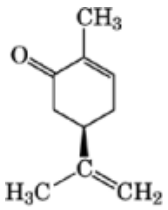
Kirk-Othmer Encyclopedia of Chemical Technology.

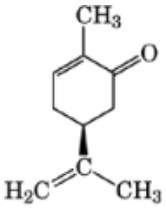
PHARMACEUTICALS, CHIRAL

Stereospecific structure-activity relationships are of sufficient complexity to warrant a clear understanding of the terms involved. Prior to discussing these relationships the following definitions are offered. Stereoisomers are compounds which have the same molecular formula but differ in the arrangement of their atoms in space. Chiral compounds are compounds which have nonsuperimposable mirror images. Enantiomers are pairs of stereoisomers which are nonsuperimposable mirror images; they possess identical physical and chemical properties within an achiral environment. Stereoisomers other than enantiomers, ie, diastereomers, are identified by distinct physical and chemical properties including melting points, spectral characteristics, and rates of reaction with both chiral and achiral reactants. Enantiomers, however, are only distinguished when in the presence of a homochiral environment such as polarized light, chiral solvents, chiral reagents, or chiral molecules such as biomolecules, eg, nucleic acids (qv), proteins (qv), and carbohydrates (qv). The two molecules in a pair of enantiomers rotate a plane of polarized light with equal intensities, but in opposite directions. The dextrorotatory isomer (+ or *d*) rotates the plane of polarized light clockwise; the levorotatory isomer (− or *l*) rotates the plane of polarized light counterclockwise. An equal mixture of (+) and (−)-enantiomers is a racemic mixture or racemic compound and does not rotate a plane of polarized light. Optical rotation, an intrinsic property of the substance, has no bearing on drug–macromolecule interactions. It is the absolute configuration of the homochiral compound that is important for its interaction with biomolecules.

Absorption, metabolism, and biological activities of organic compounds are influenced by molecular interactions with asymmetric biomolecules. These interactions, which involve hydrophobic, electrostatic, inductive, dipole–dipole, hydrogen bonding, van der Waals forces, steric hindrance, and inclusion complex formation give rise to enantioselective differentiation (1, 2). Within a series of similar structures, substantial differences in biological effects, molecular mechanism of action, distribution, or metabolic events may be observed. For example, (*R*)-carvone [6485-40-1] **(1)** has the odor of spearmint whereas (*S*)-carvone [2244-16-8] **(2)** has the odor of caraway (3, 4).

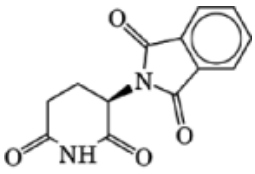


(1)



(2)

The amino acids L-leucine, L-phenylalanine, L-tyrosine, and L-tryptophan all taste bitter, whereas their D-enantiomers taste sweet (5) (see AMINO ACIDS). D-Penicillamine [52-67-5], a chelating agent used to remove heavy metals from the body, is a relatively nontoxic drug effective in the treatment of rheumatoid arthritis, but L-penicillamine [1113-41-3] produces optic atrophy and subsequent blindness (6). L-Penicillamine is roughly eight times more mutagenic than its enantiomer. Such enantioselective mutagenicity is likely due to differences in renal metabolism (7). (*R*)-Thalidomide **(3)** is a sedative–hypnotic; (*S*)-thalidomide **(4)** is a teratogen (8).



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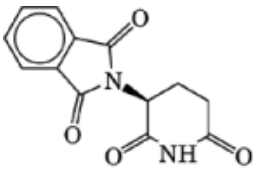


(4)

Unfortunately, (*R*)-thalidomide, containing some of the (*S*)-enantiomer, was given to pregnant women resulting in a large number of fetal deaths and congenital malformations. It is still unclear whether the administration of pure (*R*)-thalidomide **(3)** would have prevented the observed teratogenicity. The stereocenter of thalidomide is labile and may racemize under physiological conditions (9).

Care should be exercised when attempting to interpret *in vivo* pharmacological data in terms of specific chemical–biological interactions for a series of asymmetric compounds, particularly when this interaction is the only parameter considered in the analysis (10). It is important to recognize that the observed difference in activity between optical antipodes is not simply a result of the association of the compound with an enzyme or receptor target. Enantiomers differ in absorption rates across membranes, especially where active transport mechanisms are involved (11). They bind with different affinities to plasma proteins (12) and undergo alternative metabolic and detoxification processes (13). This ultimately leads to one enantiomer being more available to produce a therapeutic effect.

The importance of optical isomers with regard to biological effect has a long history (14) beginning with the observations of Pasteur, who by hand separated nonsuperimposable mirror image crystals of (+) and (-)-sodium ammonium tartrate (15). Subsequently, Pasteur showed that these enantiomers are effectively differentiated by molds and yeasts. Dramatically improved techniques in asymmetric syntheses (16), chiral separations

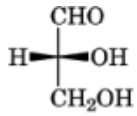
(17), analytical techniques, and stereochemical characterization have led to the widespread production and biological evaluation of numerous homochiral molecules (see Analytical methods). The appearance in the late 1980s of the journals *Chirality* and *Tetrahedron Asymmetry* provide testament to this vastly expanding research area (18–20). The U.S. FDA requires that both enantiomers of a drug be individually tested when associated toxicities occur near the effective dose of the racemic substance (21, 22). It has been suggested that the use of racemic drugs in human subjects cannot be justified until both enantiomers are tested thoroughly, both individually and in composite mixtures. Often, side effects of therapeutics are not discovered until after large-scale marketing (18). The distomer (therapeutically inactive enantiomer) may be at best a nontoxic impurity, but is often associated with dangerous side effects as exemplified by the thalidomide problem.

The thrust toward homochiral drugs by leading researchers and organizations such as the FDA, the rapidly expanding technology of asymmetric syntheses and chiral separations, the decreased side effects found with homochiral drugs, and the potential financial benefits are expected to ensure that the majority of chiral synthetic drugs will, in the future, be available in enantiomerically pure form (see Pharmaceuticals; Research/technology management).

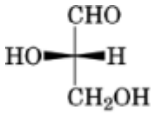
1. Background

1.1. Nomenclature

Compounds which have tetrahedral atoms having four different substituents are often chiral. These tetrahedral atoms are referred to as stereocenters or stereogenic atoms; the terms asymmetric atom or asymmetric center are considered misnomers. The letters D and L are used to denote the absolute configurations of amino acids and sugars according to Fischer-Rosanoff nomenclature (qv) (23) (see Sugar). In this system, dextrorotatory glyceraldehyde [453-17-8] **(5)** is arbitrarily assigned an absolute configuration of D (24). In a Fischer projection, the most highly oxidized carbon is placed on top and the last stereocenter determines the absolute configuration L or D. Examples of Fischer projections are shown for D- and L-glyceraldehyde **(6)** and D-glucose [492-62-6] **(7)** and L-glucose [921-60-8] **(8)** where the arrow denotes the determining stereocenter.



(5)



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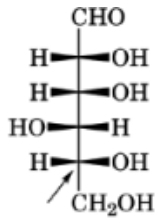
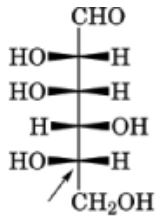


D-glucose [*492-62-6*]

(**7**)



L-glucose [*921-60-8*]

(**8**)

If the heteroatom attached to the last stereocenter projects to the right, the compound is of the D-configuration; if the heteroatom points to the left, the compound is of the L-configuration (23). There is no simple relationship between sign of rotation (*d* (+) or *l* (−)) and the absolute configuration D or L. However, optical activity may be related empirically to absolute configuration by observing changes in optical rotation with varying wavelength, ie, optical rotatory dispersion (ord) and circular dichroism (cd) (25).

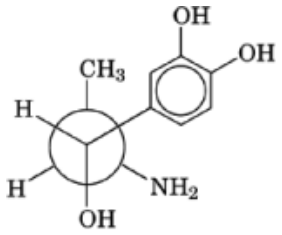
Because of ambiguities involved in this nomenclature, the Cahn-Ingold-Prelog rules were introduced and are widely used to designate the absolute configuration of stereocenters (26). Groups attached to the stereogenic atom are assigned priorities according to the atomic number of the atom attached to the stereogenic center. Highest priority is given to the atom with the highest atomic number. The molecule is drawn such that the function of lowest priority (*d*) is directed away from the viewer:

(*R*)-enantiomer

(*S*)-enantiomer

If the observed order of priority of the remaining three functions ($a > b > c$) is in a clockwise direction, the absolute configuration is designated *R* (rectus or right); if counterclockwise, the configuration is *S* (sinister or left). The concepts of stereochemistry and chirality have been extensively discussed and reviewed (27–29).

For compounds with n stereocenters, 2^n stereoisomers are possible. These stereoisomers consist of a set of diastereomers and the enantiomer of each diastereomer. Diastereomers with two stereocenters may be named using erythro and threo terminologies. Erythro indicates that the highest priority groups are on the same side of the molecule or in a cis relationship when the lowest priority groups of both stereocenters are directed away from the viewer, eg, (1*S*,2*R*)-2-methylnoradrenaline **(9)**. Threo indicates that the highest priority groups are on opposite sides of the molecule or in a trans relationship, eg, (1*S*,2*S*)-2-methylnoradrenaline **(10)**.



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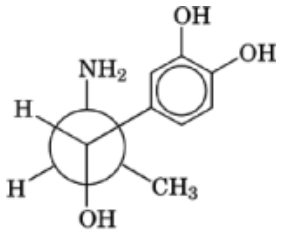
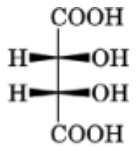


(10)

When vicinal, ie, adjacent, stereogenic carbons have identical functional groups in an erythro relationship, the term meso is used as in *meso*-tartaric acid **(11)**.



(11)

Diastereomers which differ at a single stereocenter are called epimers.

Enantiomeric purity, measured as the enantiomeric excess (ee) of an isomer, is determined by the formula (% major isomer) - (% minor isomer). Thus, if a chiral drug is said to be of 50% ee, the composite mixture contains 75% of one enantiomer and 25% of the other. Enantioselectivity refers to the greater activity of one enantiomer over its mirror image. Enantiospecificity is rarely observed and implies that one enantiomer possesses 100% of the observed activity (30); in most cases it is more accurate to use the term highly enantioselective. The pharmacologically more active enantiomer is termed the eutomer and the less active enantiomer is referred to as the distomer. The eudismic ratio is the ratio of the potency of the eutomer versus the potency of the distomer

for a specific biological or pharmacological action. Generally, highly potent drugs possess high eudismic ratios, a phenomenon referred to as Pfeiffer's rule (19). The eudismic proportion is the ratio of the concentrations of eutomer and distomer ([eutomer]/[distomer]) within a specific tissue or fluid. This is a property determined by enantioselective plasma protein binding, active transport mechanisms, and metabolism (31).

The therapeutic efficacy of a drug is generally measured in terms of ED_{50} or ID_{50} which represent the concentration of drug which produces 50% of the maximum effect or 50% of maximum inhibition. LD_{50} represents the concentration of drug that produces 50% fatalities in test animals. The therapeutic index is the ratio of the ED_{50} versus LD_{50}. Detailed descriptions of the terminology and fundamental principles of pharmacology are available (32) (see Pharmacodynamics).

1.2. Role of Homochiral Molecular Building Blocks

Generally L-amino acids and D-sugars are found in biological systems (33, 34). The evolution of stereochemical preferences in biological processes raises several interesting questions. What is the origin of this biochemical stereoselectivity (35), ie, why are proteins built from L-amino acids and not D-amino acids? What is the significance of homochiral proteins and carbohydrates? What important biological roles do D-amino acids and L-sugars possess? Quantum mechanics and mathematical calculations demonstrate that L-amino acids have a slightly lower energy than D-amino acids (34, 36). Similarly D-glyceraldehyde **(5)**, which serves as a precursor for other sugars, is at a lower energy than the corresponding L-glyceraldehyde **(6)**. These energy differences, estimated to be about 10^{-14} J/mol, arise from the influence of subatomic particles, ie, bosons, quarks, neutrinos, electrons, etc (36, 37). This energy difference, however slight, may have favored the enantioselective formation of L-amino acids and D-sugars and their subsequent selective incorporation into biomolecules.

The formation of D-amino acids in polypeptides and in monomeric form during processing of proteinaceous foods has raised considerable concern about associated nutritional and toxicity effects (37). Racemization of amino acids occurs under strongly basic or acidic conditions, which are conditions used in food processing (qv). The presence of aldehydic contaminants enhances the rate of amino acid racemization through formation of stereogenically labile α-imino acids (**12**) and (**13**) (Fig. 1). D-Amino acids may be utilized in a nutritional manner if they are converted to L-amino acids. Racemase enzymes, observed only in microorganisms, interconvert L- and D-amino acids. Mammals must rely on D-amino acid oxidases to catalyze D- to L-amino acid conversions. Oxidase-catalyzed deamination to α-keto acids (**16**) and subsequent stereoselective amination produces the nutritionally valuable L-amino acids (38). Peptides containing D-amino acid residues are considerably less prone to peptidase hydrolysis than the corresponding all-L-peptides, and this results in the excretion of the peptides without nutritional benefit (38). For the most part, D-amino acids are generally no more toxic than their L-enantiomers. Thus, foods containing proteins with high concentrations of D-amino acid residues may be useful for weight management (38).

1.3. Modeling of Drug-Receptor Interactions

The identification of molecular interactions between drugs and their receptor or enzyme targets and the three-dimensional spatial requirements of the macromolecular binding pocket are important for the rational design of new, more selective, and potent pharmaceuticals (39). Methods used to explore such interactions include nmr spectroscopy of receptor–ligand complexes, molecular modeling, point mutation analysis, and binding assays of conformationally constrained, stereochemically defined small molecules (40) (see Magnetic spin resonance; Molecular modeling (Supplement)). X-ray crystal structure analysis of macromolecule–ligand complexes provides information concerning important molecular interactions which give rise to the observed affinity between the macromolecule and ligand. Computers are used to graphically display calculated crystal structures. Numerous computer programs have been developed and refined which are capable of determining the energy minimized structures of such complexes. These programs, which take into account numerous

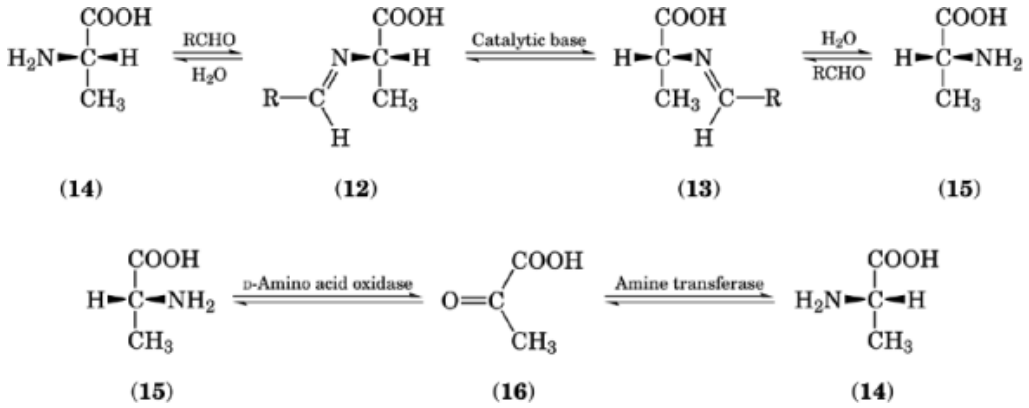


Fig. 1. Processes for the interconversion of D- and L-amino acids.

variables such as bond lengths, bond angles, hydrogen bonding, steric influences, dipole–dipole interactions, etc, provide a basis for studying and predicting the affinities new drugs will possess for their macromolecular targets (41). By using such technology it is often possible to visually discern why enantiomers bind with different affinities to their macromolecular targets.

Molecular modeling techniques, although aesthetically pleasing, are far from reliable owing to the large number of associated variables. Results from molecular modeling studies may be confirmed by comparing calculated molecular binding energies with experimentally obtained binding constants for a series of high affinity compounds. The active sites of receptors and enzymes which have not yet been crystallized may be reliably mapped by such high affinity probes. Furthermore, molecular modeling of known high affinity ligands is also useful in determining potential pharmacophore binding conformations of the substrate, ie, the conformation of functional groups on the substrate which interact with the macromolecular species (enzymes or receptors).

Molecular modeling has provided information about the binding conformation of dopamine D_2-receptor agonists. Such information is useful for the rational design of new highly selective dopamine D_2-receptor agonists. The relative positions of the phenolic hydroxyl, aromatic ring, and amine functionalities, required for binding of these receptor agonists, were determined by the active analogue approach (42) (Fig. 2). For this analysis roughly 20 electronically (MMP2 software) calculated energy minimized conformations were determined for the potent agonists (*R*)-apomorphine [58-00-4] (**17**) and the tricyclic amine (**18**). Only one low energy conformer existed, however, in which the two agonists were superimposable. This conformer was rationalized to have the conformation needed for binding. Subsequent studies provide evidence substantiating this conclusion. A series of 5- and 7-substituted 6-(*N*,*N*-diisopropyl)amino-1-(5,6,7,8-tetrahydro)naphthalenol derivatives (**19**–**24**) were synthesized. Those compounds capable of adopting the predicted binding conformation most easily, ie, had the lowest energy requirements for this conformation, were the most potent, ie, (**19**), (**21**), and (**22**) (42).

The spatial and steric requirements for high affinity binding to protein kinase C (PKC), a macromolecule that has not yet been crystallized, were determined. Protein kinase C plays a critical role in cellular signal transduction and is in part responsible for cell differentiation. PKC was identified as the macromolecular target for the potent tumor-promoting phorbol esters **(25)**. The natural agonists for PKC are diacylglycerols (DAG) **(26)**. The arrows denote possible sites of interaction.

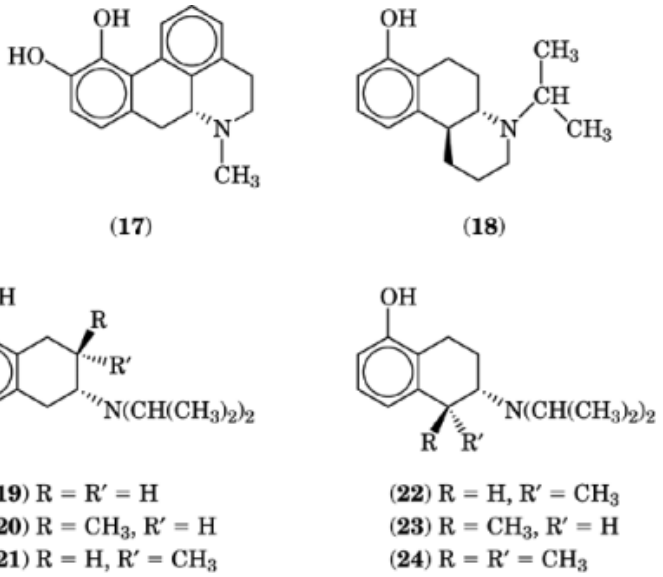
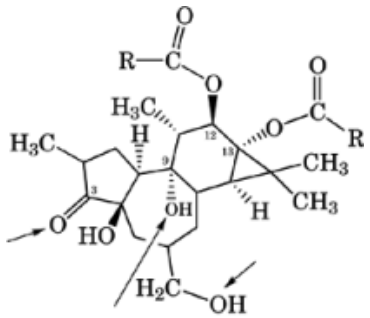
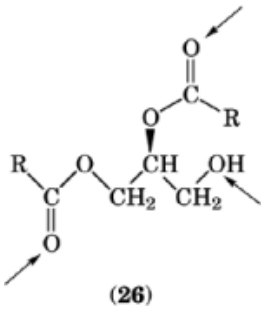


Fig. 2. Molecular modeling of dopamine D_2-receptor agonists used to define the molecular conformation needed for selective high affinity binding.





Molecular modeling demonstrates that phorbol esters act as rigid DAG analogues, in which the pharmacaphore is made up of the C_3 carbonyl, and the C_9 and C_{20} hydroxyl functionalities. Energy minimization

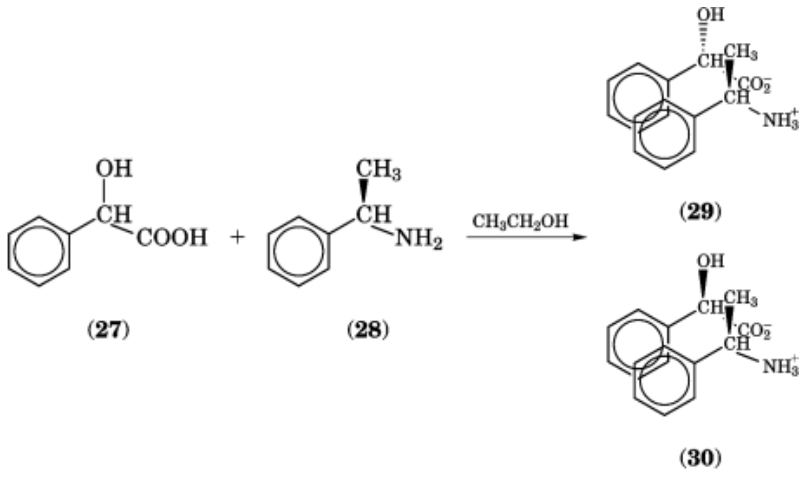
of the x-ray crystal structure of phorbol 12,13-dibutyrate provides a basis on which rigid analogues have been designed and synthesized. The relative binding affinities of these analogues were determined (43), and a correlation between the calculated energy of binding and experimentally determined binding affinities was observed. This work supports the proposed binding conformation of phorbol 12,13-dibutyrate and provides a basis for the design of simplified, novel PKC agonists.

Molecular modeling demonstrates that those compounds which most easily adopt the proposed binding conformation possess the greatest affinity for their specific macromolecular target. Similarly, enantiomers bind to the enzyme or receptor targets in a preferred conformation. Often one enantiomer of the pair requires less energy to adopt the preferred binding conformation and accordingly shows greater affinity for its macromolecular target.

2. Methods for the Preparation of Homochiral Drugs

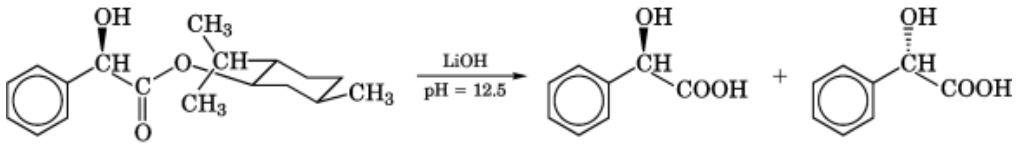
2.1. Resolution Methods

Chiral pharmaceuticals of high enantiomeric purity may be produced by resolution methodologies, asymmetric synthesis, or the use of commercially available optically pure starting materials (44, 45). Resolution refers to the separation of a racemic mixture. Classical resolutions involve the construction of a diastereomer by reaction of the racemic substrate with an enantiomerically pure compound. The two diastereomers formed possess different physical properties and may be separated by crystallization (qv), chromatography (qv), or distillation (qv). A disadvantage of the use of resolutions is that the best yield obtainable is 50%, which is rarely approached. However, the yield may be improved by repeated racemization of the undesired enantiomer and subsequent resolution of the racemate. Resolutions are commonly used in industrial preparations of homochiral compounds (16). Chiral acids and amines are generally separable by crystallization of the diastereomeric salts formed with an appropriate optically pure amine or acid, respectively (46). Racemic mixtures of mandelic acid **(27)** are resolved by treatment with optically pure (*R*)-(+)-methylbenzylamine **(28)** and formation of the diastereomeric salts **(29)** and **(30)**. (*R*)-(−)-Mandelic acid selectively crystallizes with (*R*)-(+)-methylbenzylamine **(28)** and is isolated by simple filtration.



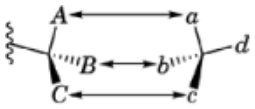
Three general methods exist for the resolution of enantiomers by liquid chromatography (qv) (47, 48). Conversion of the enantiomers to diastereomers and subsequent column chromatography on an achiral stationary

phase with an achiral eluant represents a classical method of resolution (49). Diastereomeric derivatization is problematic in that conversion back to the desired enantiomers can result in partial racemization. For example, (1*R*,2*S*,5*R*)-menthol (*R*)-mandelate **(31)** is readily separated from its diastereomer but ester hydrolysis under numerous reaction conditions produces (*R*)-(-)-mandelic acid **(32)** which is contaminated with (*S*)-(+)-mandelic acid **(33)**.

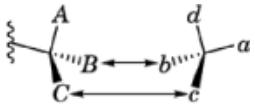


(31) **(32)** **(33)**

Direct resolution of the enantiomers without derivatization is performed by use of an achiral stationary phase with a chiral mobile phase or, more commonly, by use of a chiral stationary phase and an achiral mobile phase. Ligand-exchange chromatography (50–52), using Cu^{2+} proline, and chiral ion pair chromatography, which involves use of a chiral counterion in the mobile phase, exemplify the former method. Chromatographic resolution of enantiomers using chiral stationary phases is advantageous over the previously described methods in that no derivatization is required, there is no need to employ expensive mobile phases, and the method does not require complicated product analysis. Stationary phases include cyclodextrins, protein bonded supports, chiral polymers, and the Pirkle type (53–56) (see Polymers). Pirkle columns involve the attachment of a low molecular weight chiral molecule to a solid support. Diastereomeric interactions between the racemate and the column alter the elution times between the two enantiomers making separation possible. The greater association of one enantiomer than the other with the chiral stationary phase allows for enantiomeric differentiation and separation. The three-point rule for chiral recognition is used to rationalize the separation of enantiomers by use of a homochiral stationary phase and an achiral eluent. The (*S*)-enantiomer possesses three favorable interactions with the stationary phase and is therefore expected to traverse the column at a slower rate than its (*R*)-enantiomer, which maintains only two favorable interactions (53).



(*S*)-enantiomer



(*R*)-enantiomer

Enzymes are used in organic syntheses because they catalyze reactions under gentle conditions, ie, ambient temperatures and pressure and neutral pH, with high enantioselectivity; in addition, they are inexpensive and can be recycled (44, 57, 58) (see Enzyme applications, industrial; Enzymes in organic synthesis; Microbial transformations). The discovery that enzymes catalyze reactions in organic solvents has greatly enhanced the potential utility of these chiral catalysts (59). Hydrolase enzymes such as pig liver esterase (PLE) show broad substrate specificity and are particularly useful for labile substrates; they are used for the enantioselective hydrolysis of prochiral diesters and the kinetic resolution of racemates via ester

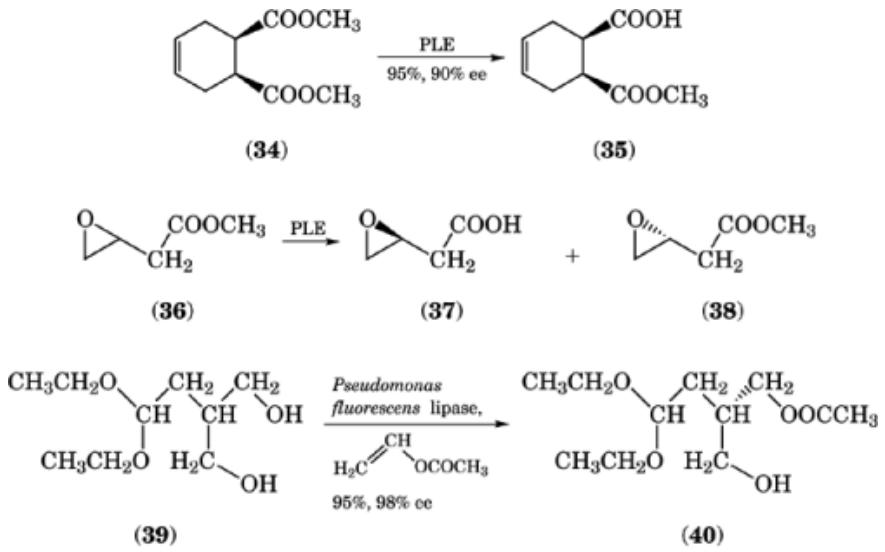
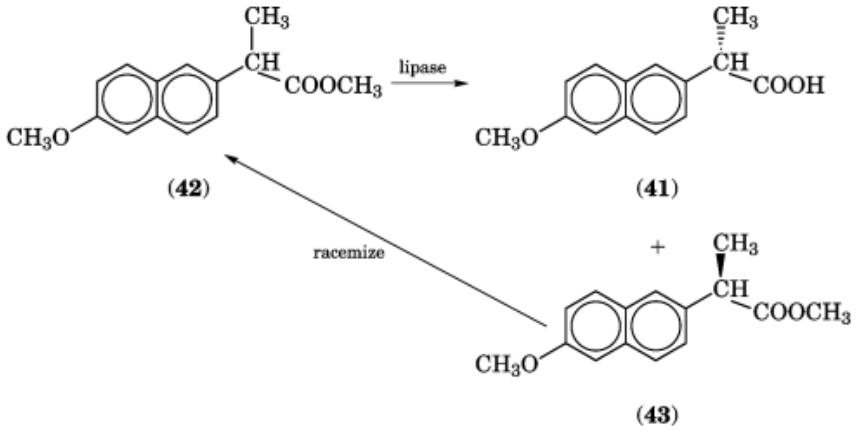


Fig. 3. Enzyme-catalyzed resolutions. PLE=pig liver esterase. See text.

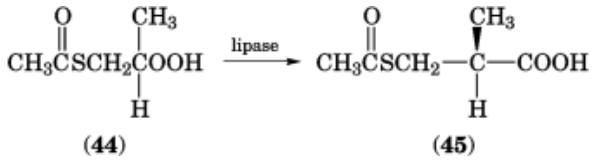
hydrolysis (60). PLE-catalyzed hydrolysis of dimethyl *cis*-cyclohex-4-ene-1,2-dicarboxylate [4841-84-3] (**34**) gives the mono-acid methyl (1*R*,2*S*)-2-carbomethoxycyclohex-4-ene-1-carboxylic acid [88335-94-8] (**35**) in nearly 95% yield and 90% ee (Fig. 3). Treatment of racemic methyl 3,4-epoxybutanoate [4509-09-5] (**36**) with PLE yields (*S*)-3,4-epoxybutanoic acid [109462-43-3] (**37**) and methyl (*R*)-3,4-epoxybutanoate [109462-42-2] (**38**). Enantioselective esterifications can also be carried out enzymatically. (*S*)-2-(2,2-Diethoxyethane)-1-acetyloxy-3-propanol [134665-24-0] (**40**), a useful synthon for the production of homochiral three-substituted butanolides, is prepared by transesterification of 2-(2,2-diethoxyethane)-1,3-propanediol [55387-85-4] (**39**) (61).

Numerous synthetic transformations have been carried out using enzymes. Oxidoreductases are commonly used to reduce prochiral ketones with high enantioselectivity. The addition of hydrogen cyanide to aldehydes, catalyzed by the enzyme mandelonitrile lyase, yields the corresponding (*R*)-cyanohydrins. Nitrile hydrolase converts cyano functionalities into the corresponding carboxylic acids, a transformation which usually requires harsh conditions, such as treatment with concentrated hydrochloric acid for 24 hours (62). A principal disadvantage in the use of enzymes is that they produce only one enantiomer; it is not always straightforward to produce the other optical isomer. However, in industry this is not problematic because large-scale production of only one isomer is usually required (63). Naproxen [22204-53-1] **(41)**, a nonsteroidal antiinflammatory drug marketed as the pure (*S*)-enantiomer, is produced from the methyl ester **(42)** in better than 98% ee using the enzyme *Candida cylindracea* lipase (64). The (*R*)-ester **(43)** is subsequently racemized and retreated with the enzyme to optimize the yield of the (*S*)-enantiomer.

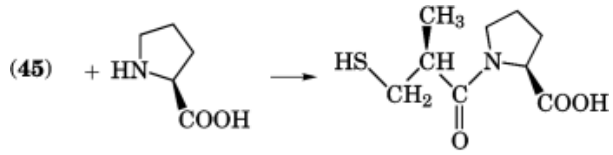


(42) (41) (43)

One of the homochiral starting materials **(45)** for the acetylcholinesterase (ACE) inhibitor captopril [62571-86-2] **(47)** is produced by a lipase enzyme-catalyzed resolution of racemic 3-methyl-4-acetylthiobutyric acid **(44)** and *S*-proline **(46)** (65).

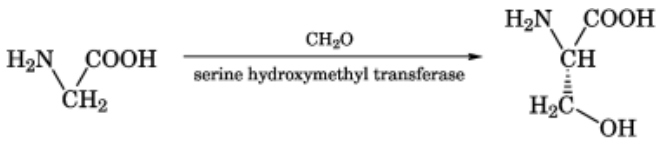


(44) (45)



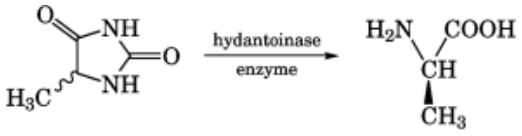
(46) (47)

Several strategies for the production of pure D- or L-amino acids rely on the use of enzymes. L-Serine **(49)** is synthesized by combining glycine **(48)** and formaldehyde in the presence of the enzyme serine hydroxymethyl transferase (66).



(48) (49)

Both pure L- and D-amino acids can be made using hydantoinase enzymes. These enzymes catalyze the stereoselective hydrolysis of racemic hydantoins such as **(50)** which is used for the production of D-alanine **(15)** (58).

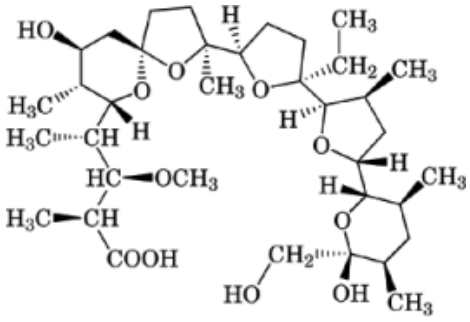


(50) (15)

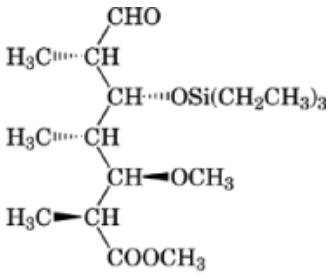
The high degree of stereoselectivity observed with enzyme reactions provides further evidence as to the importance of drug stereochemistry for pharmaceutical activity.

2.2. Methods Employing Enantiomerically Pure Starting Materials

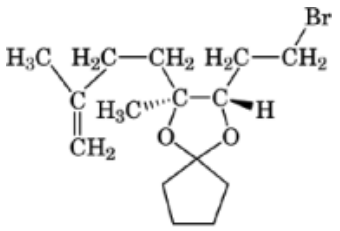
A large number of optically pure natural products are commercially available and relatively inexpensive. Amino acids, carbohydrates, and terpenes are some of the homochiral building blocks used routinely in enantiomeric syntheses (67–69). The stereocenter(s) in such building blocks are used as either chiral synthons (chirons) or as chiral auxiliaries. Chirons are incorporated directly into the desired target molecule; chiral auxiliaries are used as an external handle to direct the formation of other stereocenters within the desired molecule and are subsequently cleaved. Chirons are an inexpensive source of chirality and their use in organic synthesis generally produces enantiomerically pure compounds of known absolute configuration. The commercially available polyether antibiotic monensin [17090-79-8] **(51)** (Fig. 4), which contains 17 stereocenters, is synthesized by the preparation and coupling of three fragments, **(52)**, **(58)**, and **(63)**, each prepared from commercially available optically active starting materials (70, 71).



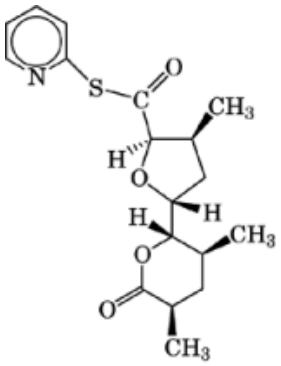
(51)



(52)



(**58**)



(**63**)

The starting material for synthesis of fragment 1 **(52)** is (+)-β-hydroxyisobutyric acid [1910-47-0] (**53**), which is protected and reduced to the aldehyde (**54**). Diastereo-selective aldol reaction with 2-methyl-2-triethylsilyloxy-3-pentanone, oxidative cleavage, and dimethylation produces the optically pure diastereomer (**55**) in 50% yield. Deprotection and oxidation produces aldehyde (**56**), which undergoes a second aldol reaction with *cis*-2-butenyldiethylaluminum at -78°C followed by spontaneous lactonization to yield lactone intermediate (**57**). This intermediate contains five stereocenters of the desired configuration for the production of monensin. Lactone (**57**) is converted to fragment 1 by ozonolysis of the corresponding methyl ester. Fragment 2, the spiroketal **(58)**, is prepared from natural (*S*)-(-)-malic acid [97-67-6] (**59**). Regioselective acetonide formation, followed by reduction of the free carboxylic acid, acid-catalyzed lactonization, and α-hydroxyl group protection produces the homochiral lactone (**60**). Grignard reaction with methyl magnesium bromide, and primary alcohol protection with *tert*-butyldimethylsilylchloride (TBS) yields ketone (**61**). Highly diastereoselective addition of 3-methyl-3-butenylmagnesium bromide affords the threo adduct (**62**) in 96% ee. This compound is subsequently converted to fragment 2. Delta-lactone **(63)**, fragment 3, is synthesized in a convergent manner by coupling aldehyde (**64**), prepared from (*R*)-citronellic acid [18951-85-4] (**65**), with the chiral triphenylphosphine derivative (**66**), synthesized from (*R*)-β-hydroxyisobutyraldehyde [38433-80-6] (**67**). Wittig reaction produces the cis-olefin (**68**), which is subsequently converted to fragment 3. Fragments 2 **(58)** and 3 **(63)** are combined via a Grignard reaction which yields ketone (**69**). Further manipulation yields intermediate (**70**). Aldol reaction of ketone (**70**) with fragment 1 provides polyol (**71**) which is converted to monensin **(51)** by deprotective hydrogenation, acid-catalyzed spiroketalization, and ester saponification (72). The synthesis of monensin provides an outstanding example of how chirons are exploited and manipulated for the construction of stereogenically complex molecules.

Many notable examples of the synthesis of complex natural products from optically pure starting materials have been reported (70). One synthesis of considerable interest is that of taxol [33069-62-4] **(74)**, a potent

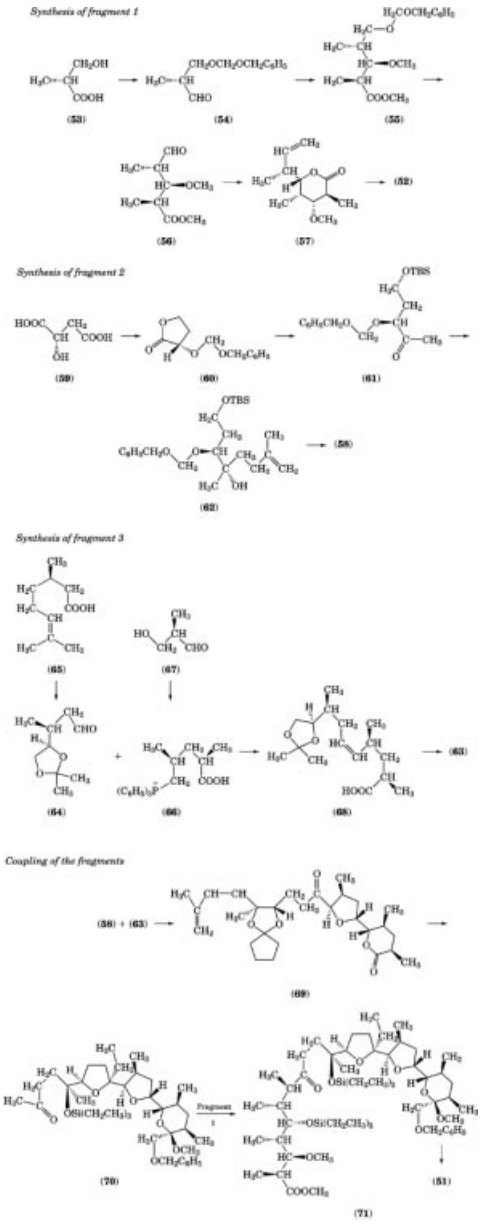
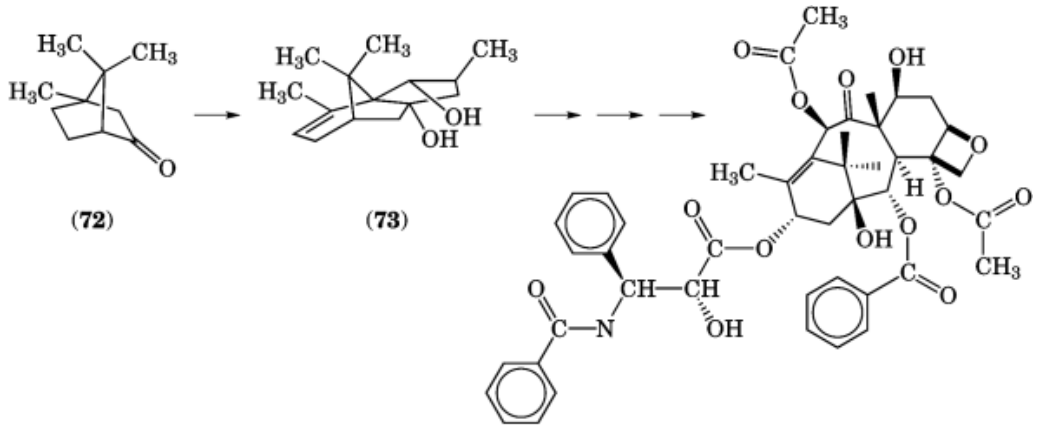


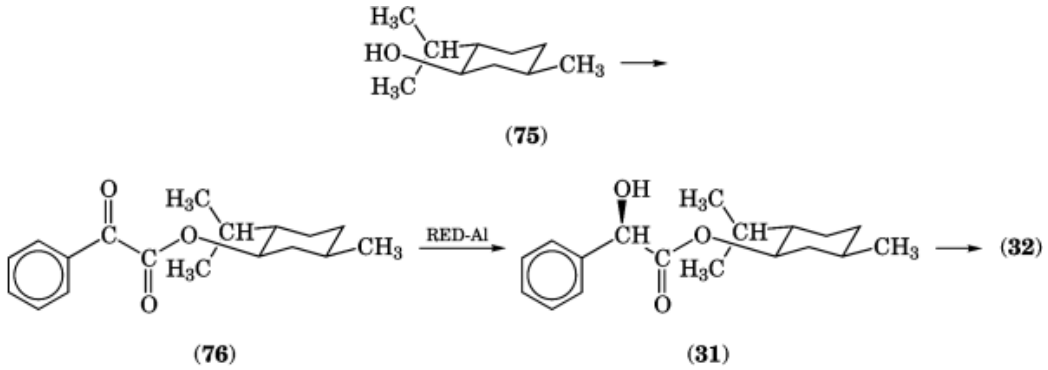
Fig. 4. Synthesis of monensin from homochiral natural products; TBS=*tert*−butyldimethylsilyl chloride.

antitumor agent used clinically. The starting material **(73)** used in the first total synthesis of taxol is produced in enantiomerically pure form from inexpensive and readily available *l*-camphor [464-48-2] **(72)** (73).



(72) (73) (74)

L-Menthol [2216-51-5] **(75)** and D-menthol [15356-70-4] have been used as chiral auxiliaries in the synthesis of optically active mandelic acids. Reduction of (-)-menthol benzoylformate **(76)** with a sterically bulky reducing agent, ie, sodium bis(2-methylethoxy)aluminum hydride (RED-Al), followed by saponification, yields (*R*)-mandelic acid **(32)** of 90% ee.



(75) (76) (31) (32)

One advantage in using chiral auxiliaries is that they may be recycled. Evan's chiral oxazolidinones, such as (**78**) (Fig. 5), are prepared from readily available amino acids such as L-phenylalanine [63-91-2] (**77**). Reduction of L-phenylalanine with borane followed by reaction with diethylcarbonate produces enantiomerically pure oxazolidinone auxiliary (**78**). The use of this auxiliary is exemplified in the preparation of an intermediate (**82**) in the synthesis of the macrolide antibiotic rutamycin B [1404-59-7] (**83**) (74). Reaction of auxiliary (**78**) with butanoyl chloride yields chiral intermediate (**79**). Enolate formation with sodium hexamethyldisilazane produces the sodium-chelated intermediate (**80**). Addition of allyl iodide results in stereoselective alkylation, from the side opposite the protruding benzyl group of the auxiliary, yielding (**81**). Lithium peroxide-catalyzed hydrolysis provides enantiomerically pure 2-ethyl-4-pentenoic acid (**82**) and the chiral auxiliary (**78**).

Oppolzer's chiral sultams, such as (-)-bornane-10,2-sultam [94594-90-8] (**85**) (Fig. 6), have been used to control stereoselective enolate formation and direct stereoselective alkylation in the synthesis of numerous nonnatural amino acids (75). Both (−)- and (+)-bornane-10,2-sultams are prepared from commercially available (+)-(**84**) and (-)-camphorsulfonic acids. The use of a chiral sultam for the synthesis of L-phenylalanine (**90**) is shown in Figure 6. Trimethylaluminum-catalyzed reaction of sultam (**85**) with a glycine methyl ester derivative

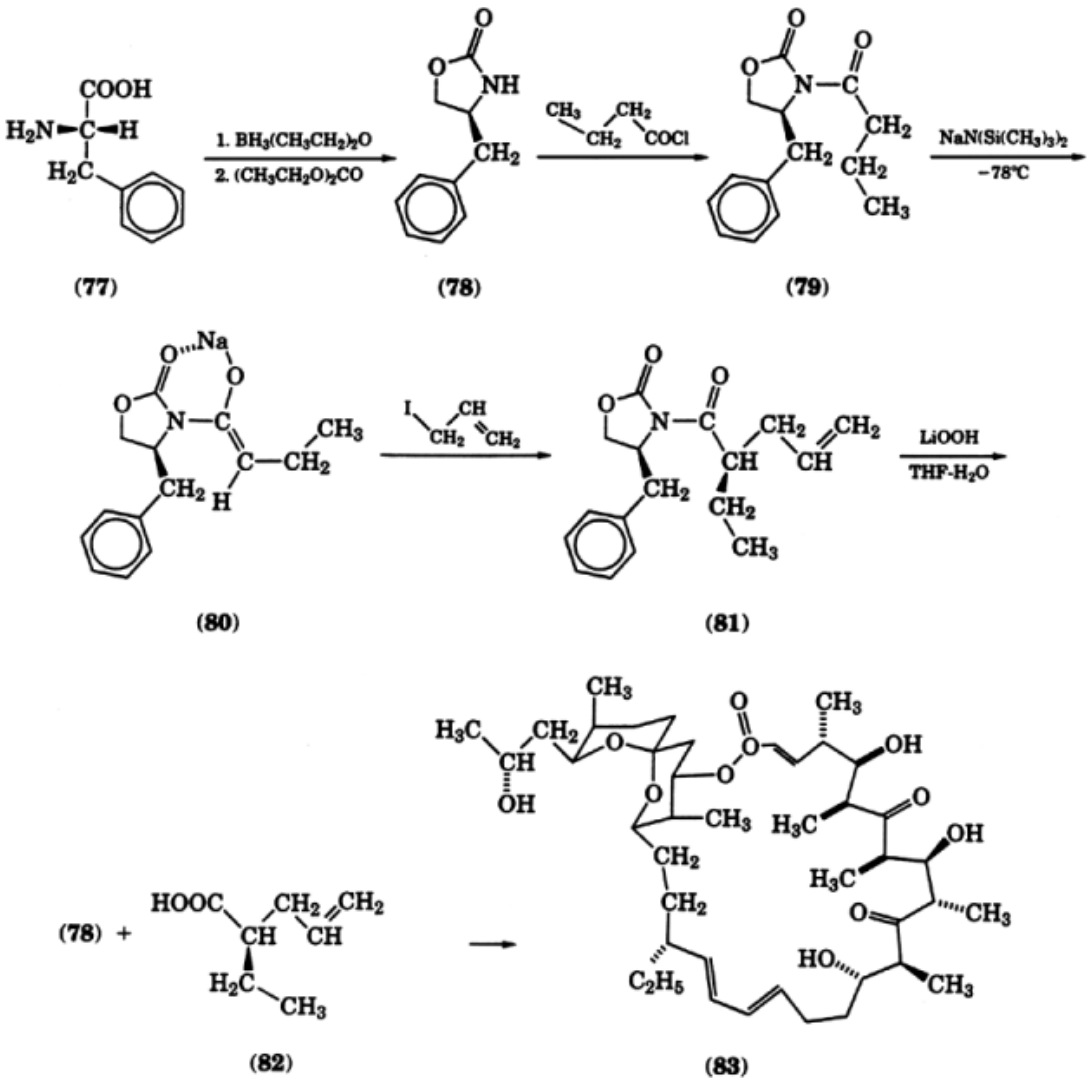


Fig. 5. Synthesis of Evan's chiral oxazolidinone auxiliary and use of this auxiliary for preparation of a chiral intermediate in the synthesis of rutamycin B.

(**86**) yields the sultam intermediate (**87**). *n*-Butyllithium-assisted enolate formation provides the *Z*-enolate–chelate structure (**88**). Stereoselective reaction with benzylbromide produces the diastereomer (**89**). Imine hydrolysis followed by removal of the auxiliary through hydrolysis (LiOH) produces (**90**) in 93% overall yield with greater than 99.8% ee.

2.3. Asymmetric Induction Methodologies

Asymmetric synthesis is defined as the construction of new chiral centers within a prochiral molecule, with the condition that one optical isomer is formed to a greater extent than the other. The most common type of asymmetric induction involves the conversion of a trigonal carbon atom to a tetrahedral carbon atom by use of

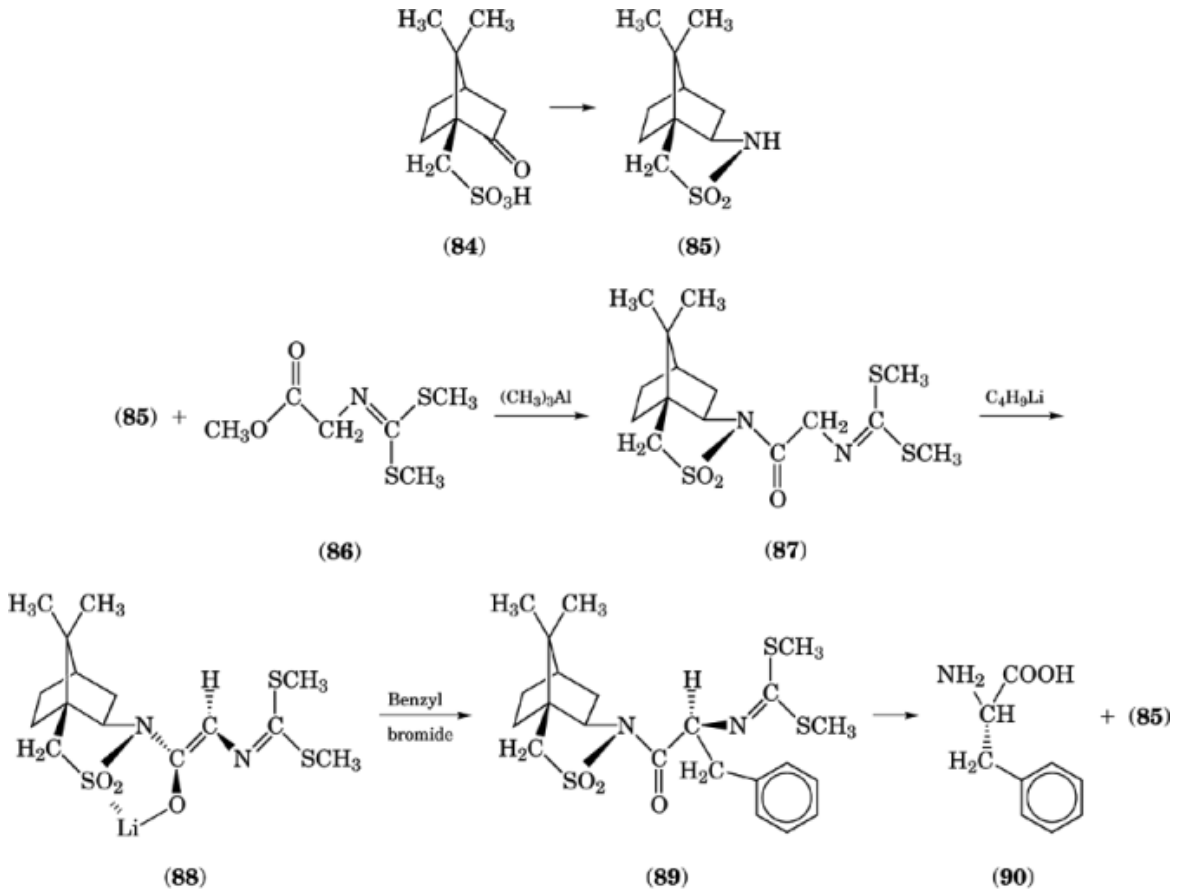


Fig. 6. Preparation of Oppolzer's chiral sultam auxiliary (**85**) and use of this chiral auxiliary for the preparation of L-phenylalanine.

a reagent that is biased toward preferential attack from one side or face of the prochiral molecule. Generally, asymmetric induction involves diastereotopic transition states wherein one transition state is favored due to steric and electronic effects which govern the selective formation of one enantiomer. An overview of methods in asymmetric syntheses is available (76). The primary advantage of asymmetric synthesis resides in the stereoselective production, in general, of either enantiomer of a compound; synthesis of both enantiomers is not always possible using chiral synthons or auxiliaries. Asymmetric syntheses avoid the use of inefficient resolutions, and often the reagent or catalyst is recyclable making the synthetic process both material and cost efficient. Asymmetric reduction of ketones, epoxidation of allylic alcohols, hydroboration, hydrogenation, and dihydroxylation reactions, as well as asymmetric cycloaddition reactions, allyl borations, and aldol condensations represent several classes of the numerous enantioselective reactions developed since the 1960s.

Several examples which demonstrate the utility of asymmetric induction in the synthesis of pharmaceutical agents follow. Alpine-borane [42371-63-1] (**93**) (Fig. 7), a chiral reducing agent useful in the enantioselective reduction of prochiral ketones, is prepared by reaction of 9-borabicyclo-[3.3.1]-nonane [21205-91-4] (**91**) with either enantiomer of optically pure α-pinene [7785-26-4] (**92**). This reagent has been employed in the enantioselective reduction of acetylenicketones (**94**) in better than 85% yield and 92% ee to produce propargyl alcohols (**95**) which can be converted to 4-substituted butyrolactones (**96**). Numerous biologically active natural products

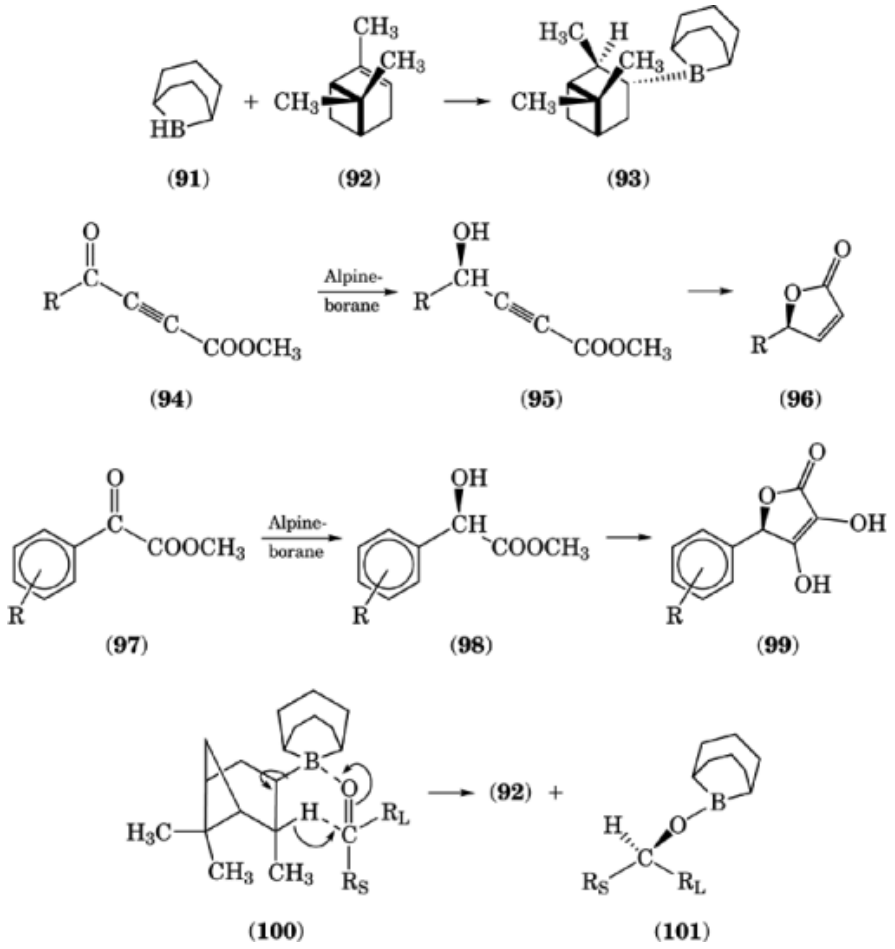


Fig. 7. Preparation of Alpine-borane (**93**) and use in the synthesis of homochiral butyrolactones and arylhydroxytetronic acids. R_S and R_L denote small and large groups, respectively.

contain the butyrolactone ring system (77). Similarly, methyl α-aryl-α-ketoacetates (**97**) have been reduced to methyl (*R*)- (**98**) or (*S*)-mandelates, useful intermediates in the synthesis of, among other compounds, optically active 4-aryl-2-hydroxytetronic acids (**99**) (78). These acidic compounds are *aci*-reductones which possess a low redox potential and numerous biological activities including reactive radical scavenging, cyclooxygenase inhibition, and antilipidemic properties. The proposed transition state (**100**) for the enantioselective reduction is a cyclic transition state wherein the boron is coordinated with the ketone carbonyl oxygen and the hydride is delivered from the β-carbon of the pinene (see Fig. 7). The large group of the ketone (R^L) is positioned in the sterically favored equatorial conformation and the small group (R^S) is in an axial position. The cyclic transition state is thought to undergo a sigmatropic-type rearrangement in which a hydride is delivered to the carbonyl carbon, α-pinene (**92**) is generated, and a boronate ester (**101**) is formed.

Asymmetric epoxidation is of high utility; two stereocenters may be constructed simultaneously. In general, allylic alcohols are oxidized in high yields and with high enantiomeric purity using titanium tetraisopropoxide and enantiomerically pure diisopropyl tartrate as catalysts, dichloromethane as solvent, and *tert*-butyl hydroperoxide as the oxidant (79) (Fig. 8). The starting epoxide (**103**) used in the enantiomeric synthesis

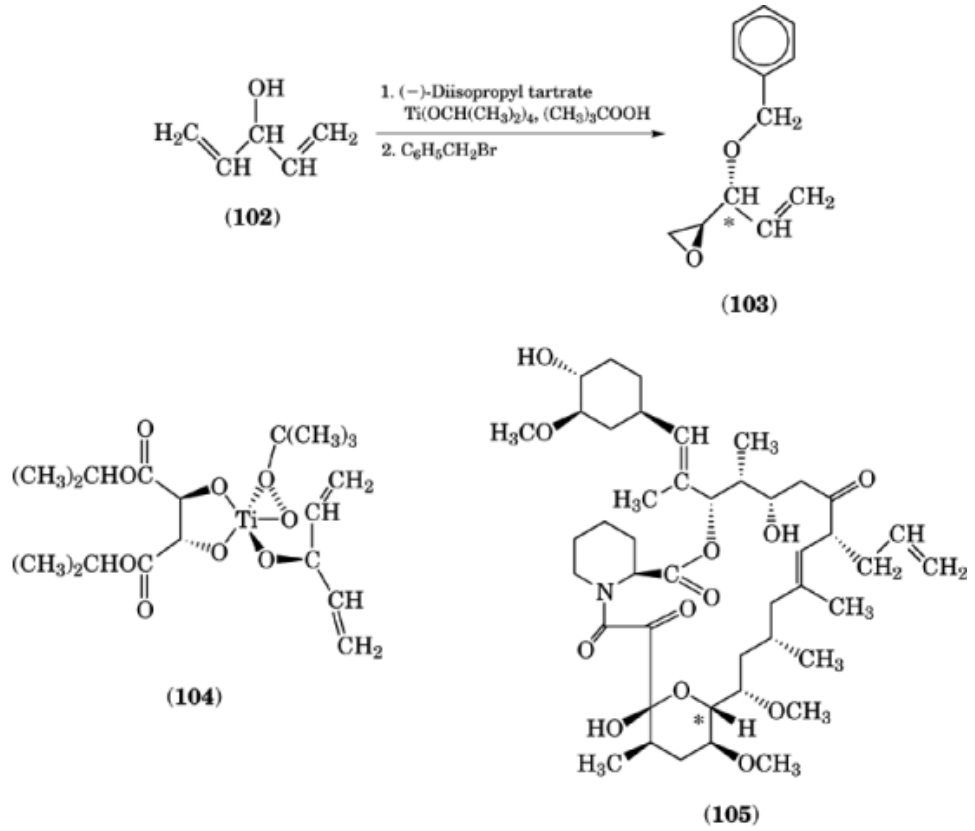


Fig. 8. Use of Sharpless asymmetric epoxidation for the preparation of an intermediate in the synthesis of FK-506 (**105**), where * represents the chiral carbon of (**103**).

of the immunosuppressant FK-506 [104987-11-3] (**105**) is prepared by Sharpless epoxidation of 1,4-pentadiene-3-ol [922-65-6] (**102**) (80). The proposed intermediate (**104**), which gives rise to the enantiofacial selectivity, involves a complex of diisopropyl tartrate, *tert*-butyl hydroperoxide and the allylic alcohol all bonded to the titanium(VI) species (81).

Catalytic asymmetric hydrogenation was one of the first enantioselective synthetic methods used industrially (82). 2,2′-Bis(diarylphosphino)-1,1′-binaphthyl (BINAP) is a chiral ligand which possesses a C_2 plane of symmetry (Fig. 9). Steric interactions prevent interconversion of the (*R*)- and (*S*)-BINAP. Coordination of BINAP with a transition metal such as ruthenium or rhodium produces a chiral hydrogenation catalyst capable of inducing a high degree of enantiofacial selectivity (83). Naproxen **(41)** is produced in 97% ee by $Ru(OCOCH_3)_2$[(*S*)-BINAP]-(**106**)-catalyzed reduction of precursor olefin (**107**). The asymmetric synthesis of analgesic tetrahydroisoquinolines makes use of this methodology (84). L-3,4-Dihydroxyphenylalanine [59-92-7] (L-dopa) (**109**), useful in the treatment of Parkinson's disease, is prepared by asymmetric catalytic hydrogenation of intermediate olefinic amide (**108**).

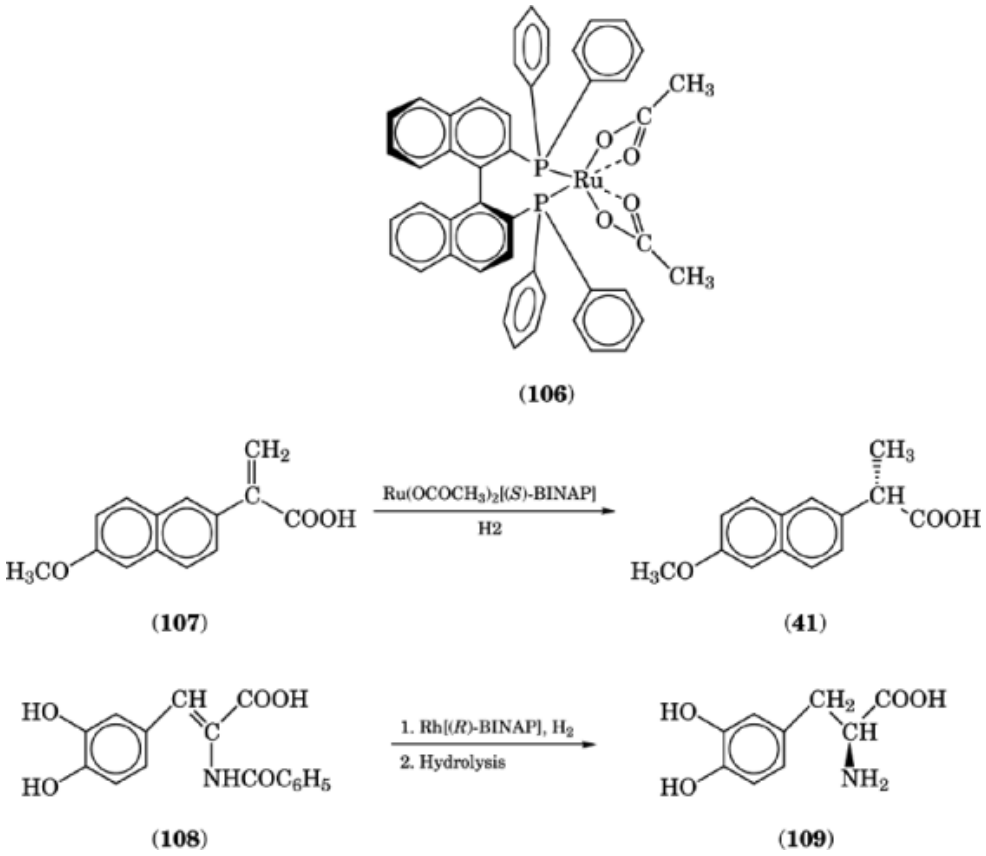


Fig. 9. Catalytic asymmetric hydrogenation.

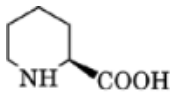
3. Analysis of Synthetic Homochiral Drugs

3.1. Determination of Absolute Configuration

X-irradiation of a crystal produces a diffraction pattern from which the relative spatial orientation of the atoms that make up the molecule may be determined. If the crystal is made of homochiral molecules, the absolute configuration of the compound may be deduced. In 1951 the absolute configuration of NaRb-(+)-tartrate was determined to be L-(+) (or (*R*)-(+)) (85). Subsequently, the absolute stereochemistry of (+)-glyceraldehyde **(5)** was deduced to be of the D-configuration by chemical correlation with L-(+)-tartaric acid. Fischer's original arbitrary assignment of D-(+)-glyceraldehyde is structurally correct; consequently the structures of the numerous compounds deduced from D-glyceraldehyde are also correct.

Chemical conversion of compounds to intermediates of known absolute configuration is a method routinely used to determine absolute configuration (86). This is necessary because x-ray analysis is not always possible; suitable crystals are required and determination of the absolute configuration of many crystalline molecules cannot be done because of poor resolution. Such poor resolution is usually a function of either molecular instability or the complex nature of the molecule. For example, the relative configuration of the macrolide immunosuppressant FK-506 (**105**) (Fig. 8), which contains 14 stereocenters, was determined by x-ray

crystallographic studies. However, the absolute configuration could only be elucidated by chemical degradation and isolation of L-pipecolic acid **(110)** (80).



(110)

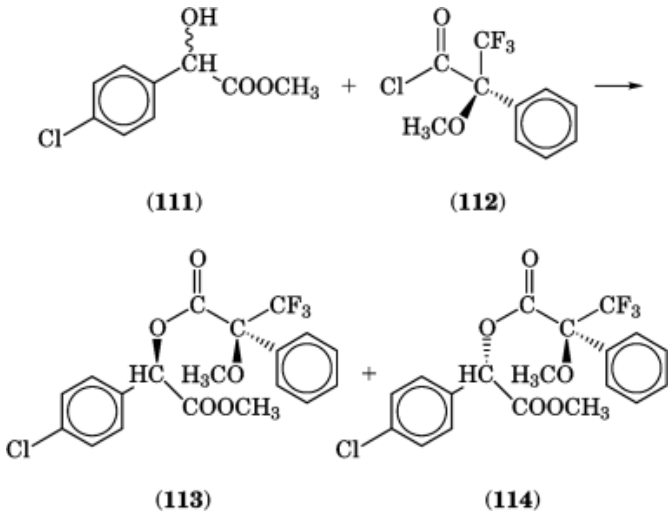
ORD and CD also provide a basis by which the absolute configuration of a compound may be correlated with that of a known compound of similar structure by observing changes in degree of rotation with wavelength (87).

3.2. Determination of Enantiomeric Purity

In order to analyze the biological properties of a single enantiomer, the optical purity of the compound should be enantiomerically pure, ie, 100% ee. Contrasting reports on the differences in pharmacological activity of single enantiomers, as well as the misinterpretation of data, are often a result of unknowingly testing enantiomerically impure material (88). The oldest and perhaps easiest method for determining optical purity is by measuring optical rotation and comparing the value with that reported for the enantiopure compound. Although simple, there are several drawbacks to this method. The assumption must be made that the reported literature value is without error, and truly represents the optically pure compound. Numerous examples exist in which unambiguous methods, ie, chiral gc, hplc, nmr, for determination of optical purity reveal that the previously reported values for optically pure compounds were in error. Variables such as temperature, solvent, concentration, purity of the compound, type of cell, and even differences between polarimeters employed in the measurement influence the observed degree of rotation. Therefore, polarimetry measurements for determination of optical purity deviate by at least $\pm 4\%$ (89).

^{1}H-nmr is commonly used to determine enantiomeric purity and is reliable to above 98% ee. Chiral shift reagents are employed to separate the resonance signals of enantiomers (90). Chiral shift reagents exemplified by tris(dipivaloylmethanato)europium, Eu(dpm)$_3$, act as weak Lewis acids and their association with organic compounds results in the spreading or separation of their proton resonance signals. Furthermore, the association of the chiral shift reagent creates a diastereotopic environment resulting in the resolution of the proton resonance signals for the individual enantiomers.

Diastereomeric derivatization of a chiral alcohol **(111)** with an enantiopure compound such as Mosher's reagent [20445-33-4] (α-trifluoromethyl-α-methoxy-α-phenylacetylchloride) **(112)** (91) results in two distinct compounds **(113)** and **(114)** with nonequivalent chemical shifts in the^{1}H-nmr spectrum (92).



Integration of the peaks for the two diastereomers accurately quantifies the relative amounts of each enantiomer within the mixture. Such diastereomeric derivatives may also be analyzed by more accurate methods such as gc or hplc. One drawback to diastereomeric derivatization is that it requires at least 15 mg of material, which is likely to be material painstakingly synthesized, isolated, and purified. The use of analytical chiral chromatographic methods allows for the direct quantification of enantiomeric purity, is highly accurate to above 99.8% ee, and requires less than one milligram of material.

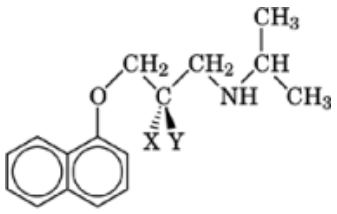
4. Chiral Pharmaceuticals

4.1. Enantiomeric Pairs

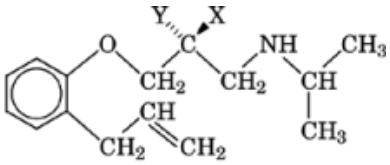
Enantioselective differences in absorption, metabolism, clearance, drug– macromolecule binding affinity, and other factors, which culminate in the observed enantioselective efficacy of chiral drugs, are considered herein. More inclusive lists of optically active drugs and their enantioselective differences are available (93).

4.1.1. Antihypertensive Agents

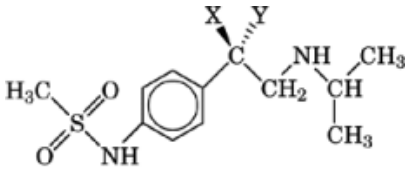
Hypertension (high blood pressure) is a significant risk factor for cardiovascular diseases such as angina, heart attacks, and strokes. β-Adrenoceptor (adrenergic nervous system receptors of the β-type) antagonists (β-blockers), calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and potassium channel activators (KCAs) are among the numerous classes of drugs developed to control hypertension (see Cardiovascular agents; Enzyme inhibitors; Neuroregulators). β-Adrenoceptor antagonists exemplified by the phenoxypropanolamine derivatives propranolol propranolol **(115)** and **(116)** and alprenolol **(117)** and **(118)** or the phenethanolamine drugs such as sotalol **(119)** and **(120)** require for activity both the ethanolamine portion and an aromatic ring. Furthermore, the correct spatial arrangement of the phenyl, ethylamine, and hydroxyl moieties is critical for β-blockade (94). For example, in guinea pig atria, the (*R*)-enantiomer of alprenolol [23846-72-2] **(118)** is over 100-fold more active than is the (*S*)-enantiomer [23846-71-1] **(117)**. Similarly, the (*S*)-enantiomer of sotalol [30236-32-9] **(120)** is 50 times as potent as (*R*)-sotalol [30236-31-8] **(119)** (95).



(115) X = OH; Y = H
(116) X = H; Y = OH



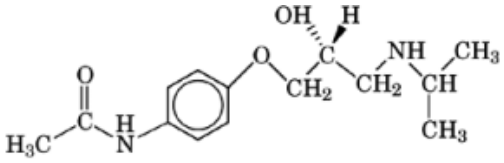
(117) X = OH; Y = H
(118) X = H; Y = OH



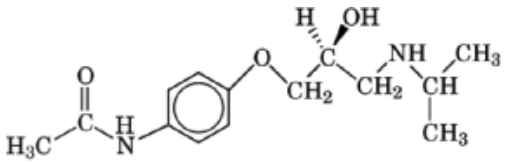
(119) X = OH; Y = H
(120) X = H; Y = OH

Note that the relative spatial arrangement of the phenyl, amine, and hydroxyl functionalities are identical for (*R*)-alprenolol and (*S*)-sotalol. In addition to β-blocking activities, some of these compounds also possess potent local anaesthetic activity (see Anesthetics). The membrane stabilizing activity, however, is not stereoselective and correlates directly with the partition coefficient (hydrophobicity) of the compound.

Two different types of β-adrenoceptors have been characterized and categorized as β_1- and β_2-subtypes. The β_1-receptors are associated primarily with the cardiac muscle, whereas the β_2-subtype is located peripherally. Selective β_1-blockers include practolol **(121)** and **(122)**, atenolol **(123)** and **(124)**, and betaxolol **(125)** and **(126)**.



(121)



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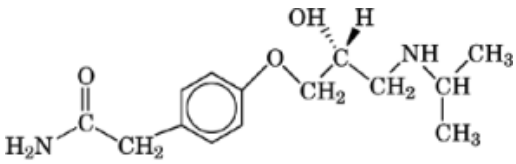

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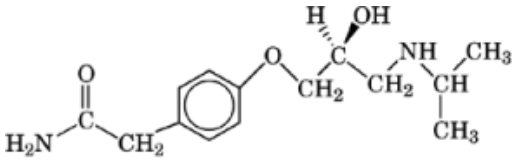
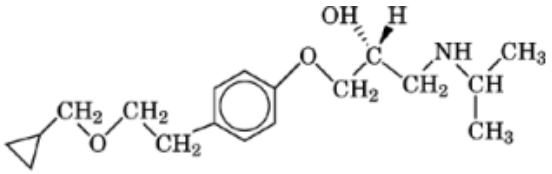


(124)



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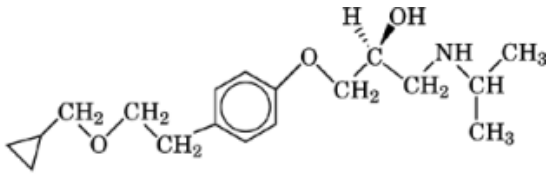
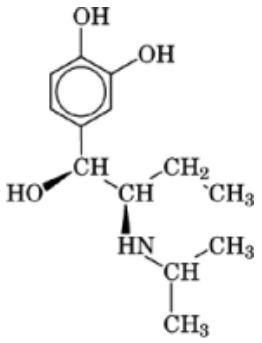
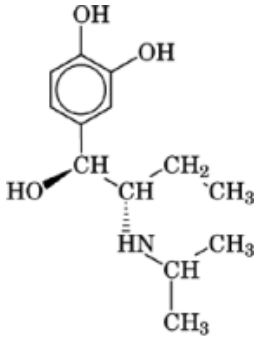


(126)

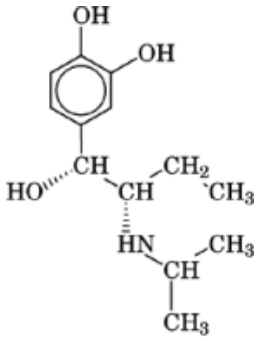
It has been demonstrated that the β_1-selectivity is due to the para-substituents of these drugs (96). In contrast, (-)-erythro-isoetharine **(127)**, a bronchodilator, is 80 times more selective for β_2-adrenergic receptors than for β_1-receptors. Isoetharine (97) contains an α-alkyl substituent, thus producing four isomeric compounds. The (−)-erythro isomer **(127)** is 100-fold more active than the (−)-threo isomer **(128)** and has more than 500 times the activity of either of the (+)-isomers **(129)** and **(130)** in blocking electrically stimulated spasms in guinea pig trachea. In general, introduction of α-alkyl substituents on both β-blockers and agonists provides diastereomers with increased β_2-selectivity, but often with compromised potency.



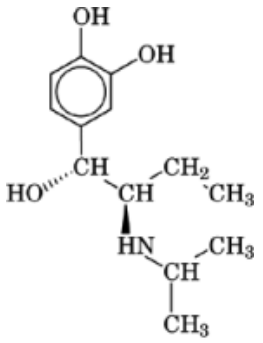
(**127**)



(**128**)

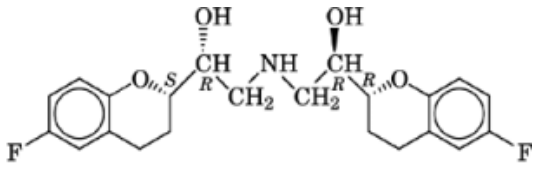


(**129**)



(130)

Racemic nebivolol **(131)** and **(132)**, a nonclassical β-blocker, contains four stereocenters with the (*S*,*R*,*R*,*R*)-(+)-diastereomer **(131)** being a long-acting, potent, and highly selective β_1-blocker (50-fold more selective for β_1 versus β_2). The (−)-enantiomer **(132)** does not possess significant β_1-activity. When nebivolol is administered in racemic form sharp decreases in both diastolic and systolic blood pressure, attributable to the (*R*,*S*,*S*,*S*)-(−)-diastereomer **(132)**, are observed. The hemodynamic effects cannot be explained by β_1-adrenergic antagonism of the (+)-isomer and this effect is not shared by other β-blockers. The mechanism of the observed synergy between the two enantiomers is not known (98).



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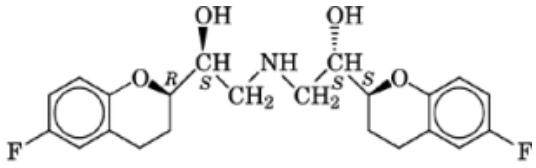
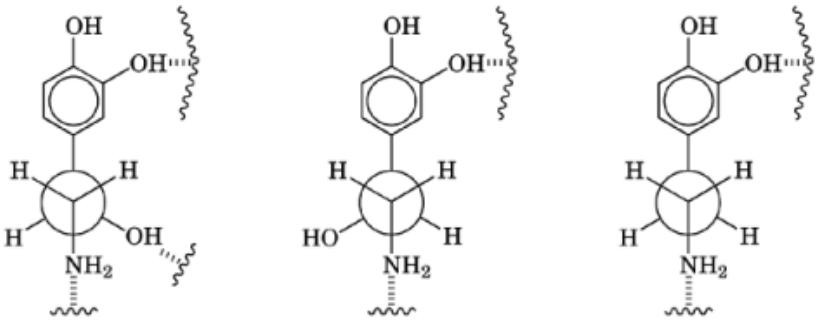


(132)

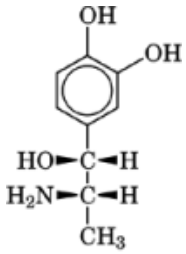
α-Adrenergic adrenoceptors (99–101) exist in two isoforms designated α_1 and α_2. Both subtypes are observed in equal concentrations post-junctionally on vascular smooth muscle, while the α_2-subtype occurs more frequently at the presynaptic junction (102). α-Adrenoceptor agonists, which induce vasoconstriction, include the phenethylamines noradrenaline (**133**) and (**134**) (Fig. 10) and α-methylnoradrenaline **(9,10)**. The diastereomeric (1*R*,2*S*)-(-)-α-methylnoradrenaline erythro isomer **(136)** (103) stereoselectively binds 550-fold more tightly to the α_2-receptor subtype than to the α_1-receptor subtype in guinea pig ileum. The other three isomers are relatively inactive. The relative biological activities of two of the noradrenaline diastereomers and dopamine, a related compound, are (*R*)-(−)-noradrenaline (**133**) > (*S*)-(+)-noradrenaline (**134**) = dopamine (**135**). The receptor subtype selectivity, as well as the stereoselectivity observed with these agonists, has been explained by the three-point interaction hypothesis (104, 105). This hypothesis suggests that only one enantiomer is capable of existing in a conformation (Fig. 10) such that favorable interactions exist between



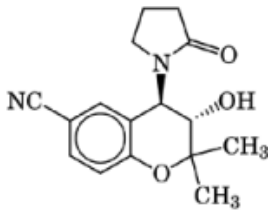
(133) (134) (135)

Fig. 10. The postulated interaction of α-adrenoceptor agonists with the receptor. The Easson-Stedman hypothesis suggests that (*R*)-noradrenaline is most potent owing to its three points of attachment (〰) to the adrenoceptor, whereas dopamine and (*S*)-noradrenaline are equal in activity, but less active than (*R*)-noradrenaline because they each possess two binding domains (100).

the receptor and the cationic amine, substituted phenyl, and β-hydroxyl groups of the agonist. The hypothesis further states that symmetrical phenethylamines such as dopamine which are devoid of a β-hydroxyl moiety, should be equal in activity to the less active enantiomer of the β-hydroxyphenethylamines. This hypothesis successfully predicts the stereoselectivity of both agonists and antagonists of the α-adrenoceptors and the β-adrenoceptors (106).



(136)

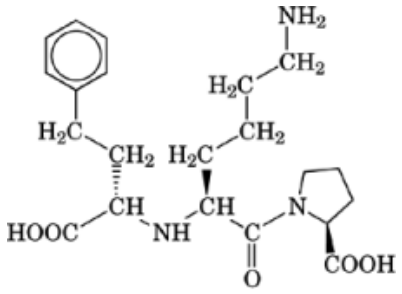


(137)

Cromakalim **(137)** is a potassium channel activator commonly used as an antihypertensive agent (107). The rationale for the design of cromakalim is based on β-blockers such as propranolol **(115)** and atenolol **(123)**. Conformational restriction of the propanolamine side chain as observed in the cromakalim chroman nucleus provides compounds with desired antihypertensive activity free of the side effects commonly associated with β-blockers. Enantiomerically pure cromakalim is produced by resolution of the diastereomeric

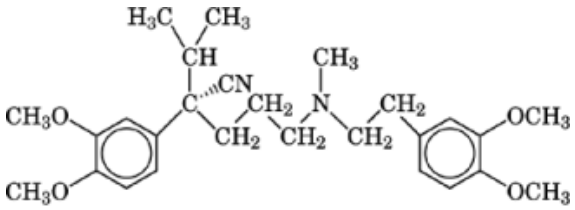
(*S*)-α-methylbenzylcarbamate derivatives. X-ray crystallographic analysis of this diastereomer provides the absolute stereochemistry of cromakalim. Biological activity resides primarily in the (−)-(3*S*,4*R*)-enantiomer [94535-50-9] **(137)** (108). In spontaneously hypertensive rats, the (−)-(3*S*,4*R*)-enantiomer, at dosages of 0.3 mg/kg, lowers the systolic pressure 47%, whereas the (+)-(3*R*,4*S*)-enantiomer only decreases the systolic pressure by 14% at a dose of 3.0 mg/kg.

Angiotensin converting enzyme (ACE) inhibitors alleviate hypertension by blocking the endogenous synthesis of angiotensinII via the renin pathway. ACE is a zinc-containing carboxyprotease which cleaves the His–Leu dipeptide from the C-terminal end of angiotensin I. Captopril **(47)**, 1-[(2*S*)-3-mercapto-2-methylpropanoyl]-(2*S*)-proline, is a prototype ACE competitive inhibitor with a Ki of 1.7 n*M*. The diastereomer 1-[(2*R*)-3-mercapto-2-methylpropanoyl]-(2*S*)-proline is 100 times less active than captopril (109). Lisinopril [83915-83-7] **(138)**, a dipeptide containing an (*S*)-lysine, is more than five times as potent as the epimeric mixture consisting of (*R*) + (*S*)-lysine moieties in inhibiting hog plasma ACE (110).

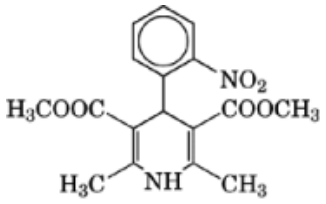


(138)

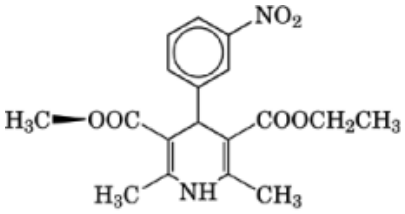
Calcium channel antagonists such as verapamil **(139)**, diltiazem, prenylamine, and the 1,4-dihydropyridines nifedipine [21829-25-4] **(140)**, nitrendipine **(141)** and **(142)**, and nimodipine **(143)** and **(144)** are effective in the treatment of angina (111). The 1,4-dihydropyridine, nifedipine **(140)**, is not chiral owing to the symmetry of the dihydropyridine ring system. However, replacement of one of the methyl esters with a different substituent introduces asymmetry into the molecule and enantioselective calcium antagonism is observed. (−)-Nitrendipine [80873-62-7] **(142)**, consisting of methyl and ethyl esters, is 10 times more potent in rabbit aorta than is the (+)-isomer **(141)** (112). When the esters are methyl and isopropyl, the (+)-isomer **(145)** is 100 times more effective than the (−)-isomer **(146)**. However, the (−)-enantiomer **(146)** is 10-fold more potent on the guinea pig ileum (112). (*S*)-Verapamil [38321-02-7] **(139)** produces vasodilation 2.5 times better than its enantiomer. (*S*)-Verapamil, however, is metabolized in the liver faster than its mirror image isomer after oral dosing. This generally results in 3 to 10 times more (*R*)-verapamil [36622-29-4] in the systemic circulation.



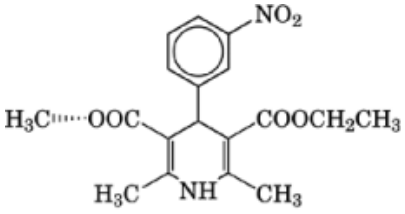
(139)



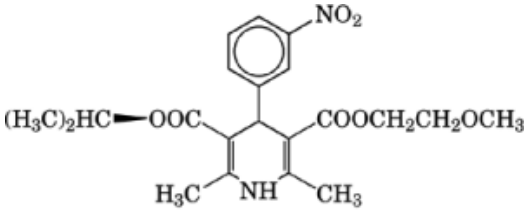
(**140**)



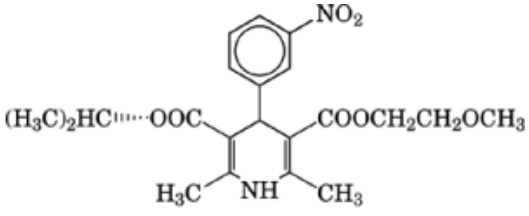
(**141**)



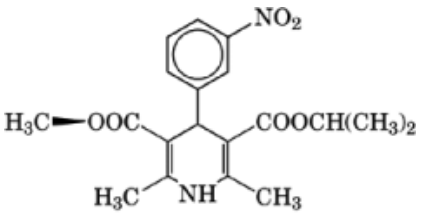
(**142**)



(**143**)



(**144**)



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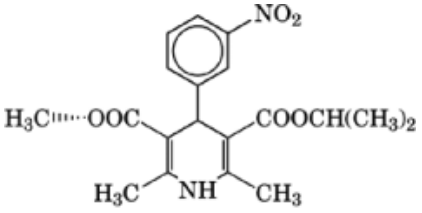
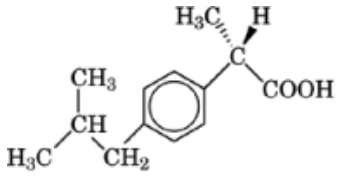


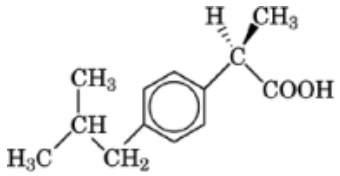
(146)

4.1.2. Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) include, among the numerous agents of this class, aspirin (acetylsalicylic acid), the arylacetic acids indomethacin and sulindac, and the arylpropionic acids, (*S*)-**(147)** and (*R*)-**(148)** ibuprofen, (*S*)-**(149)** and (*R*)-**(150)**, flurbiprofen naproxen **(41)**, and fenoprofen (see Analgesics, antipyretics, and antiinflammatory agents; Salicylic acid and related compounds).



(147)



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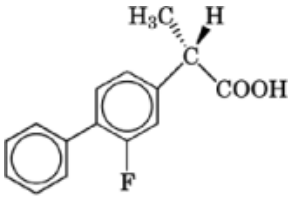
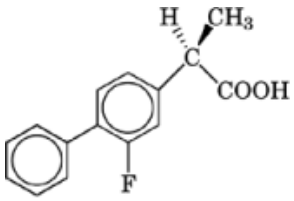


(149)

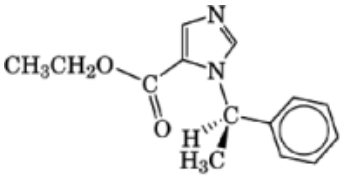


(150)

Although the arylpropionic acids contain a stereogenic center they are generally marketed as racemic mixtures. The only exception is naproxen **(41)**, which is marketed as its (*S*)-enantiomer. NSAIDs produce their antiinflammatory effects by inhibiting cyclooxygenase (COX), the enzyme which catalyzes the first transformation in the biosynthetic conversion of arachidonic acid to the 20 carbon prostaglandins. The (*S*)-arylpropionic acids are the active enantiomers. (*S*)-(+)-Ibuprofen **(147)** is 160 times more potent than its enantiomorph *in vitro*. However, although (*R*)-(-)-ibuprofen **(148)** is inactive *in vitro*, there is no difference between the antiinflammatory activity of the two enantiomers *in vivo*. The activity *in vivo* of the (*R*)-enantiomorph is due to the enzyme mandelate racemase, which selectively converts inactive (*R*)-ibuprofen into the active (*S*)-enantiomer. Two COX isoforms, COX-1 and COX-2, have been identified, and the crystal structure of COX-1 containing (*S*)-flurbiprofen **(149)** has been elucidated. The carboxylate anion of the drug forms an ionic bond with Arg-243 of the cyclooxygenase. The distal flurbiprofen phenyl ring appears to be associated with the phenyl ring of Tyr-245; the methyl group projects into a hydrophobic pocket. The lower activity of the (*R*)-enantiomer **(150)** is likely to be due to unfavorable interactions between its methyl group and the enzyme.

4.1.3. CNS Depressant Drugs

Central nervous system (CNS) depressant drugs (113) including antianxiety agents (benzodiazepines) (114), sedative–hypnotics, general anesthetics, and certain spasticity agents all demonstrate high degrees of enantioselective activity (see Hypnotics, sedatives, anticonvulsants, and anxiolytics; Psychopharmacological agents). (*R*)-(+)-Etomidate [33125-97-2] **(151)** is a short-acting and potent hypnotic, whereas the (*S*)-(−)-isomer **(152)** is devoid of hypnotic activity. The exact mechanism of action of etomidate is speculative; however, the observed enantioselectivity provides evidence that a receptor is involved. Brain levels of each enantiomer are equal. Barbiturates are commonly prescribed for their sedative–hypnotic activities. In general, the (*S*)-(−)-enantiomers possess CNS depressant activities, whereas the (*R*)-(+)-isomers often produce an excitatory effect (115). In humans, (*R*)-(+)-pentobarbital [21045-50-1] **(153)** is found bound to human plasma proteins to a lesser extent than the (*S*)-(−)-isomer **(154)** (36.6% free vs 26.5% free) and is subsequently cleared 14% faster (116). This increased rate of clearance is not sufficient to account for the two- to threefold greater duration of action of (*S*)-(-)-pentobarbital [5767-32-8] **(154)**, and suggests that the difference in activity between the enantiomers is due to the pharmacodynamics of the more potent (*S*)-isomer. (*S*)-(+)-Hexobarbital [7245-04-7] **(155)**, the eutomer, is eliminated about 2.5 times more slowly than the inactive (*R*)-(−)-isomer **(156)**, a result of differences in hepatic metabolism (115, 117). Diazepam [439-14-5] **(157)**, an achiral benzodiazepine, undergoes stereoselective metabolism to (*S*)-(+)-oxazepam [52432-56-1] **(158)** in the liver (118). (*S*)-(+)-Oxazepam produces antianxiety effects to a greater degree than the mirror image isomer **(159)**.



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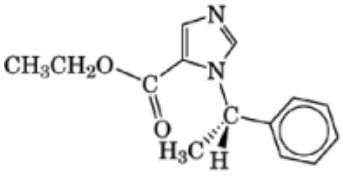

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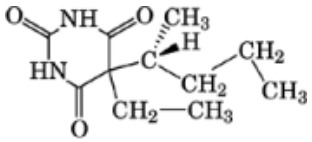

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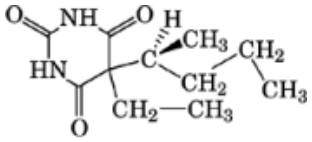

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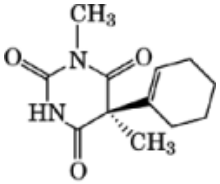

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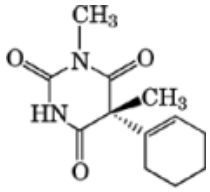

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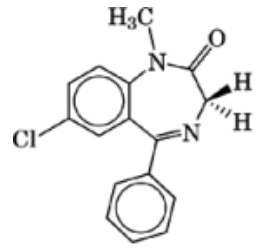

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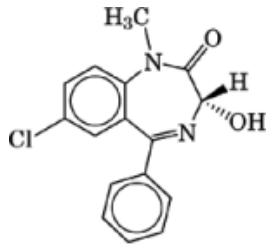

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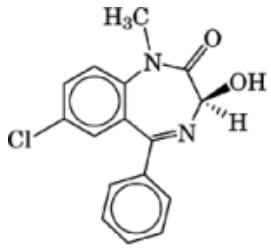
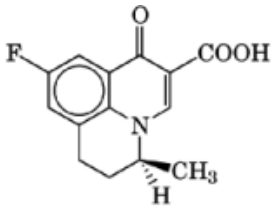


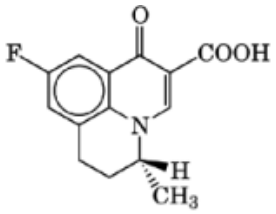
(159)

4.1.4. Antibiotic and Antimicrobial Drugs

The antimicrobial agents (119) flumequine **(160)** and **(161)**, and methylflumequine (S-25930) **(162)** and **(163)** effectively eliminate a number of microbial pathogens via inhibition of the topoisomerase II enzyme of c-DNA containing bacteria (120) (see Antibacterial agents, synthetic). The (*S*)-enantiomers **(160)** and **(162)** of both drugs are much more potent than the (*R*)-enantiomers **(161)** and **(163)**. The potent analogue (*S*)-(-)-ofloxacin [82419-36-1] **(164)** is 8–125 times more potent than its enantiomer **(165)** (121) although it is sold only as the racemate. In humans the disposition of (*R*)- and (*S*)-enantiomers of ofloxacin is stereoselective due to differences in renal clearance rates (122). This difference, however, does not fully explain the large enantioselective difference in antibacterial potency. β-Lactam antibiotics (see Antibiotics, β-lactams), such as the penicillins and cephalosporins, require the (3*S*,5*R*,6*R*)-configuration of the β-lactam functionality combined with a D-amine in either the 6-position (penicillins) or 7-position (cephalosporins) to produce optimal activity (119). The β-lactam antibiotic 7-L-cephalexin **(166)** is stereoselectively absorbed across the intestinal mucosa via the dipeptide transport system. However, only the 7-D-cephalexin [15686-71-2] **(167)** epimer is observed in serum and urine after oral administration owing to rapid and highly stereoselective enzymatic hydrolysis of the L-epimer **(166)** (123).



(**160**)



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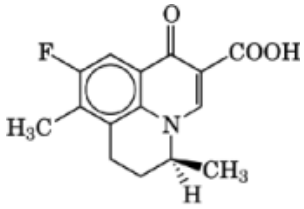

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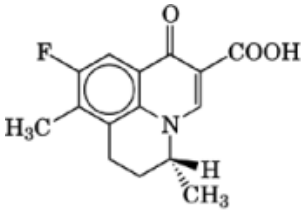

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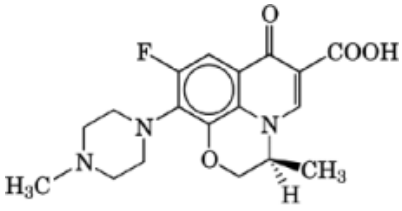
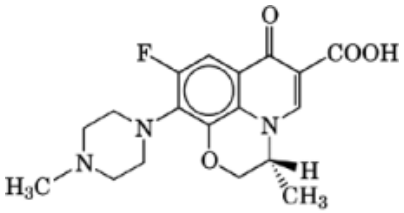


(**164**)



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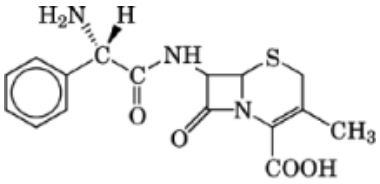

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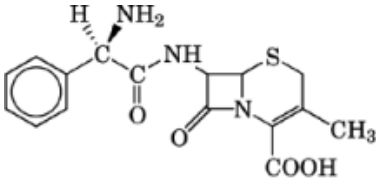
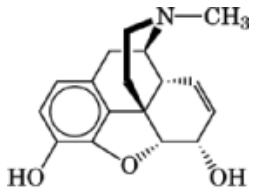


(167)

4.1.5. Opioid Analgesic Drugs

(5*R*,6*S*,9*R*,13*S*,14*R*)-(-)-Morphine [57-27-2] **(168)** and its closely related relatives (-)-codeine [76-57-3] **(169)** and (-)-heroin [561-27-3] **(170)** are potent analgesics, while their (+)-isomers possess no analgesic effects (124). α-Dextropropoxyphene (DARVON) **(171)** is a marketed analgesic whereas its enantiomer, α-levopropoxyphene (NOVRAD) **(172)** is sold as an antitussive devoid of analgesic activity (125) (see Expectorants, antitussives, and related agents). These analgesics produce their biological effects via stimulation of the opioid receptor subclasses mu-, delta-, kappa-, and sigma. 5-(*m*-Hydroxyphenyl)-2-methylmorphan **(173)** and **(174)** maintains the basic pharmacophore of morphine: a *m*-hydroxyphenyl functionality bonded to a quaternary carbon containing a tertiary aminoethyl moiety. The (1*R*,5*S*)-(−)-enantiomer **(174)** binds weakly to μ-receptors and is similar to morphine in potency with respect to pain relief. This isomer, however, does not support characteristic opioid dependence in monkeys or rats. In contrast the (1*S*,5*R*)-(+)-isomer **(173)**, binds strongly to the μ-receptor and is similar to morphine in its biological effects, including dependence (126). (-)-Methadone **(175)** enantioselectively binds to opiate receptors in rat brain, produces respiratory depression in humans, and blocks serotonin uptake; it is a 30-fold more potent analgesic in rats than is (+)-methadone **(176)** (127). *N*-Allylnormetazocine (NANM) enantiomers **(177)** and **(178)** bind selectively to different receptors in mouse brain. The (−)-enantiomer **(177)**, which selectively binds to the μ-opiate receptor with a K_D of 2.1 n*M*, is a weak agonist in antinociceptive assays and a formidable narcotic antagonist. The (+)-NANM isomer **(178)** binds selectively to the PCP opioid receptor with a K_D of 12 n*M* and does not compete with its (−)-isomer for the μ-receptor (128).



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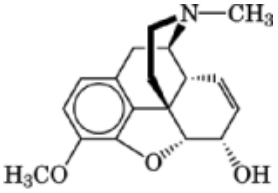

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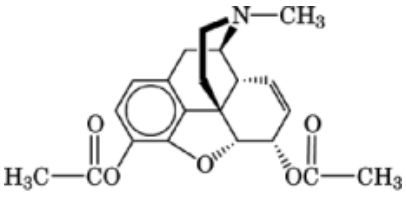

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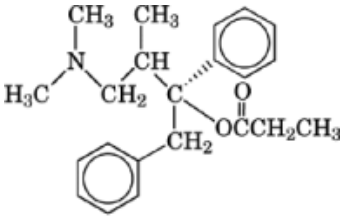

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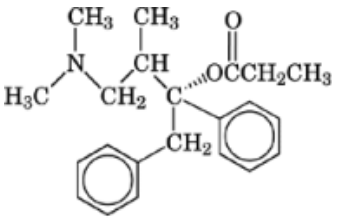

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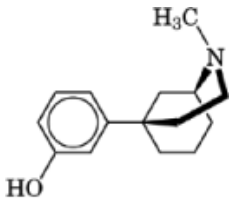

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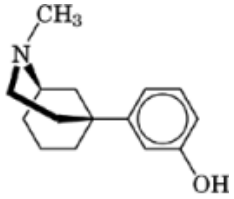

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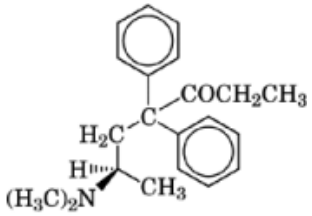

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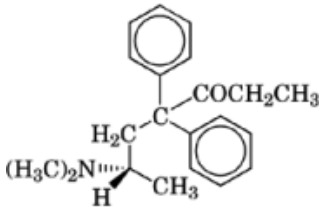

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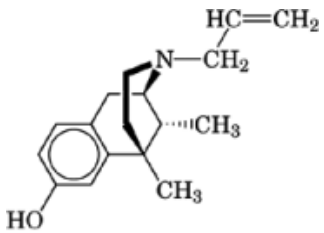

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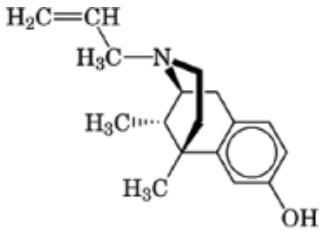
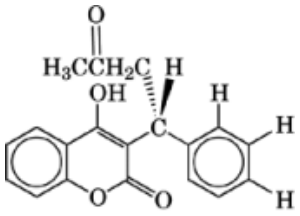


(178)

Opioid peptides include the pentapeptides Met-enkephalin (Tyr^1–Gly^2–Gly^3–Phe^4–Met^5) and Leu-enkephalin (Tyr^1–Gly^2–Gly^3–Phe^4–Leu^5) β-endorphin, a 31-emino acid peptide which is a long-lasting analgesic, and the dynorphins which are highly selective and potent kappa-receptor ligands (129) (see Opioids, endogenous). Numerous analogues of these opioid receptor ligands have been synthesized and considerable knowledge of the stereochemical binding requirements of the receptors has been acquired. A positively charged N-terminal tyrosine residue is critical for enkephalin activity. Substituents at the C-terminal end such as esters or amides do not significantly alter enkephalin opioid activity, although activity decreases with hydrophilic substituents. Replacement of L-Tyr^1 or L-Phe^4 with D-Tyr^1 or D-Phe^4 results in loss of activity. However, substitution of D-aliphatic amino acids for Gly^2 provides compounds with improved opioid activity owing, in part, to decreased enzymatic hydrolysis of the terminal Tyr^1 residue (130). Dermorphin, a heptapeptide (*H*–Tyr^1–D-Ala^2–Phe^3–Gly^4–Tyr^5–Pro^6–Ser^7–NH_2) isolated from the skin of a South American frog, is considerably more potent than morphine (2000-fold in the hot-plate tail flick test), β-endorphin, or endogenous enkephalins in blocking electrically stimulated contractions of guinea pig ileum and mouse vas deferens *in vitro*. Dermorphin contains D-Ala at position 2; the all L-heptapeptide is 100 times less active (131).

4.1.6. Anticoagulant Drugs

Warfarin **(179)** and **(180)**, a potent anticoagulant, was first isolated from spoiled clover hay and identified as the agent responsible for the hemorrhagic symptoms associated with the death of livestock in the 1930s. This functionalized coumarin derivative exerts its effect via competitive inhibition of vitamin K-dependent carboxylation of blood clotting factors. Warfarin is generally administered as the racemate, even though (*S*)-warfarin [5543-57-7] **(180)** is fivefold more active than (*R*)-warfarin [5543-58-8] **(179)** in both rats and humans (132). The (*S*)-enantiomer is eliminated at a higher rate than its antipode in humans, but in rats, (*R*)-warfarin is more rapidly eliminated. (*S*)-Warfarin and its 3′- and 4′-substituted derivatives, ie, methoxy derivatives **(181)** and **(182)**, demonstrate stereoselective serum albumin protein binding. However, the (*R*)-2′-substituted warfarin derivative **(183)** undergoes a greater degree of protein binding than its enantiomer (133). Co-administration with the antiinflammatory drug phenylbutazone increases warfarin's anticoagulant properties (134).



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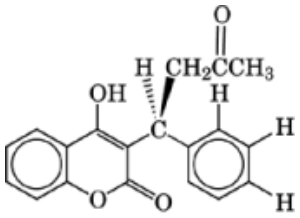
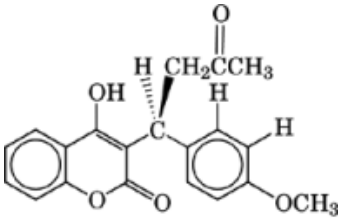
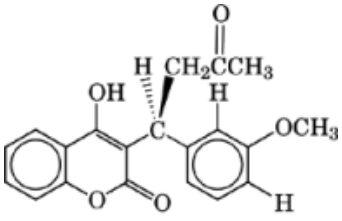


(180)



(181)



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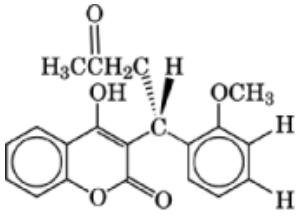
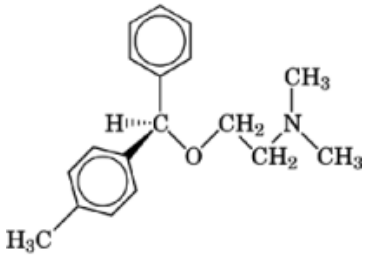


(183)

4.1.7. Neurotransmitters

Histamine receptors are found in at least two subtypes designated H_1 and H_2 (see Histamine and histamine antagonists). H_1-receptor antagonists produce vasoconstriction, while H_2-receptor antagonists inhibit gastric secretion. Neobenodine **(184)** and **(185)**, the chiral *p*-methylphenyl analogue of benadryl [58-73-1] **(186)**, is an antihistamine marketed as the racemate. The (*R*)-(+)-isomer **(184)** is 65 times more potent than its (−)-enantiomer **(185)** when tested in guinea pig ileum (135). Chlorpheniramine **(187)** and **(188)** is also an enantioselective H_1-antagonist, wherein the (*S*)-enantiomer **(187)** is most potent (101). It has been demonstrated that the more potent enantiomer of diphenhydramine and pheniramine drugs is the one in which the aryl moiety, alkylamine group, and the *p*-substituted aryl functionality occur in a clockwise orientation (136).



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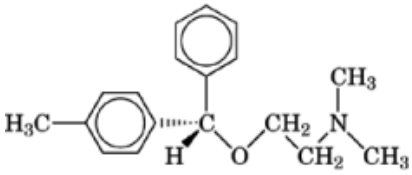

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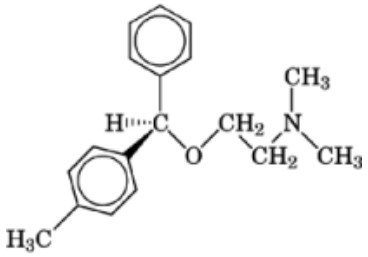

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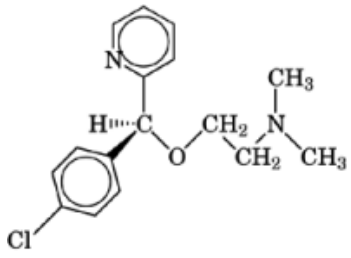

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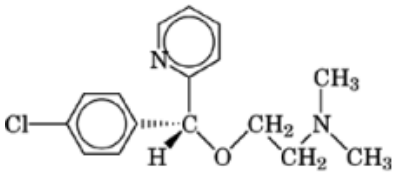
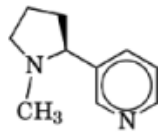


(188)

Acetyl choline is the natural neurotransmitter for the cholinergic receptor. Two distinct receptor subtypes have been characterized based on their binding affinity for either nicotine **(189)** and **(190)** or muscarine **(191)**.



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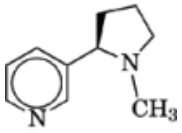
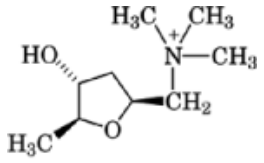


(190)

(*S*)-(-)-Nicotine [54-11-5] **(189)** is highly selective for the nicotinic receptor and is modestly more potent as an agonist than its (*R*)-(+)-isomer **(190)** (101). A 10-fold difference in binding density of (−)- and (+)-nicotine ((*S*)-(−)-nicotine favored) in the rat brain P_2 fraction indicates that nicotine enantiomers may bind to different high affinity sites. Furthermore, (+)-nicotine enhances the binding of (−)-nicotine at the (−)-nicotine high affinity receptor site (137). The muscarinic receptor is highly stereoselective; (2*S*,3*R*,5*S*)-(+)-muscarine [300-54-9] **(191)** binds specifically to this receptor subtype whereas the other seven isomers are relatively inactive. Oxidation of (2*S*,3*R*,5*S*)-(+)-muscarine to (2*S*,5*S*)-muscarone **(192)** eliminates the stereoselectivity and receptor subtype selectivity observed for natural (+)-muscarine, while maintaining the cholinergic effects (138).



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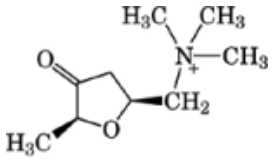
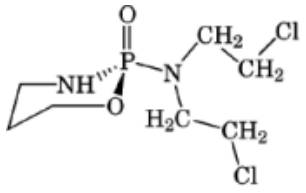


(192)

4.1.8. Antineoplastic Drugs

Cyclophosphamide **(193)** produces antineoplastic effects (see Chemotherapeutics, anticancer) via biochemical conversion to a highly reactive phosphoramide mustard **(194)**; it is chiral owing to the tetrahedral phosphorus atom. The therapeutic index of the (*S*)-(-)-cyclophosphamide [50-18-0] **(193)** is twice that of the (+)-enantiomer due to increased antitumor activity; the enantiomers are equally toxic (139). The effectiveness of the DNA intercalator drugs adriamycin [57-22-7] **(195)** and daunomycin [20830-81-3] **(196)** is affected by changes in

stereochemistry within the aglycon portions of these compounds. Inversion of the carbohydrate C-1 stereocenter provides compounds without activity. The carbohydrate C-4 epimer of adriamycin, epirubicin [56420-45-2], is as potent as its parent molecule, but is significantly less toxic (139). (*R*)-3-Ethyl-3(4-pyridyl)piperidine-2,6-dione **(197)**, useful in the treatment of certain breast cancers, is a 20-fold more potent aromatase inhibitor (IC_{50} = 10 μM) than is its (*S*)-enantiomer (140).



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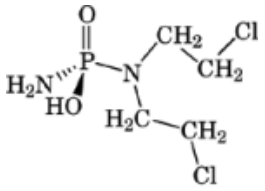

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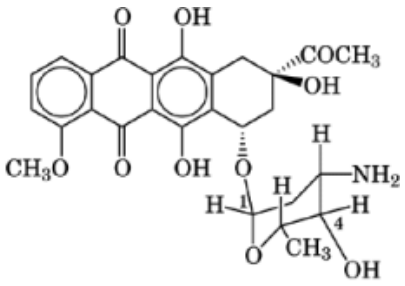

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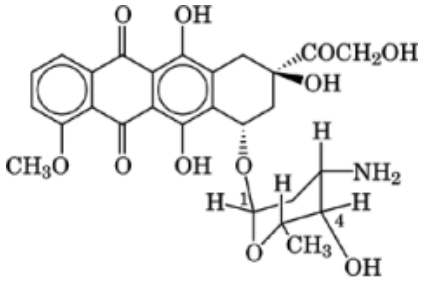

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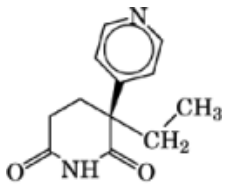
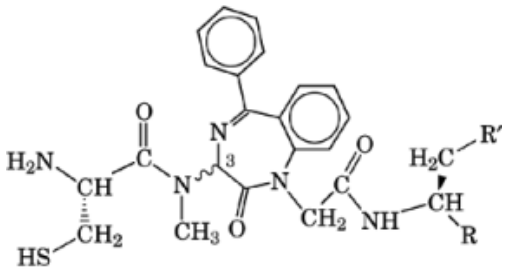


(197)

4.1.9. Peptidomimetics

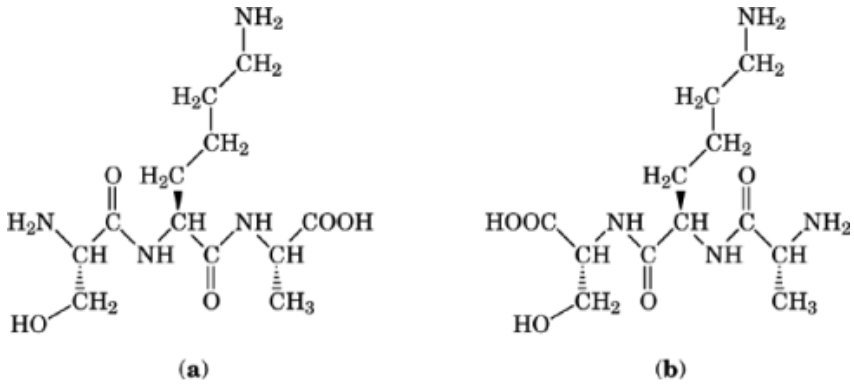
Many drugs mimic natural small peptides. For example, morphine **(168)** is believed to be a natural peptidomimetic for the enkephalins. Similarly, FK-506 (**105**) mimics the binding of peptidal FK-506 to the intracellular receptor, FKBP12 (141). Numerous small endogenous peptides have been characterized which possess potent cellular signaling and homeostatic regulating activities. The regulation of glycolysis, growth, mitosis, and apoptosis, as well as the maintenance of blood pressure and the natural relief of pain, exemplify a few of the regulatory actions of peptide hormones (qv). Exogenous control, through the use of synthetic compounds, of the activities of these regulatory elements is highly desirable as demonstrated by the use of drugs such as the ACE inhibitor captopril **(47)**. The design of peptidomimetics is complicated owing to the flexibility and stereochemical complexity of such hormones. Numerous small peptides have been synthesized which possess tremendous enzyme inhibitory and receptor binding activities *in vitro*; HIV protease inhibitors are one example. Unfortunately, the use of such peptides *in vivo* generally is not successful, as peptidase enzymes rapidly degrade synthetic peptides.

Several methods are being studied to enhance the stability of peptide mimics and improve their stereochemical similarity to the endogenous peptides. For example, the tetrapeptide Cys–Val–Phe–Met, a potent inhibitor of *Ras* farnesyltransferase, is proposed to exist in a turned conformation, which mimics the endogenous peptide during enzyme binding. This conformation is successfully mimicked by 3-amino-1-carboxymethyl-5-phenyl-benzodiazepin-2-one derivatives **(198)** (142).



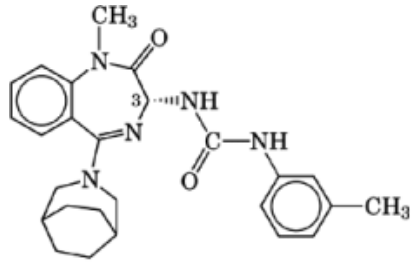
(198)

Such benzodiazepine derivatives are potent inhibitors of the *Ras* farnesyltransferase enzyme. This, combined with their increased *in vivo* stability compared to peptide inhibitors, makes them good candidates for the treatment of *Ras* oncogene-dependent cancer. The benzodiazepine ring system has been successfully used in the development of other peptide mimics. Cholecystokinin (CCK) is a polypeptide hormone which occurs in numerous molecular forms throughout the peripheral and central nervous systems. CCK exerts a variety of actions on peripheral organs, such as regulating pancreatic secretion, gut motility, and gall bladder contraction. The actions of CCK are mediated by two receptor subtypes designated as CCK^{A} and CCK_{B}. The CCK receptor subtype selectivity of benzodiazepine L-740,093 **(199)** is regulated by the C3 stereochemistry of the benzodiazepine ring system.



(a) (b)

Fig. 11. Use of D-amino acids in the synthesis of a hairpin loop portion from the CD4 receptor: (**a**) all L-Ser–Lys–Ala tripeptide constructed in the natural direction; (**b**) all D-Ser–Lys–Ala tripeptide constructed in the reverse direction.



(**199**)

L-740,093, possessing an (*R*) absolute stereochemistry, is highly selective for the CCK_B receptor (CCK_B/CCK_A = 16, 000) with an IC_{50} of 0.1 n*M* (143). The (*S*)-enantiomer demonstrates a fourfold selectivity for the CCK_A receptor with an IC_{50} of 6.5 n*M*.

Use of D-amino acids in the synthesis of a hairpin loop portion from the CD4 receptor provides a stable CD4 receptor mimic, which blocks experimental allergic encephalomyelitis (144). This synthetic construct is not simply the mirror image or enantiomer of the CD4 hairpin loop, but rather an all-D-construct in the reverse sequence, thus providing stereochemically similar side-chain projections of the now inverted backbone (Fig. 11). This peptide mimetic, unlike its all-L amino acid counterpart, is resistant to enzyme degradation. As one would expect, the all-D amino acid CD4 hairpin loop, synthesized in the natural direction, the enantiomer of the natural construct, is inactive.

5. Economic Aspects of Homochiral Pharmaceuticals in Industry

Drugs classified as either natural or semisynthetic in origin accounted for ∼22% of the market share in 1991 (145). Nearly 94% of the agents are chiral compounds and are sold as single enantiomers. Chiral synthetic drugs make up 38% of the market share and 43% of these are sold as single enantiomers, a two- to threefold increase since 1981. Achiral or symmetrical synthetic drugs make up 40% of the drug market. The vast number of marketed racemic drugs are being reinvestigated and newer pharmacological data as well as production technology are being patented (146).

The world sales of homochiral drugs grew 22% from 1992 to an estimated $\$35.6 \times 10^6$ in 1993. Enantiomeric cardiovascular drugs grossed $\$11.3 \times 10^6$ followed closely by antibiotics ($\$10.8 \times 10^6$), whereas hormones, CNS agents, antiinflammatory drugs, and antineoplastic drugs yielded a combined $\$9 \times 10^6$ (147). A steady increase in the number of homochiral drugs on world markets has created an increased demand for enantiomerically pure intermediates as well as for enantioselective technologies. Many pharmaceutical companies are pursuing new financial opportunities and gaining improved bargaining positions by producing patent protected and more expensive enantiomerically pure drugs from unprotected racemic pharmaceuticals.

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