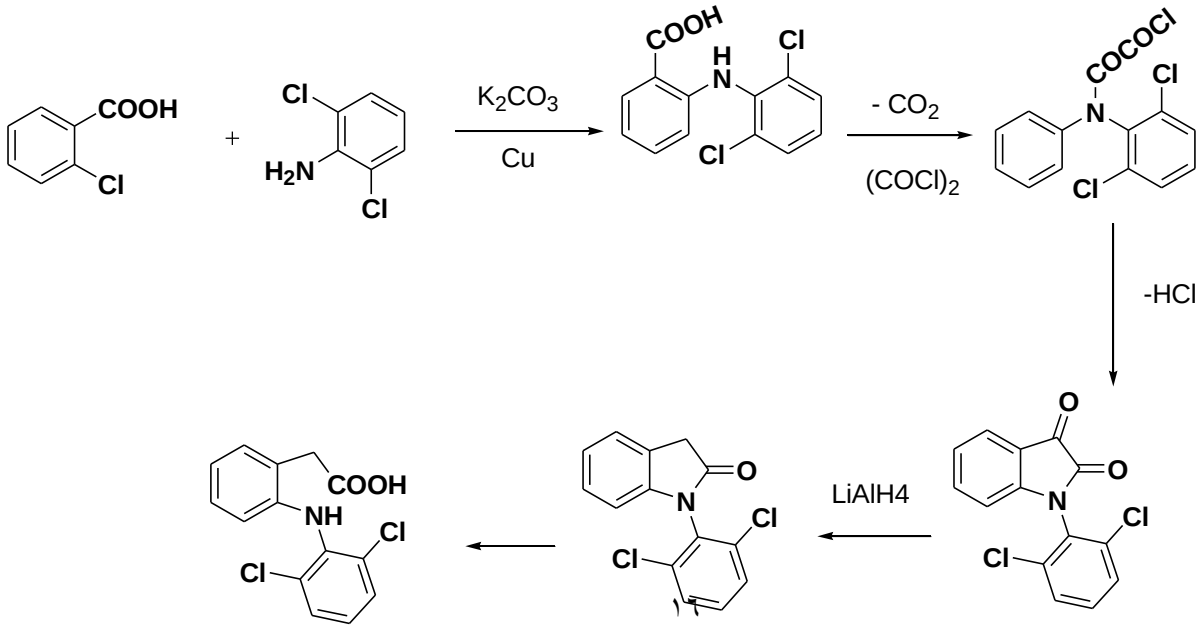
Substitution of a methyl group on the carbon atom separating the acid center from the aromatic ring tends to increase anti-inflammatory activity groups .



Phenylacetic acid derivatives (diclofenac sodium)

Diclofenac is available in 120 different countries and the most widely used NSAIDA in the world It is 6 time more potent than indomethacin and 40 time more potent than aspirin as antipyretic.

Synthesis of diclofenac

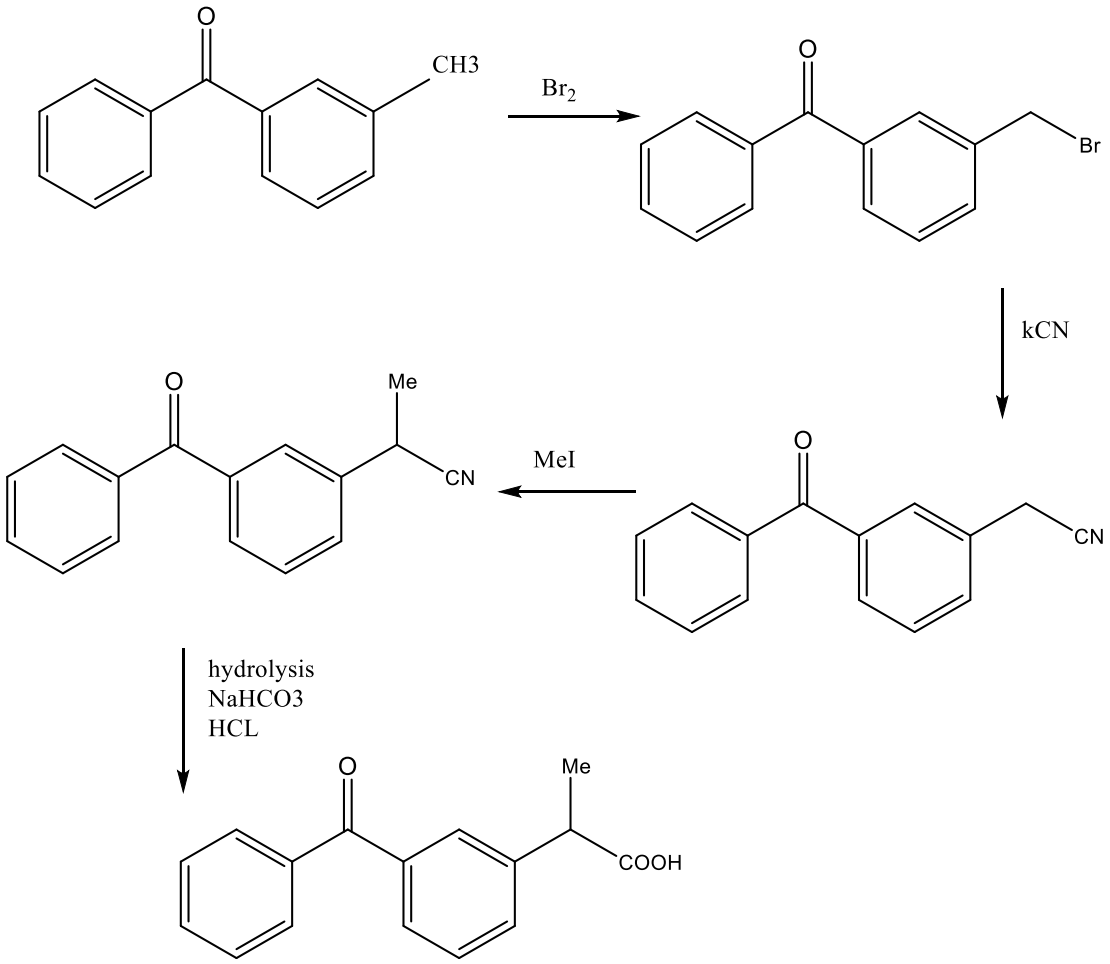


Ketoprofen

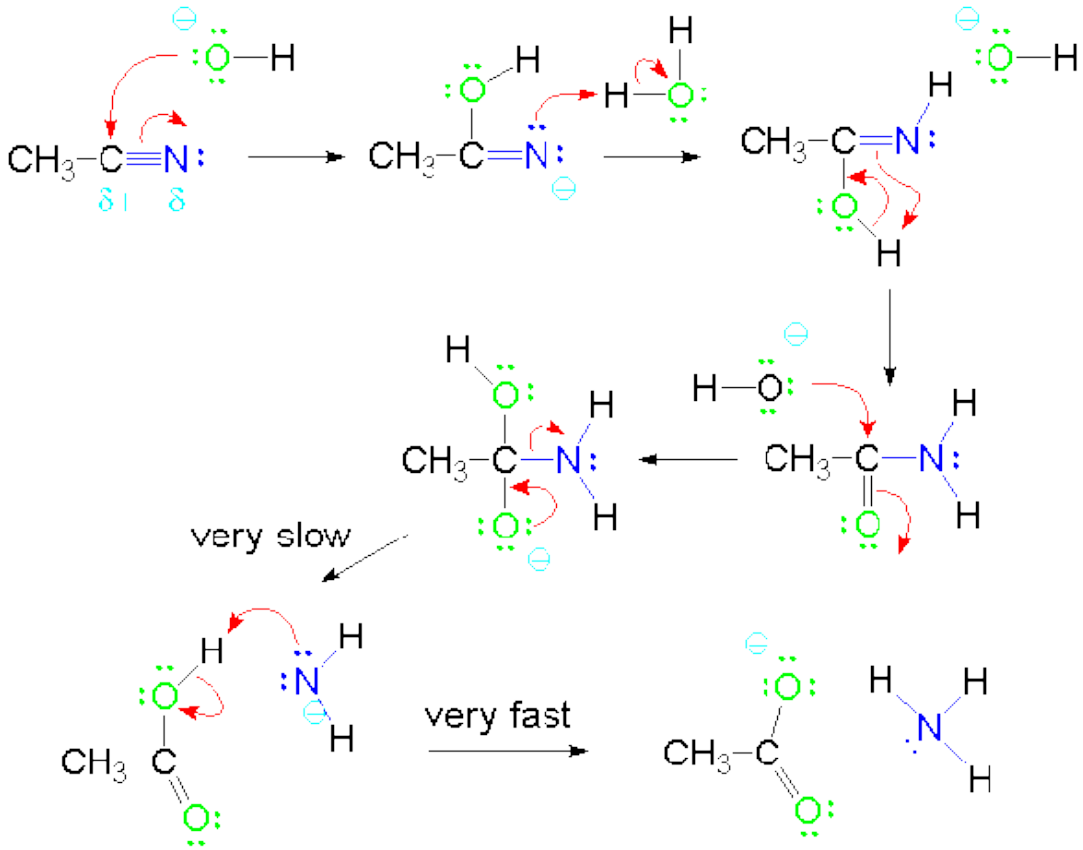
is one of the propionic acid class of nonsteroidal anti-inflammatory drugs (NSAID)with analgesic and antipyretic effects It acts by inhibiting the body's production of prostaglandin.

(The prostaglandins are **a group of lipids made at sites of tissue damage or infection that are involved in dealing with injury and illness**. They control processes such as inflammation, blood flow, the formation of blood clots and the induction of labour)

Synthesis of ketoprofen

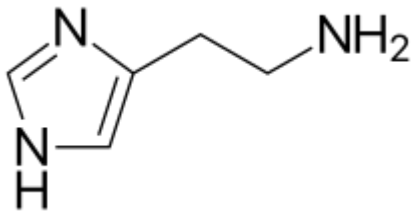

O
CH3
Br2
O
Br
kCN
O
CN
MeI
O
Me
CN
hydrolysis
NaHCO3
HCL
O
Me
COOH

Hydrolysis of cyanide group to carboxylic group



Antihistamine

Histamine



Histamine is an organic nitrogenous compound involved in local immune responses, histamine is produced by basophils and by mast cells found in nearby connective tissues. Histamine increases the permeability of the capillaries to white blood cells and some proteins, to allow them to engage pathogens in the infected tissues.

The discovery of the H1and H2 antagonist burimamide in the early 1970 opened a new ear in the history of the attempt to explane histamine related physiologic processes

Antihistamine

Antihistamines are drugs which treat allergic rhinitis, common cold, influenza, and other allergies. Typically, people take antihistamines as an inexpensive, not patented (generic), drug that can be bought without a prescription and relieves from nasal congestion, sneezing, or hives caused by pollen, dust mites, or animal allergy with few side effects. Antihistamines are usually for short-term treatment.

Mechanism of action

1-Antihistamines are reversible blockers of histamine H1 receptor (**H_1 antagonists**, also called **H_1 blockers**, are a class of medications that block the action of histamine at the H_1 receptor, helping to relieve allergic reactions.) on tissues, such as skin ,bronchi ,eye….etc.

2- Antihistamines are reversible blockers of histamine H2 receptor on tissues, such as stomach ,intestine….etc.

3-Many of antihistamines also possess adrenaline-antagonism which act as anesthetic

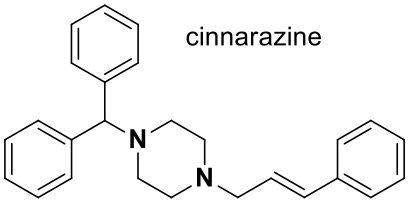
(The adrenal (suprarenal) glands are located at the top of both kidneys. The produce hormones that regulate the immune system, blood pressure, metabolism, and the stress response. In addition, also helps your body do the following:

- Promoting proper cardiovascular function
- Helps in how we respond to stress
- Properly utilizing carbohydrates and fats
- Helps distribute stored fat
- Gives you body odor and pubic hair
- Promotes healthy gastrointestinal functions

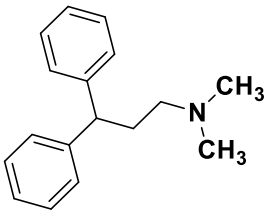
4- many of the traditional antihistamines (first generation) possess some sedative and antimuscarinic effects

5-Now developed antihistamines (second generation) free from these side effect which known as " non-sedating antihistamines "

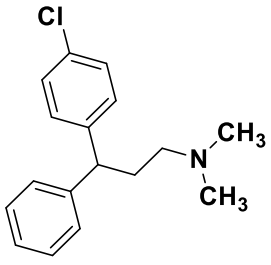
6-some like cinnarazine (second generation) act by inhibiting calcium ions transfer from the outside to inside of the cell so it is value in motion sickness and in vascular disorders



7- Substituents in one of the aryls influence the antihistaminic potency



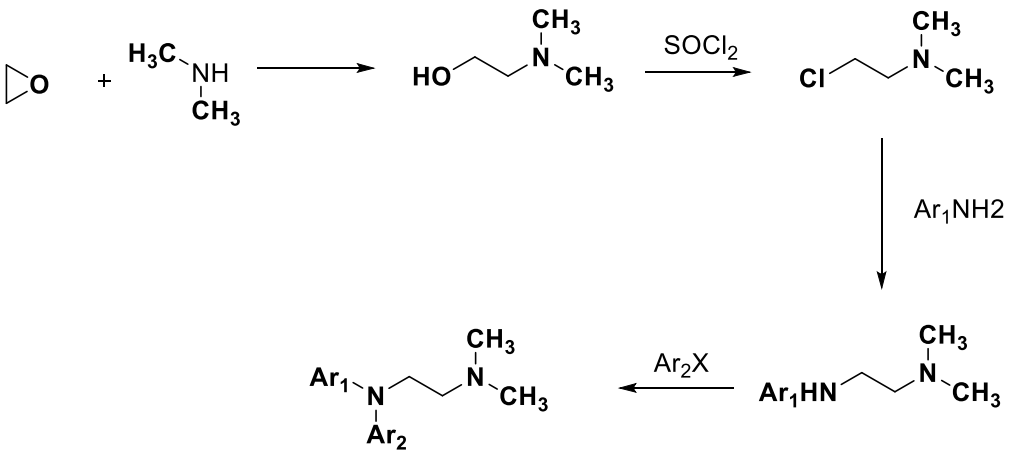
Pheniramine
Usual dose is 20-40mg
Three times daily

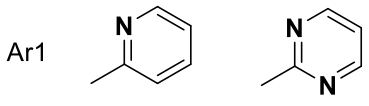


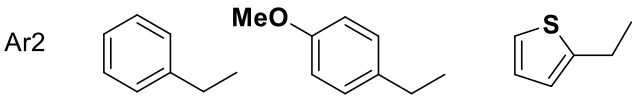
chlorpheniramine
Usual dose is 2-4mg
Three times daily

8- antazoline is a weak antihistamine but potent local anesthetic which used in the eye allergic condition.

General Synthesis of Antazoline derivatives



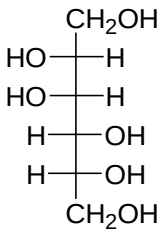


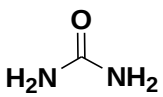


Diuretic

A diuretic is any substance that promotes the production of urine.

In medicine, diuretics are used to treat heart failure, liver cirrhosis, influenza, water poisoning, and certain kidney diseases.

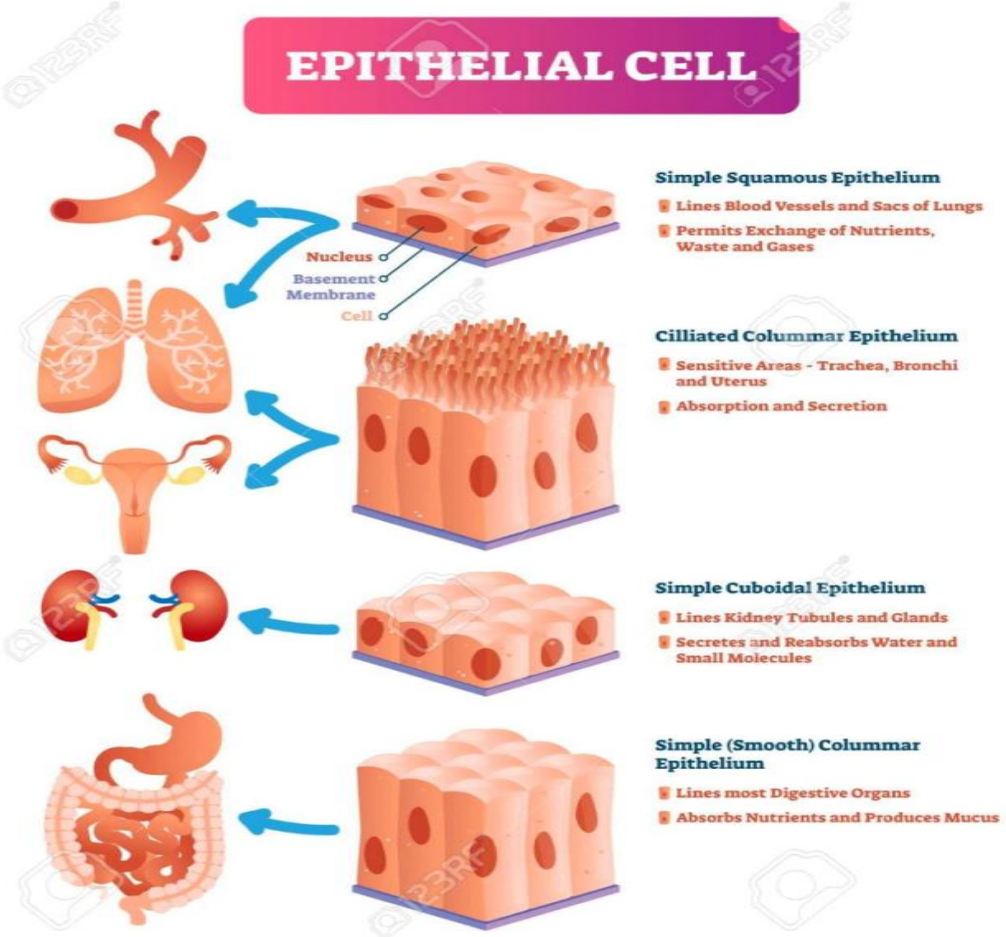




Osmotic diuretics

Osmotic diuretics (e.g. mannitol and urea) are substances that increase osmotlality but have limited tubular **epithelial cell** permeability.

They work primarily by expanding extracellular fluid and plasma volume, therefore increasing blood flow to the kidney.



Mechanism of action

1-Diuretics they effectively reduce blood pressure

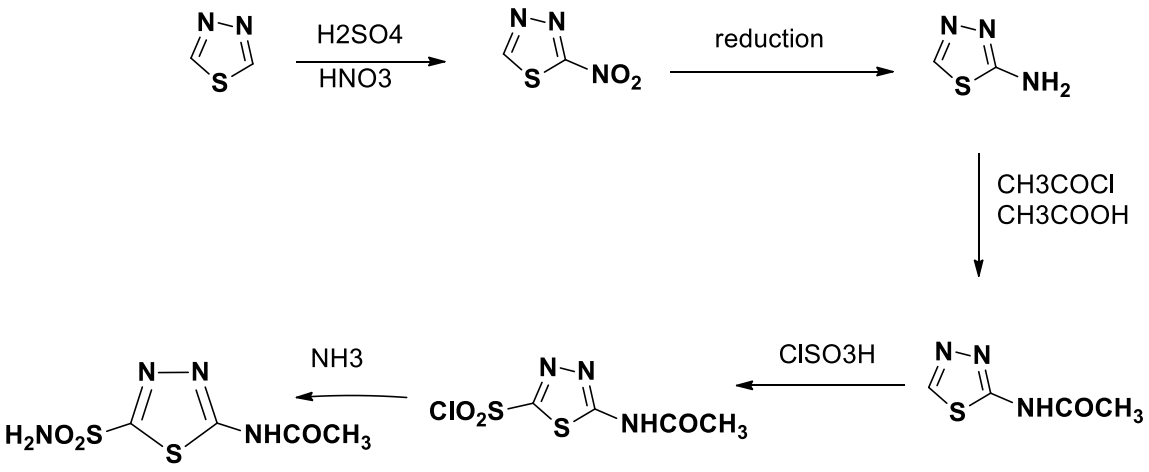
2- Diuretics are a diverse group of compounds that either stimulate or inhibit various hormones that naturally occur in the body to regulate urine production by the kidneys .

Carbonic anhydrase inhibitors: They increase the excretion of sodium, potassium, bicarbonate, and water. Some types of carbonic anhydrase inhibitors include:

Methazolamide .

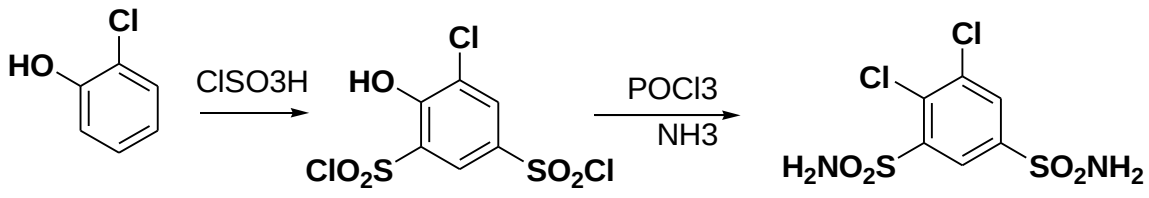
acetazolamide

carbonic anhydride inhibitors (acetazolamide)



2-acetylamino-1,3,4-thiadiazole-5-sulfonamide

dichlorphenamide (Daranide)

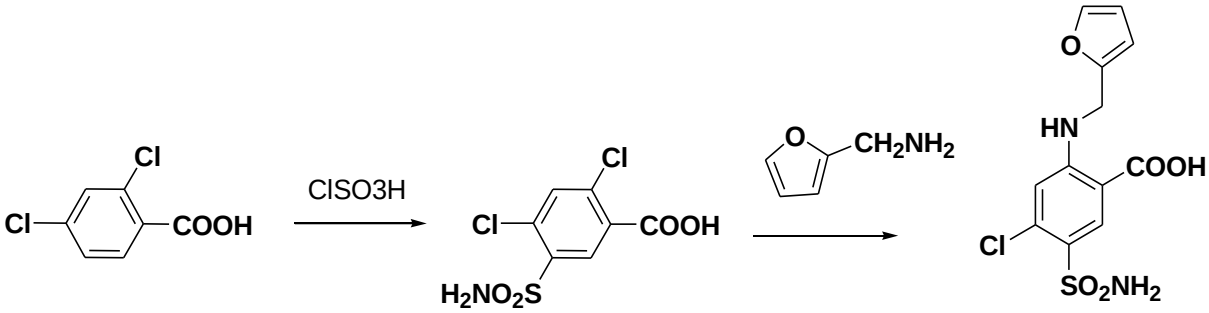


4,5-Dichloro-benzene-1,3-disulfonic acid diamide

Lasix

is a drug choice for urine secretion

(it reduce the body water content and the undesirable salts.)



Local anesthesia

is any technique to induce the absence of sensation in a specific part of the body by block the generation and the conduction of impulses analog a nerve fiber .

It uses :-

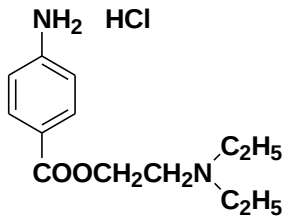
It allows patients to undergo surgical , spinal cord anesthesia and dental procedures with reduced pain and distress Reduced pain caused by minor burns, insect bites, allergic response .

Chemistry

1- ester derivatives e.g cocaine which dose not penetrate the skin ,but absorbed from mucous membranes

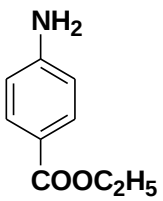
2- amino benzoic acid derivative

a- procaine.HCl



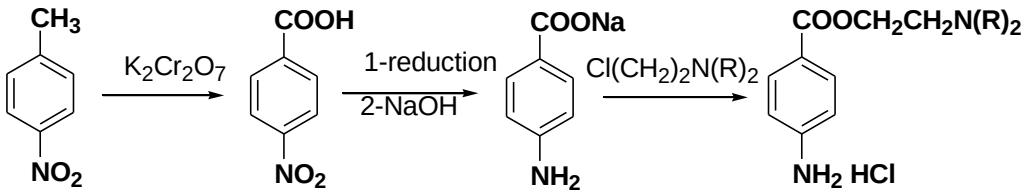
Effective in contact skin or mucous membrane

b- Ethyl p-aminobenzoate



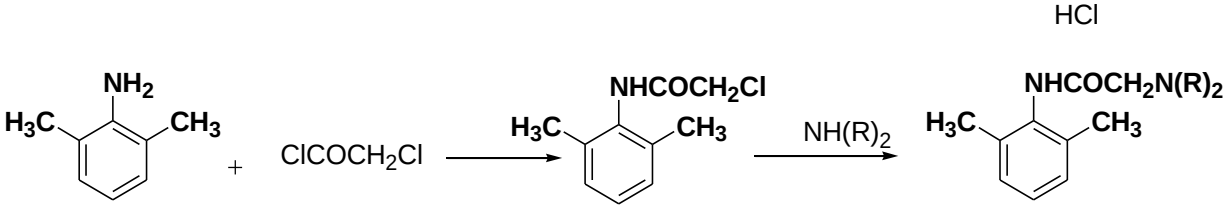
It used in the form of ointment and cream

synthesis of procaine and it's derivative



3-amide derivatives

lidocaine which used in injection, ointment, eye drop .



R= C_2H_5

Diabetes

Diabetes is a disease that occurs when your blood glucose, is too high. Blood glucose is your main source of energy and comes from the food you eat.

Insulin, a hormone made by the pancreas, helps glucose from food get into your cells to be used for energy.

Sometimes your body doesn't make enough—or any—insulin or doesn't use insulin well. Glucose then stays in your blood and doesn't reach your cells.

Antidiabetics

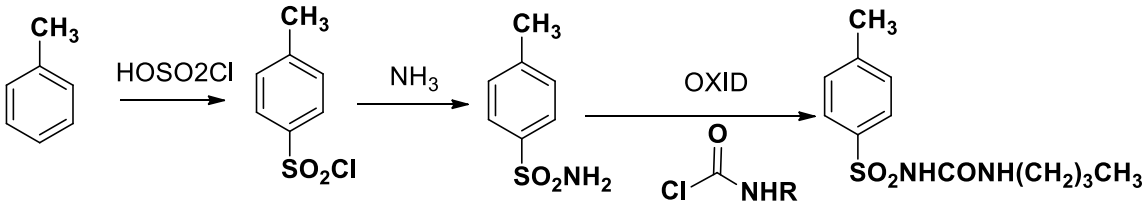
Drugs used in diabetes treat diabetes mellitus by lowering glucose levels in the blood for example :-

1- Type 1 diabetes is a condition in which your immune system destroys insulin-making cells in your pancreas. These are called beta cells. The condition is usually diagnosed in children and young people which treatment with insulin.

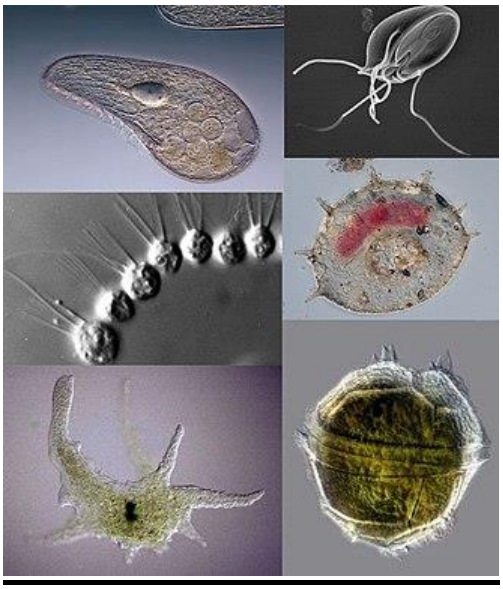
2- type 2 diabetes, in which your body doesn't respond to insulin which treatment with different kind of drug like

sulfonylurea (tolbutamide)

Synthesis of tolbutamide



Anti protozoa drugs

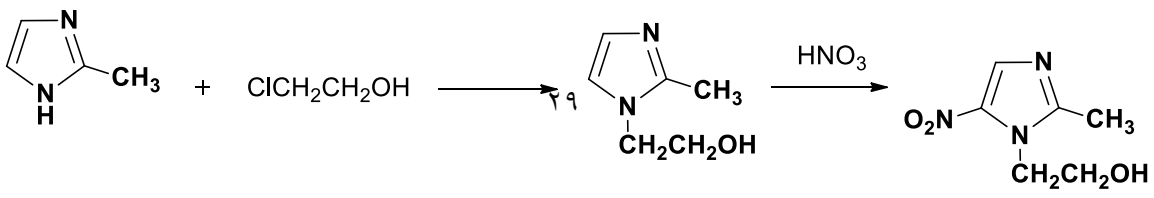


Protozoa Historically, the protozoa were regarded as "one-celled animals", either free-living or parasitic, which feed on organic matter such as other microorganisms or organic tissues

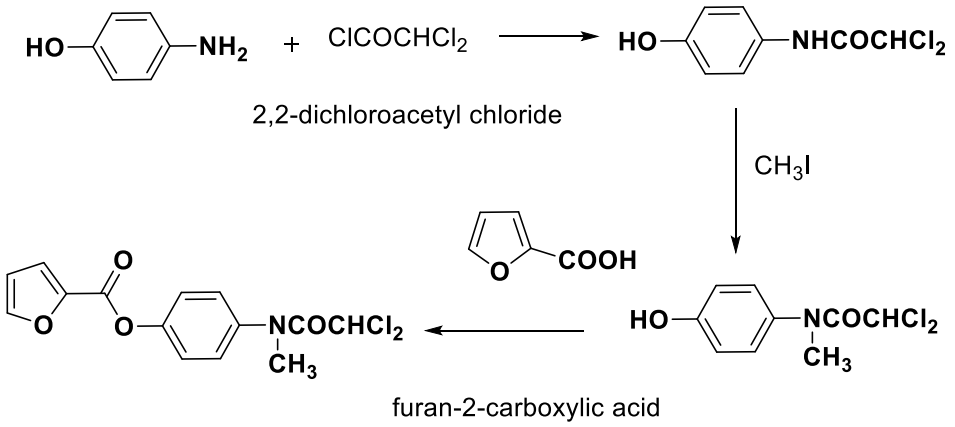
which considered a tropical disease

Treatment:-

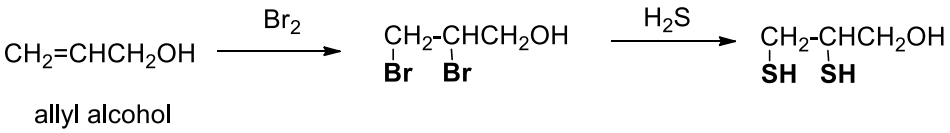
1-Metronidazole (M)



Diloxanide furoate



Dimercaptal



Antifungal agent

Fungi infect skin and lungs and cause diseases

Fungi treatment include:-

1- polyenes :- is a molecule with multiple conjugated double bonds

2- thiazole

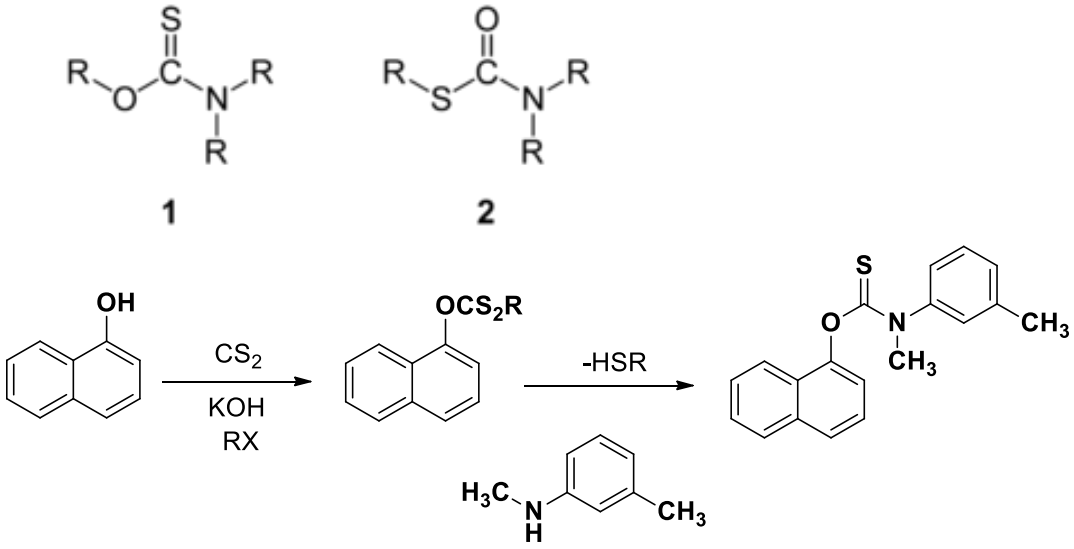
3- unsaturated fatty acid derived from natural castor oil

4-Imidazoles

5- tolnaftate – a thiocarbamate antifungal

synthesis of tolnaftate

Tolnaftate is a synthetic thiocarbamate



Antibiotics

Antibiotics or antibacterials are a type of antimicrobial used in the treatment and prevention of bacterial infection. They may either kill or inhibit the growth of bacteria. Several antibiotics are also effective against fungi and protozoans, and some are

toxic to humans and animals, even when given in therapeutic dosage. Antibiotics are not effective against viruses such as the common cold or influenza, and may be harmful when taken inappropriately

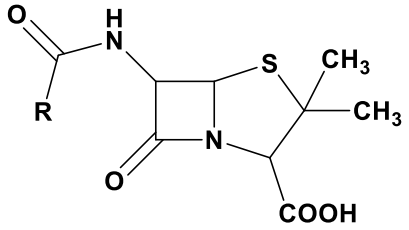
Penicillin (PCN or pen) is a group of antibiotics which include penicillin G (intravenous use), penicillin V (oral use), and benzathine penicillin (intramuscular use). They are derived from Penicillium fungi.

Penicillin antibiotics were among the first medications to be effective against many bacterial infections caused by staphylococci and streptococci.

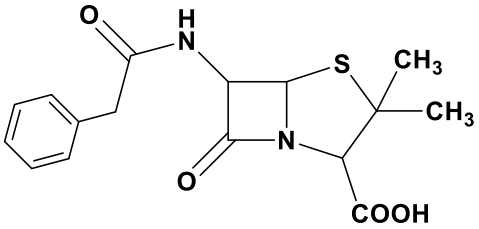
Penicillins are still widely used today, though many types of bacteria have developed resistance following extensive use. All penicillins are β-lactam antibiotics.

About 10% of people report that they are allergic to penicillin

Pencilline derivative

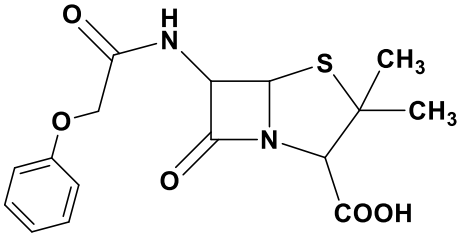


Pencilline G
Benzylpenicillin



As an antibiotic, Penicillin G is noted to possess effectiveness mainly against Gram-positive organisms. Some Gram-negative organisms

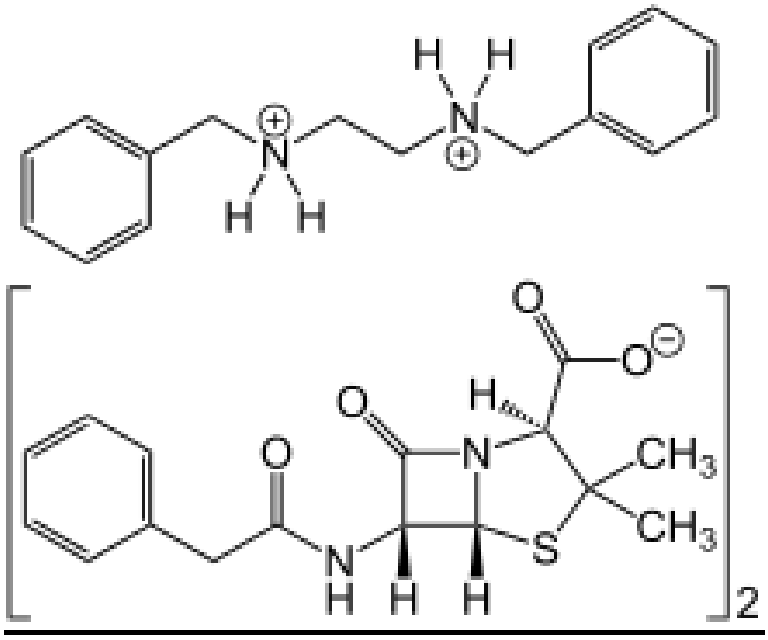
Pencilline v
Phenoxymethylpenicillin



penicillin V, is an antibiotic useful for the treatment of a number of bacterial infections. It is a penicillin that is orally

active. It is less active than benzylpenicillin (penicillin G) against Gram-negative bacteria.

benzathine penicillin
Benzathine benzylpenicillin



It is slowly absorbed into the circulation, after intramuscular injection, and hydrolysed to benzylpenicillin in vivo. It is the drug-of-choice when prolonged low concentrations of benzylpenicillin are required and appropriate, allowing prolonged antibiotic action over 2–4 weeks after a single IM dose

Medical uses for benzathine penicillin include: prevention of rheumatic fever