

Secondary Metabolites: An Introduction to Natural Products Chemistry

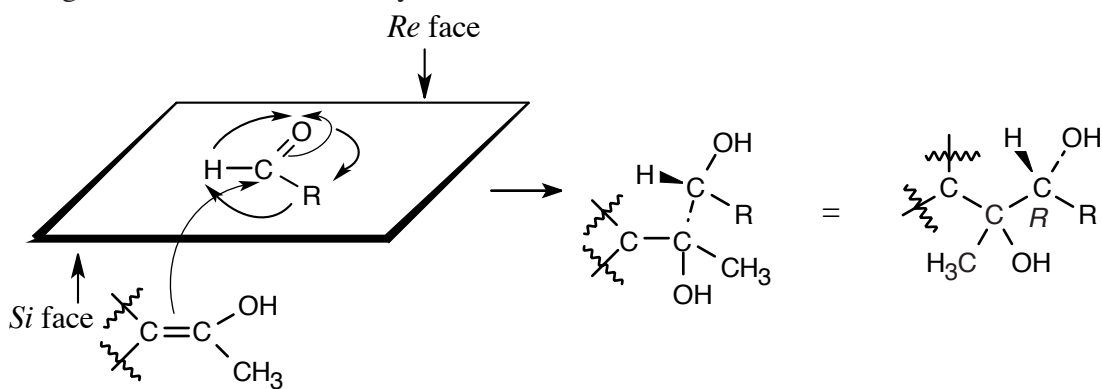
Chapter Outline

- I. Classification of natural products (Section 25.1).
 - A. A secondary metabolite is not necessary for the growth of the organism and is not classified by structure.
 - B. Types of secondary metabolites.
 - 1. Terpenoids and steroids.
 - 2. Alkaloids.
 - 3. Fatty-acid derived substances and polyketides.
 - 4. Nonribosomal polypeptides.
 - 5. Enzyme cofactors.
- II. Synthesis of secondary metabolites (Sections 25.2 – 25.4).
 - A. Biosynthesis of pyridoxal phosphate (Section 25.2).
 - 1. D-Erythrose 4-phosphate is oxidized to D-erythronate 4-phosphate, which is oxidized to 3-hydroxy-4-phosphohydroxy-2-ketobutyrate.
 - 2. 3-Hydroxy-4-phosphohydroxy-2-ketobutyrate undergoes transamination and decarboxylation to yield 1-amino-3-hydroxyacetone 3-phosphate.
 - 3. Pyruvate combines with glyceraldehyde 3-phosphate to form 1-deoxyxylulose 5-phosphate.
 - 4. 1-Deoxyxylulose 5-phosphate combines with 1-amino-3-hydroxyacetone 3-phosphate.
 - a. The initial product is an enamine.
 - b. The enamine cyclizes in an aldol reaction to give pyridoxine 5'-phosphate.
 - 5. Oxidation of pyridoxine 5'-phosphate results in the product, pyridoxal 5'-phosphate.
 - B. Morphine (Section 25.3).
 - 1. Morphine-like compounds share structural similarities.
 - a. An aromatic ring...
 - b. ..attached to a quaternary carbon...
 - c. ..followed by two more carbons...
 - d. ..and a tertiary amine.
 - 2. Biosynthesis of morphine.
 - a. Tyrosine is converted to dopamine by a hydroxylation, followed by a decarboxylation.
 - b. A second tyrosine is converted to *p*-hydroxyphenylacetaldehyde by transamination, followed by decarboxylation.
 - c. Dopamine and *p*-hydroxyphenylacetaldehyde form (*S*)-norcoclaurine.
 - d. Three methylations and an epimerization yield (*R*)-reticulene.
 - e. An oxidative coupling of (*R*)-reticulene gives salutaridine.
 - f. Reduction and cyclization of salutaridine produce thebaine.
 - g. Demethylation and reduction of thebaine yields the final product, morphine.
 - C. Erythromycin (Section 25.4).
 - 1. Polyketides.
 - a. Polyketides are synthesized by a massive synthase enzyme.
 - b. The components of polyketides are simple acyl CoA molecules joined by Claisen condensations.
 - c. The synthase consists of several enzyme domains, each of which adds an acyl CoA to the polyketide.

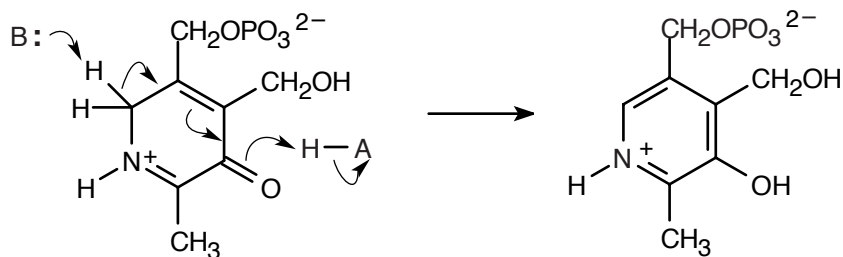
- d. The loading module consists of an acyl transfer (AT) domain and an acyl carrier (ACP) domain.
 - e. Each extension module consists of an AT, an ACP and a ketosynthase (KT) domain.
 - f. Other domains may also be present.
2. Biosynthesis of erythromycin.
- a. Loading: A propionyl CoA binds to an AT and is transferred to an ACP.
 - b. Chain extension.
 - i. The ACP acyl group is transferred to KS1 of module 1.
 - ii. A methylmalonyl CoA is loaded onto the ACP1 thiol group.
 - iii. Claisen condensation and decarboxylation take place.
 - iv. Epimerization and reduction complete the cycle.
 - c. Other extension modules.
 - i. Modules 2,5, and 6 are similar.
 - ii. In module 3, no reduction occurs.
 - iii. The reactions in module 4 are identical to the reactions of fatty acid biosynthesis.
 - d. Release.
 - i. A nucleophilic acyl substitution on the heptaketide is followed by lactonization, and the polyketide is released.
 - ii. Hydroxylation occurs at C6.
 - iii. L-Mycarose is attached to C3.
 - e. Final steps include a glycosylation, a hydroxylation and a methylation.

Solutions to Problems

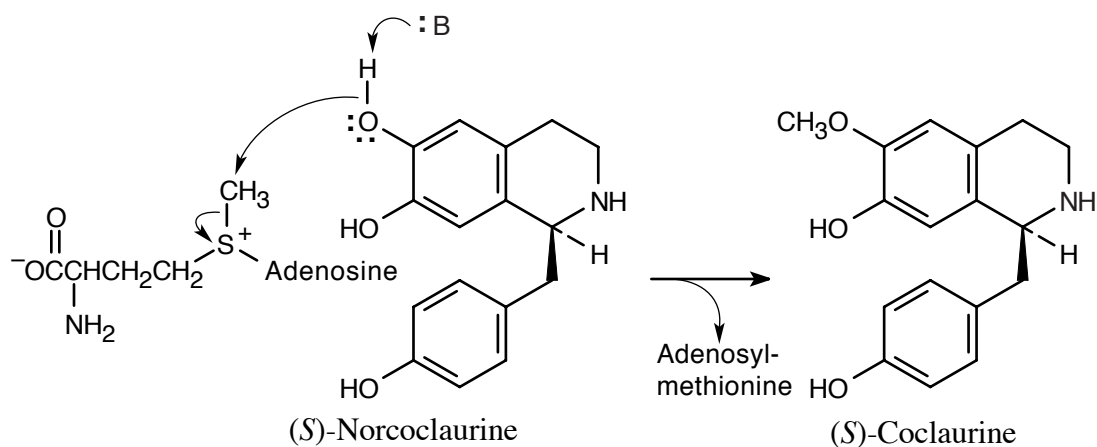
- 25.1** Addition takes place at the *Si* face of glyceraldehyde 3-phosphate to yield a product with *R* configuration at the new chirality center.



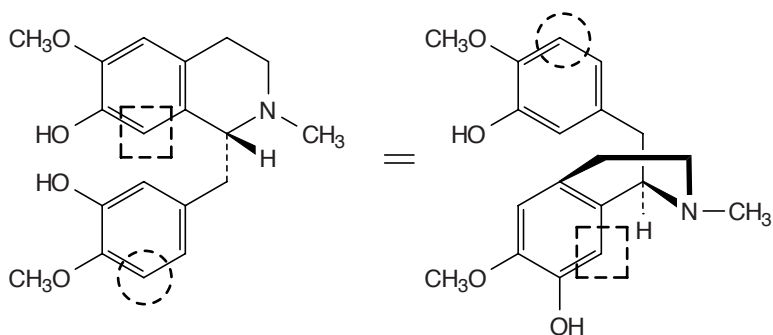
25.2



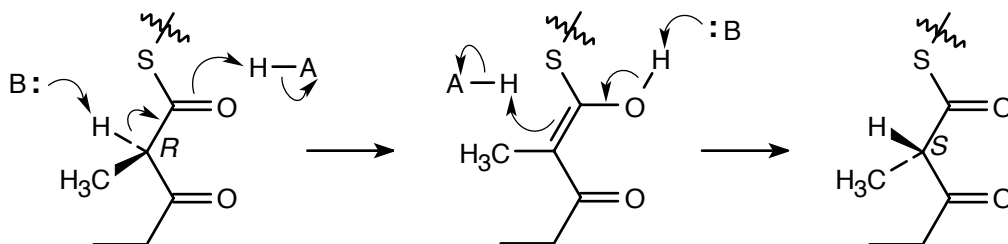
25.3 The reaction is an S_N2 substitution, with adenosylmethionine as the leaving group.



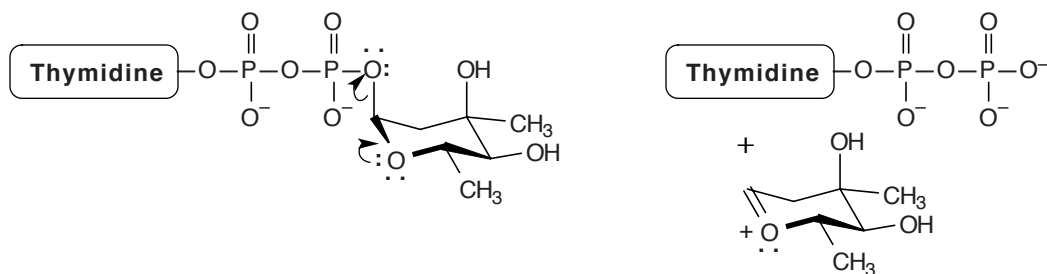
25.4



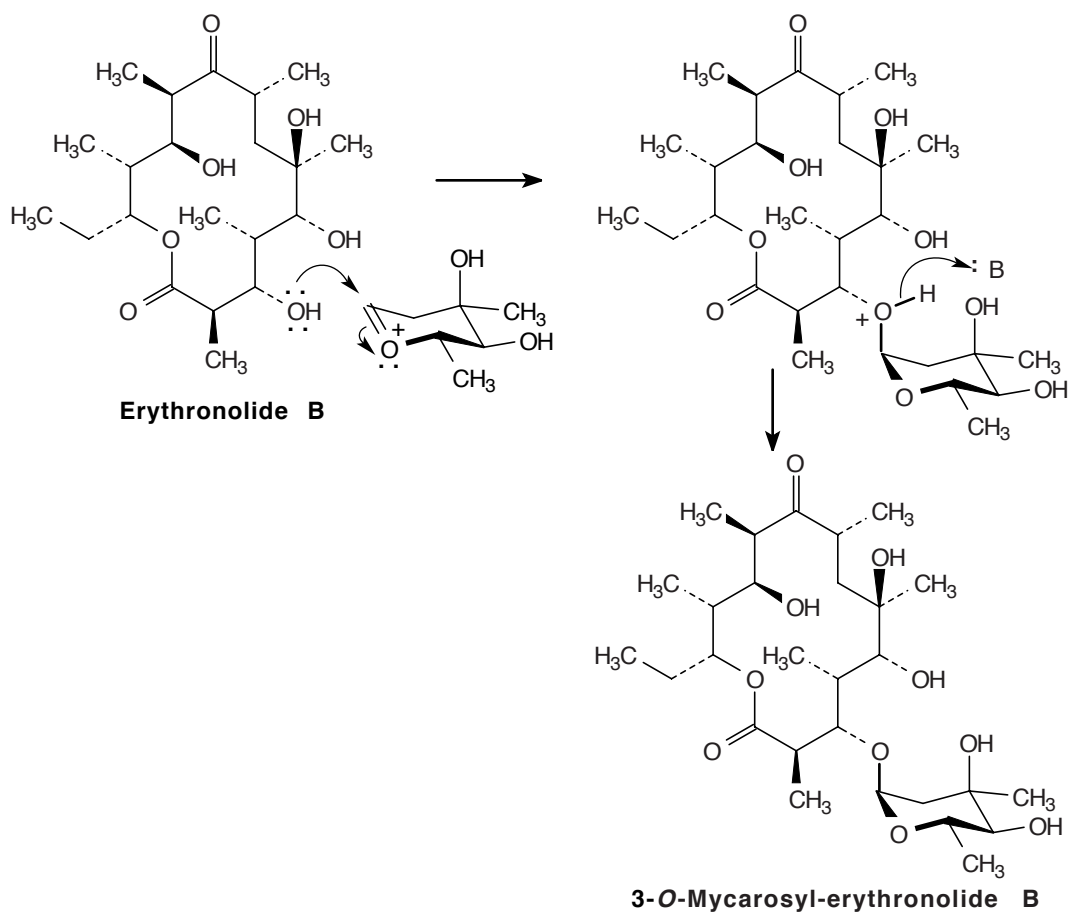
25.5 Epimerization is caused by enolization at the carbon flanked by two carbonyl groups.



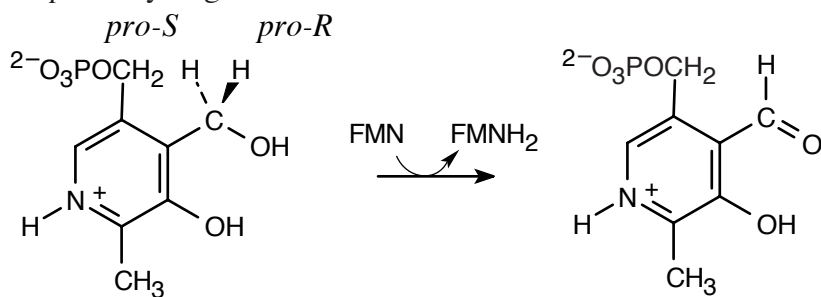
25.6 (1) A glycosyl cation is formed.



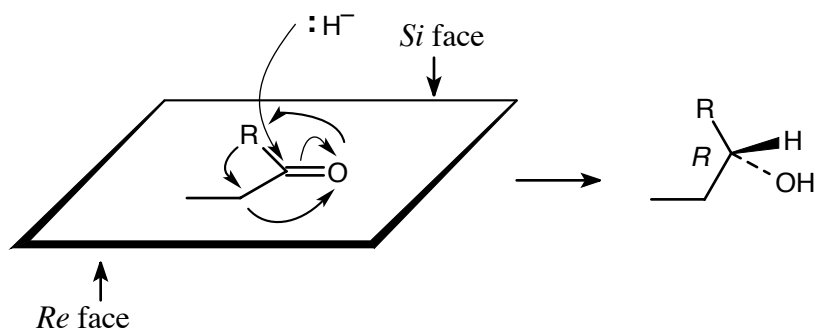
(2) The cation undergoes an S_N1 -type reaction with erythronolide B.



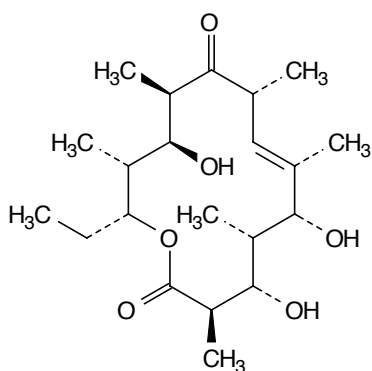
25.7 The *pro-S* hydrogen is removed.



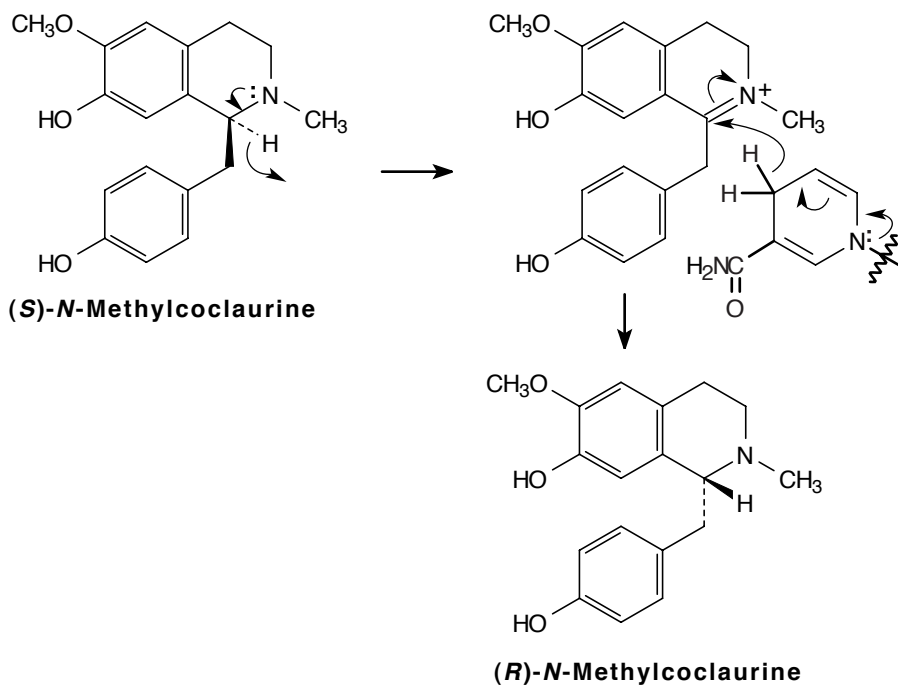
- 25.8** Addition takes place at the *si* face to form a product with *R* configuration at the chirality center.



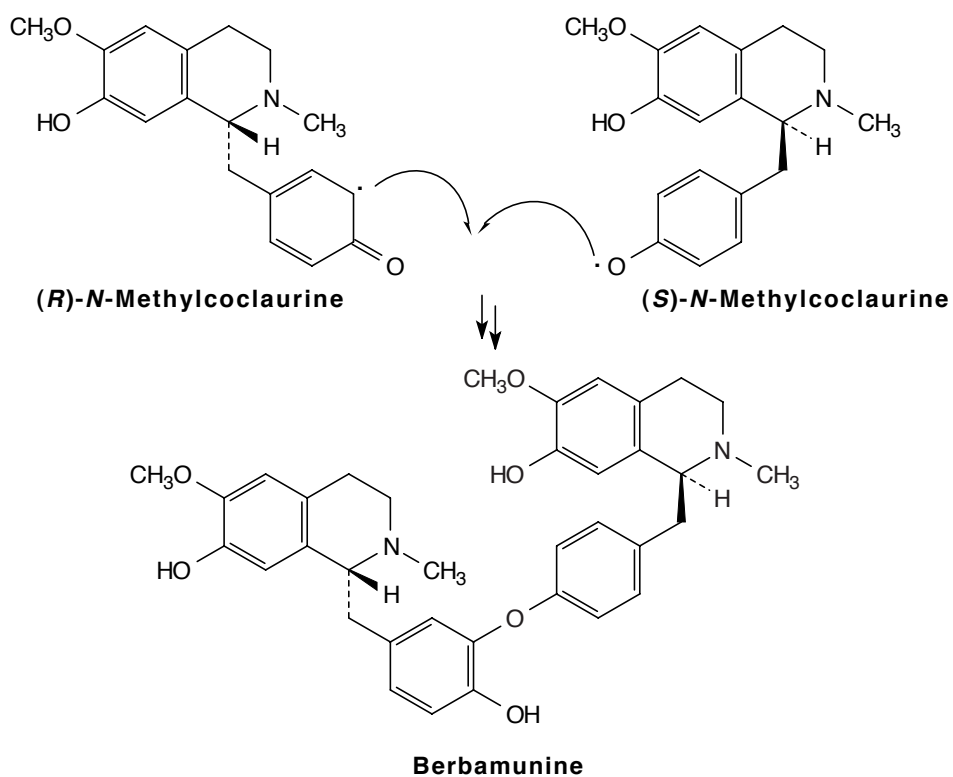
- 25.9** The lactone resembles 6-deoxyerythronolide in all respects except for the double bond. The reduction carried out by enoyl reductase doesn't take place because the enzyme is not active.



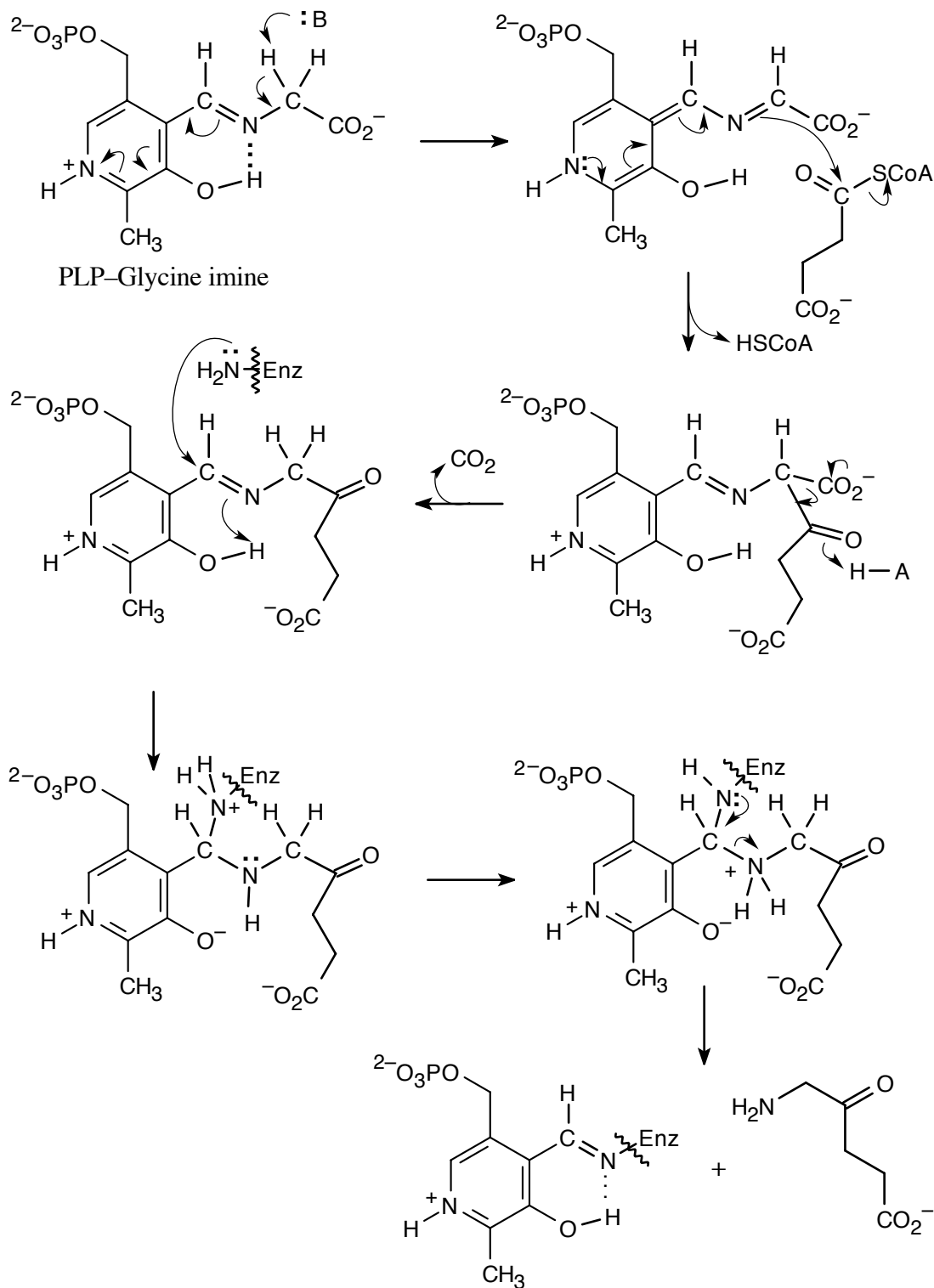
25.10 (*S*)-*N*-Methylcoclaurine is oxidized to an iminium ion by a mechanism that is not understood. Reduction of the iminium ion by NADPH gives the epimeric (*R*)-*N*-methylcoclaurine



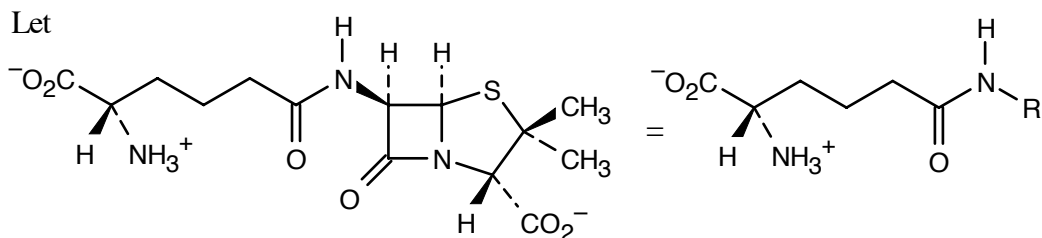
25.11 This is an oxidative coupling reaction similar to the one shown in Figure 25.12. Tautomerization of the adduct gives berbamunine.



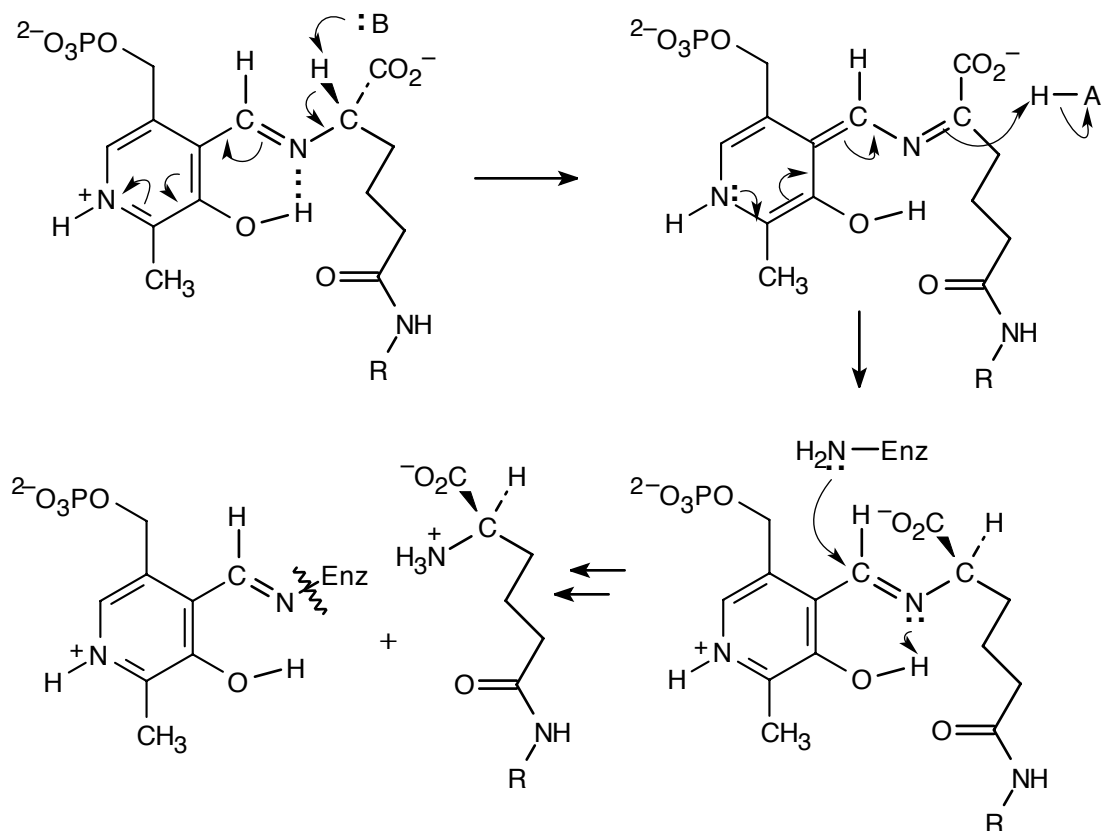
25.12 Section 20.2 gives the mechanism for formation of PLP-amino acid imine.



25.13

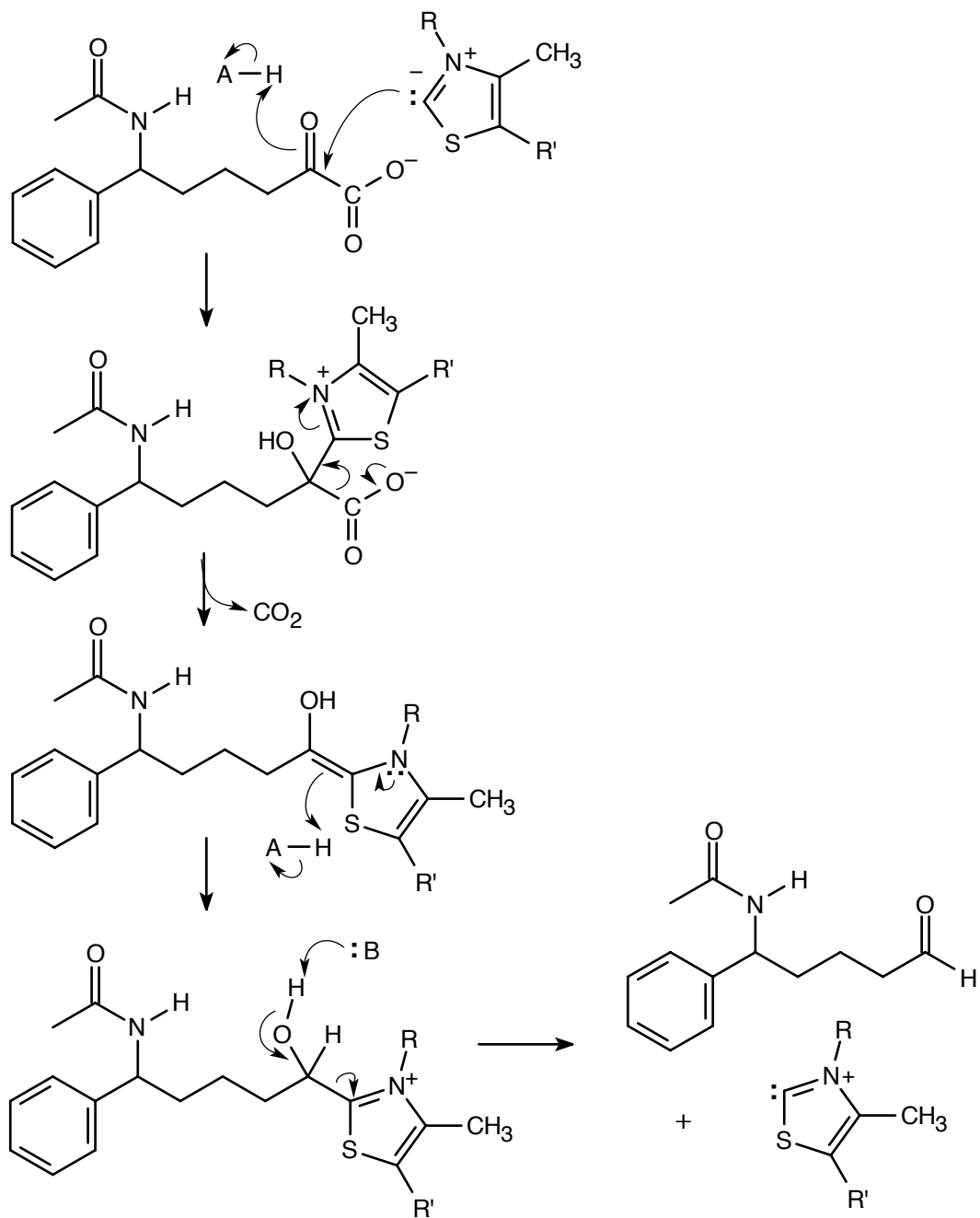


The formation of the PLP-imine of isopenicillin N occurs by a route we have seen many times.

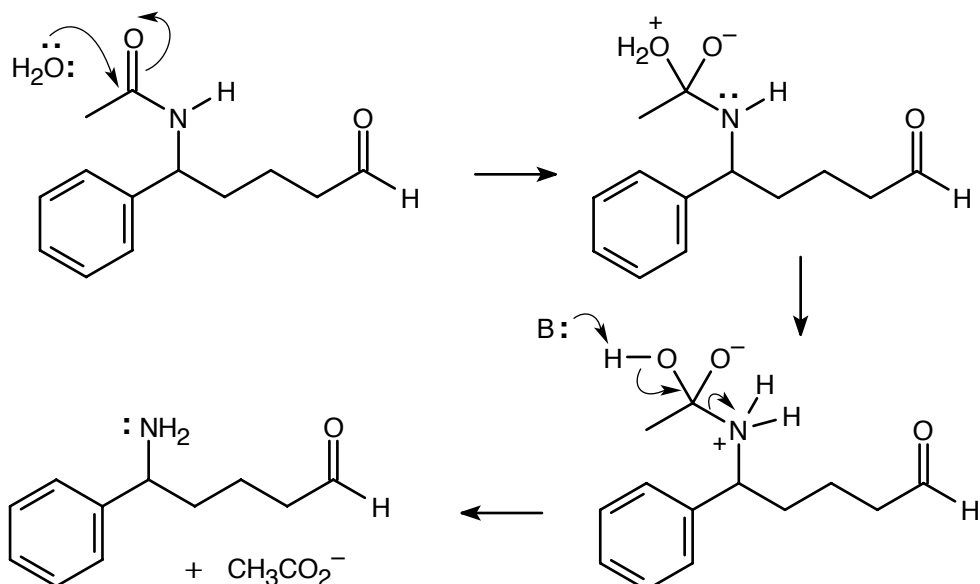


Base removes a proton, and the resulting imine tautomer is protonated to give the epimeric product penicillin N. The mechanism of the last steps is shown in the previous problem.

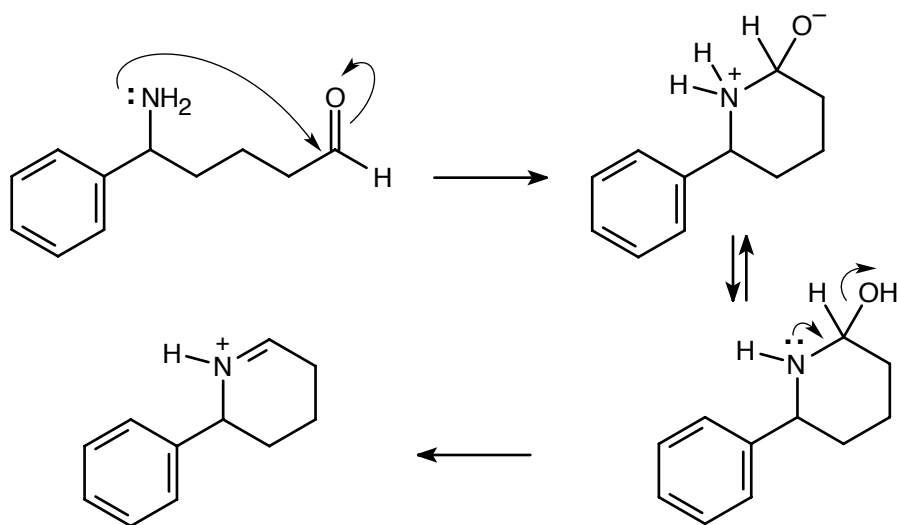
25.14 The mechanism of this problem divides into three parts:
 (1) TPP-catalyzed decarboxylation;



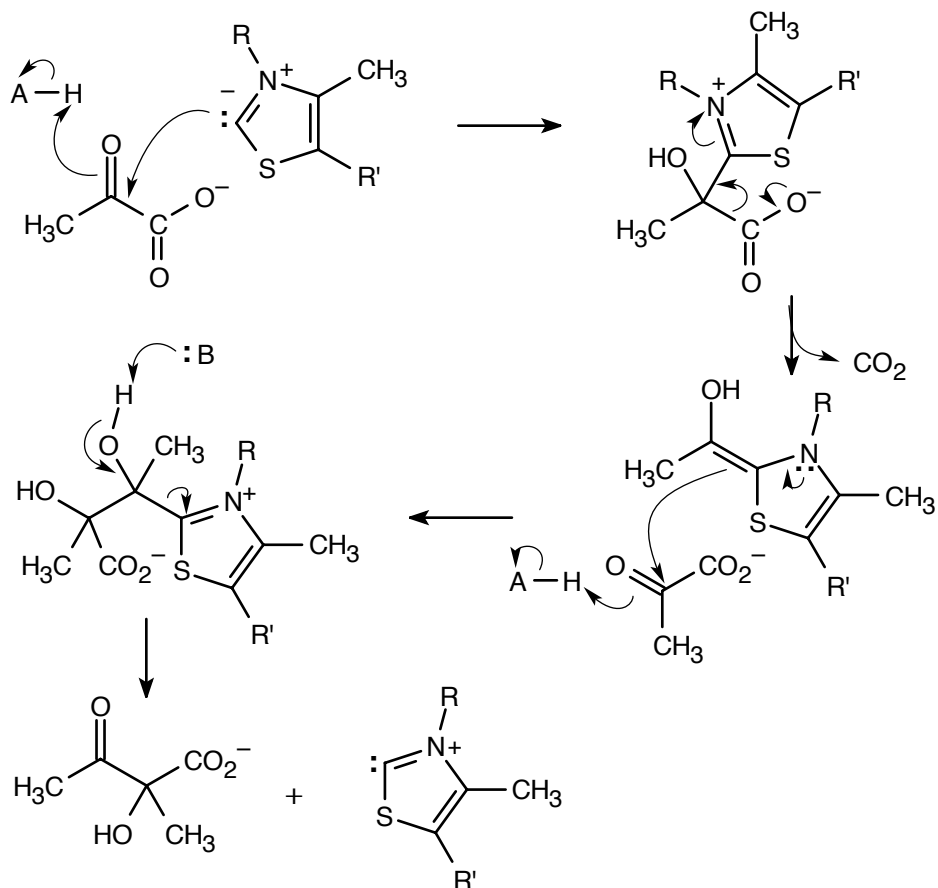
(2) Hydrolysis of the amide bond;



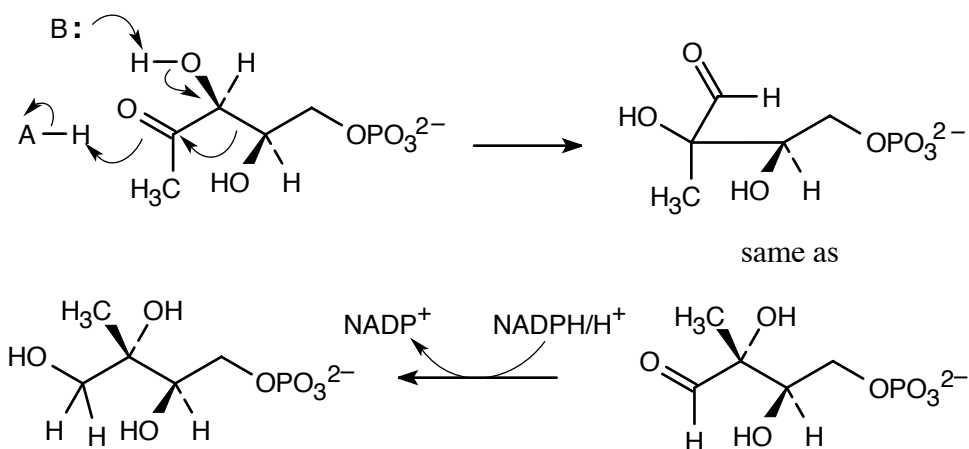
(3) Nucleophilic addition, followed by loss of $^- \text{OH}$, to give the iminium product.



25.15 The first two steps are identical to the first steps in the previous problem.



25.16



25.17

