CHAPTER 1

PROSTAGLANDINS, PEPTIDOMIMETIC COMPOUNDS, AND RETINOIDS

1.1. PROSTAGLANDINS

It is highly likely that those not themselves involved in scientific research perceive the development of new knowledge within a given area of science as a linear process. The popular view is that the understanding of the specific details of any complex system depends on prior knowledge of the system as a whole. This knowledge is in turn believed to derive from the systematic stepwise study of the particular system in question. The piecemeal, almost haphazard, way in which the details of the existence and later the detailed exposition of the arachidonic acid cascade were put together is much more akin to the assembly of a very complex jigsaw puzzle. This particular puzzle includes the added complication of incorporating many pieces that did not in fact fit the picture that was finally revealed; the pieces that would in the end fit were also found at very different times.

The puzzle had its inception with the independent observation in the early 1930s by Kurzok and Lieb [1] and later von Euler [2] that seminal fluid contained a substance that caused the contraction of isolated guinea pig muscle strips. The latter named this putative compound prostaglandin in the belief that it originated in the prostate gland; the ubiquity of those substances was only uncovered several

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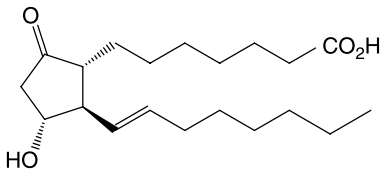
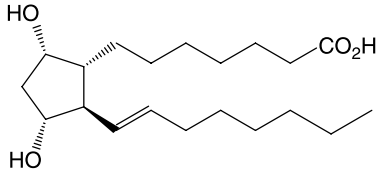
decades later. The discovery remained an isolated oddity until the mid-1960s, by which time methods for chromatographic separation of complex mixtures of polar compounds and spectroscopic methods for structure determination were sufficiently advanced for the characterization of humoral substances that occur at very low levels. The isolation and structural assignment of the first two natural prostaglandins, PGE_1 and PGF_2, were accomplished by Bergstrom and his colleagues at the Karolinska Institute [3]. (The letter that follows PG probably initially referred to the order in which the compounds were isolated: E refers to 9-keto-11-hydroxy compounds and F refers to 9,11-diols; the subscripts refer to the number of double bonds.) The carbon atoms of the hypothetical, fully saturated, but otherwise unsubstituted carbon skeleton, prostanoic acid, are numbered sequentially starting with the carboxylic acid as 1, and then running around the ring and resuming along the other side chain.



PGE_1

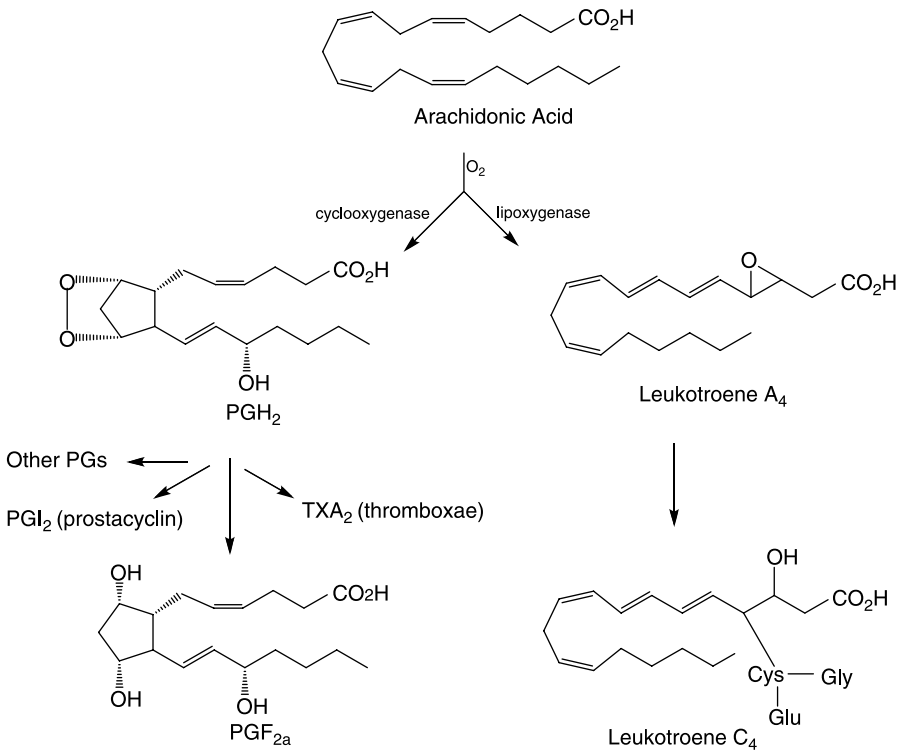


$PGF_{1\alpha}$

The identification of these two prostaglandins in combination with their very high potency in isolated muscle preparations suggested that they might be the first of a large class of new hormonal agents. Extensive research in the laboratories of the pharmaceutical industry had successfully developed a large group of new steroid-based drugs from earlier similar leads in that class of hormones; this encouraged the belief that the prostaglandins provided an avenue that would lead to a broad new class of drugs. As in the case of the steroids, exploration of the pharmacology of the prostaglandins was initially constrained by the scarcity of supplies. The low levels at which the compounds were present, as well as their limited stability, forced the pace toward developing synthetic methods for those compounds. The anticipated need for analogues served as an additional incentive for elaborating routes for their synthesis.

Further work on the isolation of related compounds from mammalian sources, which spanned several decades, led to the identification of a large group of structurally related substances. Investigations on their biosynthesis made it evident that all eventually arise from the oxidation of the endogenous substance, arachidonic acid. The individual products induce a variety of very potent biological responses, with inflammation predominating. Arachidonic acid, once freed from lipids by the enzyme phospholipase A_2, can enter one of two branches of the arachidonic acid

cascade [4] (Scheme 1.1). The first pathway to be identified starts with the addition of two molecules of oxygen by a reaction catalyzed by the enzyme cyclooxygenase to give PGG_2. That enzyme, now known to occur in two and possibly three forms, is currently identified by the acronym COX; it is sometimes called prostaglandin synthetase. The reaction comprises the addition of one oxygen across the 9,11 positions to give a cyclic peroxide while the other adds to the 14 position in a reaction reminiscent of that of singlet oxygen to give a hydroperoxide at 14, with the resulting shift of the olefin to the 12 position and with concomitant isomerization to the *trans* configuration. The initial hydroperoxide is readily reduced to an alcohol to give the key intermediate PGH_2. The reductive ring opening of the bridging oxide leads to the PGF series while an internal rearrangement leads to the very potent inflammatory thromboxanes. It was found later that aspirin and indeed virtually all nonsteroid anti-inflammatory drugs (NSAIDs) owe their efficacy to the inhibition of the cylcooxygenase enzymes.

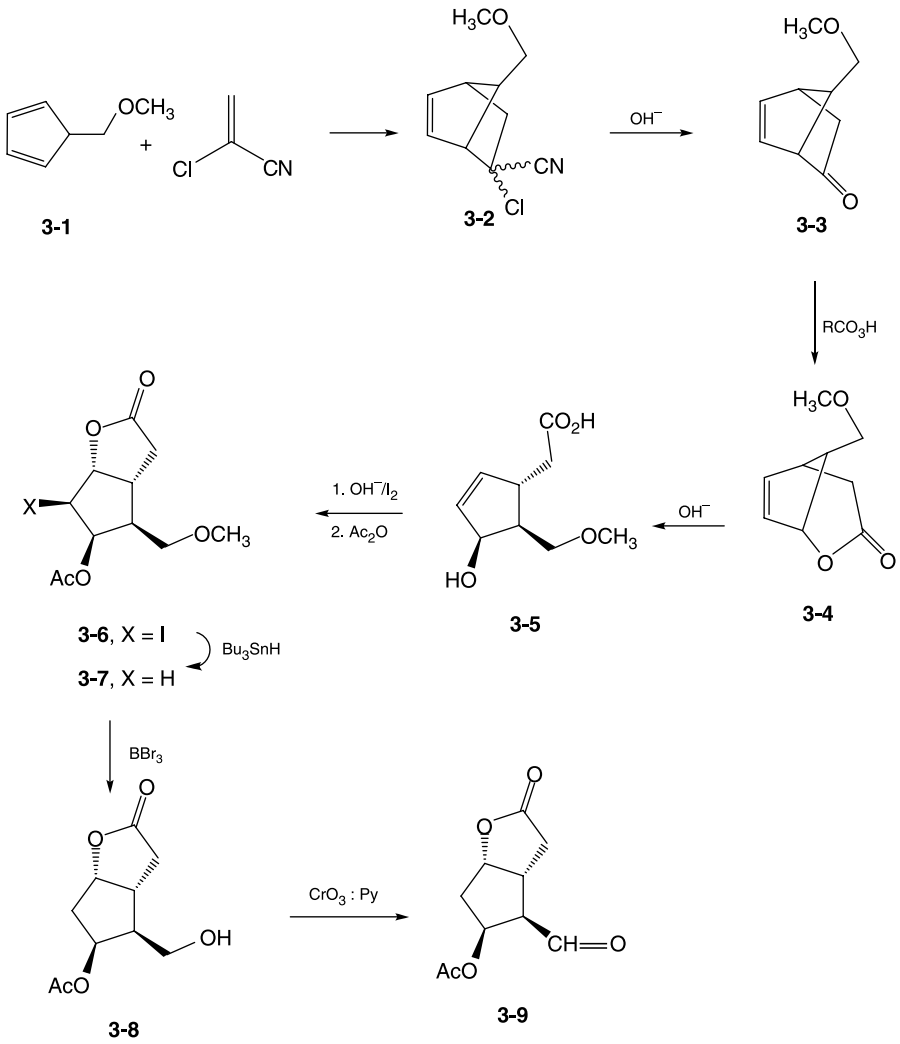


Scheme 1.1. Arachidonic Acid Cascade.

The reaction of arachidonic acid with the enzyme lypoxygenase (LOX), on the other hand, leads to an attack at the 5 position and rearrangement of the double bonds to the 7,9-*trans*-11-*cis* array typical of leukotrienes; the initial product closes to an epoxide, thus yielding leukotriene A_4. The reactive oxirane in that compound in turn reacts with endogenous glutathione to give leukotriene C_4. This compound and some of its metabolites, it turned out, constitute the previously well-known "slow reacting substance of anaphylaxis" (srs-A), involved in allergic reactions and asthma.

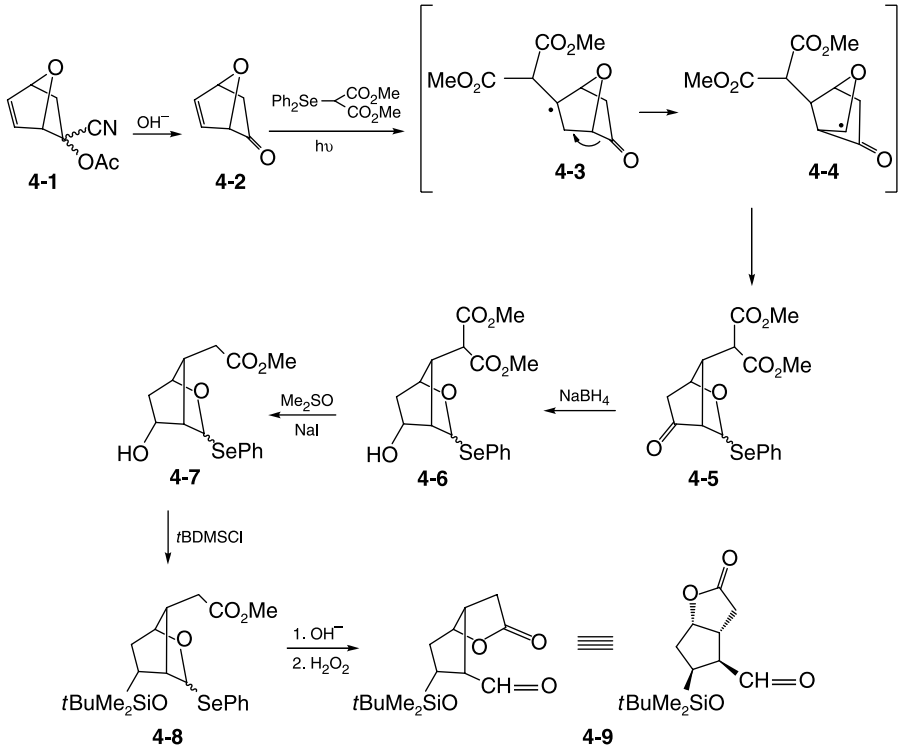
Much of the early work on this class of compounds focused on developing routes for producing the agents in quantities sufficient for biological investigations. There was some attention paid to elaborating flexible routes as it was expected that there might be some demand for analogues not found in nature. This work was hindered by the relative dearth of methods for elaborating highly substituted five-membered rings that also allowed control of stereochemistry. The unexpected finding of a compound with the prostanoic acid skeleton in a soft coral, the sea whip *plexura homomalla* [5], offered an interim source of product. The group at Upjohn, in fact, developed a scheme for converting that compound to the prostagland, which they were investigating in detail [6]. The subsequent development of practical total syntheses in combination with ecological considerations led to the eventual replacement of that marine starting material.

The methodology developed by E. J. Corey and his associates at Harvard provides the most widely used starting material for prostaglandin syntheses. This key intermediate, dubbed the "Corey lactone," depends on rigid bicyclic precursors for controlling stereochemistry at each of the four functionalized positions of the cyclopentane ring. Alkylation of the anion from cyclopentadiene with chloromethylmethyl ether under conditions designed to avoid isomerization to the thermodynamically more stable isomer gives the diene (**3-1**). In one approach, this is then allowed to react with α-chloroacrylonitrile to give the Diels–Alder adduct (**3-2**) as a mixture of isomers. Treatment with an aqueous base affords the bicyclic ketone (**3-3**), possibly by way of the cyanohydrin derived from the displacement of halogen by hydroxide. Bayer–Villiger oxidation of the carbonyl group with peracid gives the lactone (**3-4**); the net outcome of this reaction establishes the *cis* relationship of the hydroxyl that will occupy the 11 position in the product and the side chain that will be at 9 in the final product. Simple saponification then gives hydroxyacid (**3-5**). The presence of the carboxyl group provides the means by which this can be resolved by conventional salt formation with chiral bases. Reaction of the last intermediate with base in the presence of iodine results in the formation of iodolactone; the reaction may be rationalized by positing the formation of a cyclic iodonium salt on the open face of the molecule; attack by the carboxylate anion will give the lactone with the observed stereochemistry. Acetylation of the hydroxyl gives (**3-6**); halogen is then removed by reduction with tributyltin hydride (**3-7**). The methyl ether on the substituent at the future 11 position is then removed by treatment with boron tribromide. Oxidation of the primary hydroxyl by means of the chromium trioxide : pyridine complex (Collins reagent) gives Corey lactone (**3-9**) as its acetate [7].



A somewhat more direct route to the Corey lactone, developed later, depends on a radical photoaddition/rearrangement reaction as the key step. The scheme starts with the Diels–Alder addition of α-acetoxyacrylonitrile to furan to give the bridged furan (**4-1**) as a mixture of isomers. Hydrolysis by means of aqueous hydroxide gives the ketone (**4-2**); this reaction may also proceed through the intermediate cyanohydrin. This cyanohydrin is in fact produced directly by treatment of the mixture of isomers with sodium methoxide in a scheme for producing the ketone in chiral form. The crude intermediate is treated with brucine. Acid hydrolysis of the solid "complex" that separates affords quite pure dextrorotary ketone (**4-2**) [8]; this complex may consist of a ternary imminium salt formed by a sequential reaction

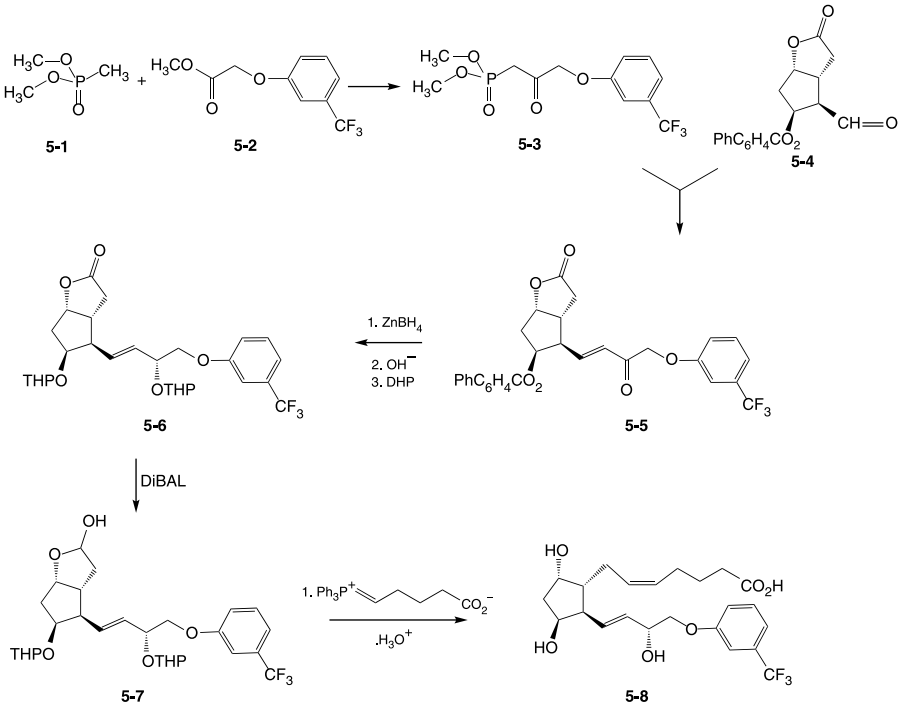
with the cyanohydrin function. Irradiation of the ketone in the presence of phenylselenylmalonate leads to the rearranged product (**4-5**) in quite good yield. The structure can be rationalized by postulating the homolytic cleavage of the C-Se bond in the malonate to give intermediate (**4-3**) as the first step; the resulting malonate radical would then add to the olefin. Acyl migration would then give the rearranged carbon skeleton of (**4-4**). Addition of the phenylselenyl radical to that intermediate will then give the observed product. Reduction of the carbonyl group by means of sodium borohydride gives the product of approach of hydride from the more open *exo* face (**4-6**). Decarboxylation serves to remove the superfluous carboxyl group to afford (**4-7**); treatment with *tertiary*-butyldimethylsilyl chloride in the presence of imidazole gives the protected intermediate (**4-8**) that contains all the elements of the Corey lactone with the future aldehyde, however, in the wrong α configuration. Saponification of the ester followed by acid hydrolysis, in fact, gives the all *cis* version of the lactone [9]. The desired *trans* isomer (**4-9**) can be obtained by oxidizing the selenide with hydrogen peroxide in the presence of sodium carbonate [10].



Biological investigations, once supplies of prostaglandins were available, revealed the manifold activities of this class of agents. The very potent effect of

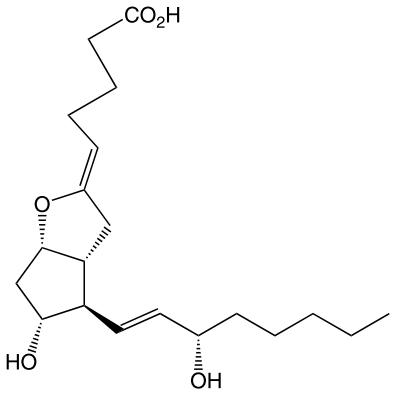
$PGF_{2\alpha}$ on reproductive function was particularly notable. Ovulation in most mammalian species is marked by the formation on the ovary of a corpus luteum that produces high levels of progesterone if a fertile ovum has implanted in the uterus. Administration of even low doses of $PGF_{2\alpha}$ was found to have a luteolytic effect, with loss of the implanted ovum due to the withdrawal of progestin. This prostaglandin was in fact one of the first compounds in this class to reach the clinic under the United States Adopted Name (USAN) name **dinoprost**. The development of drugs for use in domestic animals tends to be faster and much less expensive than those that are to be used in humans. This is particularly true if the animals are not used as food, since this dispenses with the need to study tissue residues. It is of interest, consequently, that one of the early prostaglandins that reached the market is **fluprostenol** (**5-8**). This compound differs from $PGF_{2\alpha}$ in that the terminal carbon atoms in the lower side chain are replaced by the trifluromethylphenoxy group; this modification markedly enhances potency as well as stability. This drug is marketed under the name Equimate® for controlling fertility in racing mares, a species in which costs are probably of little consequence.

Reaction of the anion from phosphonate (**5-1**) with ethyl *meta*-triflurophenoxymethylacetate results in acylation of the phosphonate by the displacement of ethoxide and the formation of (**5-3**). Condensation of the ylide from this intermediate with the biphenyl ester at position 11 of Corey lactone (**5-4**) leads to the enone (**5-5**) with the usual formation of a *trans* olefin expected for this reaction. The very



bulky biphenyl ester comes into play in the next step. Reduction of the side chain ketone by means of zinc borohydride proceeds to give largely the 15α alcohol as a result of the presence of that bulky group. The ester is then removed by saponification, and the two hydroxyl groups are protected as their tetrahydropyranyl ethers (**5-6**). The next step in the sequence involves the conversion of the lactone to a lactol; the carbon chain is thus prepared for attachment of the remaining side chain while revealing potential hydroxyl at the 9 position. This transform is affected by treating (**5-6**) with diisobutylaluminum hydride at $-78^{\circ}C$; over-reduction to a diol occurs at higher temperatures. Wittig reactions can be made to yield *cis* olefins when carried out under carefully defined, "salt-free" conditions [11]. Condensation of the lactol (**5-7**) with the ylide from 5-triphenylphosphoniumpentanoic acid under those conditions gives the desired olefin. Treatment with mild aqueous acid serves to remove the protecting groups, thus forming **fluprostenol** (**5-8**) [12].

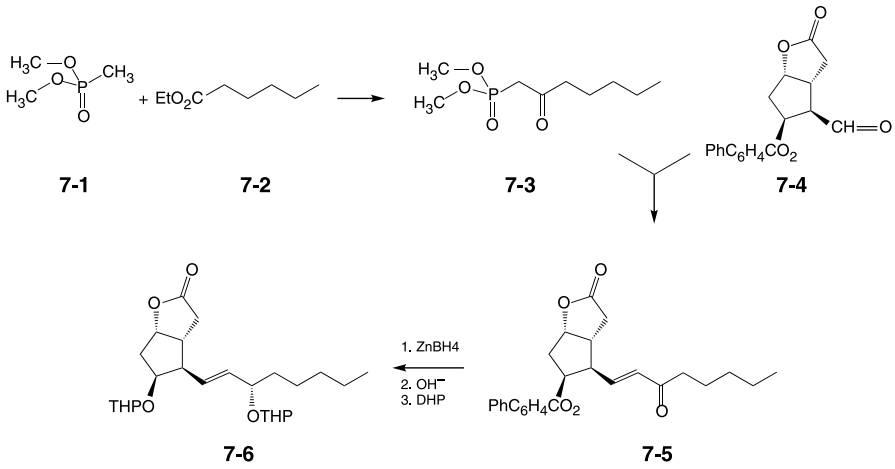
Prostaglandins have been called hormones of injury since their release is often associated with tissue insult. Most of these agents consequently exhibit activities characteristic of tissue damage. Many prostaglandins cause vasoconstriction and a consequent increase in blood pressure as well as the platelet aggregation that precedes blood clot formation. Thromboxane A_2 is, in fact, one of the most potent known platelet aggregating substances. Prostacyclin, PGI_2, one of the last cyclooxygenase products to be discovered, constitutes an exception; the compound causes vasodilation and inhibits platelet aggregation. This agent may be viewed formally as the cyclic enol ether of a prostaglandin that bears a carbonyl group at the 6 position of the upper side chain. This very labile functionality contributes to the short half-life of PGI_2. The fact that the lifetime of this compound is measured in single-digit minutes precludes the use of this agent as a vasodilator or as an inhibitor of platelet aggregation.



PGI_2

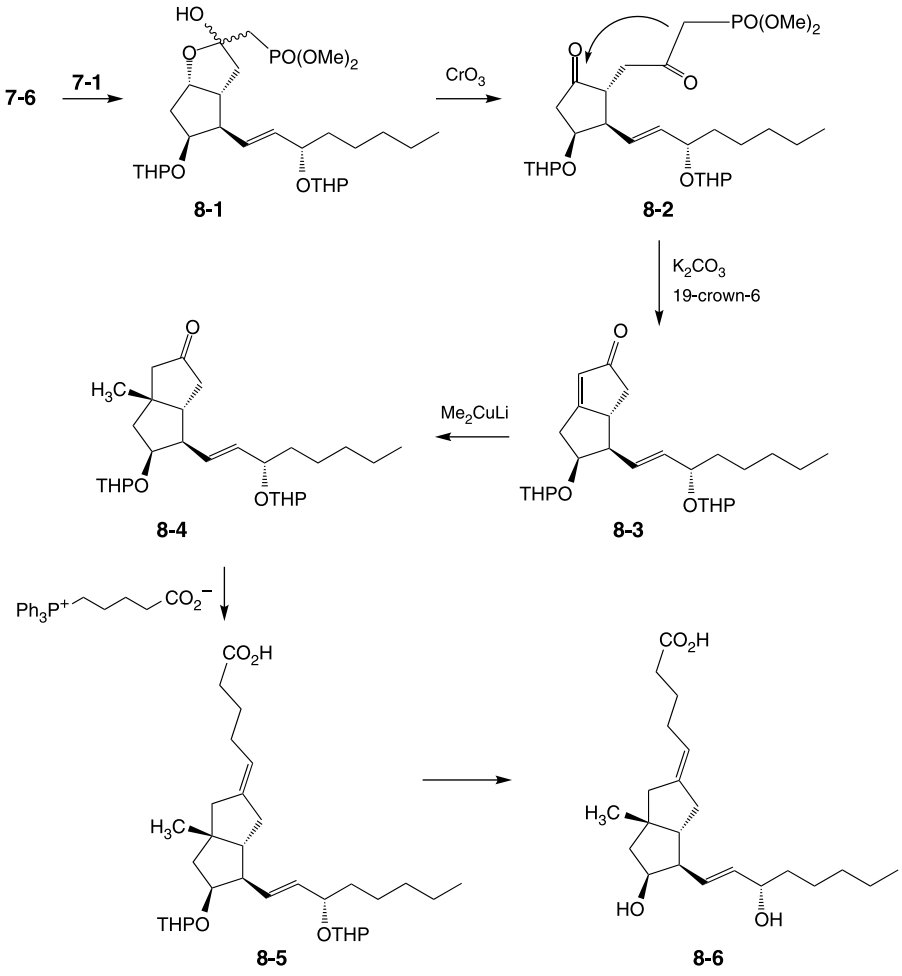
Prostacyclin

The analogue in which carbon replaces oxygen in the enol ring should of course avoid the stability problem. The synthesis of this compound initially follows a scheme similar to that pioneered by the Corey group. Thus, acylation of the ester (**7-2**) with the anion from trimethyl phosphonate yields the activated phosphonate (**7-3**). Reaction of the ylide from that intermediate with the lactone (**7-4**) leads to a compound (**7-5**) that incorporates the lower side chain of natural prostaglandins. This is then taken on to lactone (**7-6**) by sequential reduction by means of zinc borohydride, removal of the biphenyl ester by saponification, and protection of the hydroxyl groups as tetrahydropyranyl ethers.



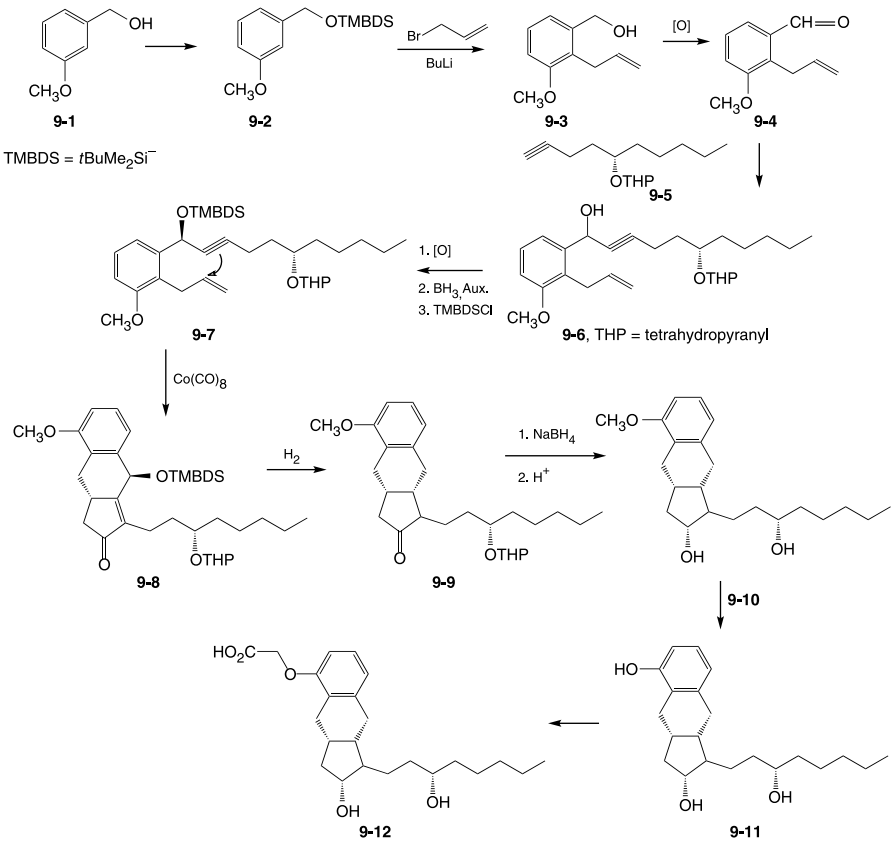
7-1 **7-2** **7-3** **7-4** **7-6** **7-5**

The first step in building the carbocyclic ring consists, in effect, of a second acylation on trimethyl phosphonate. Thus, the addition of the anion from that reagent to the lactone carbonyl in (**7-6**) leads to the product as its cyclic hemiketal (**8-1**); this last, it should be noted, now incorporates an activated phosphonate group. Oxidation of that compound with Jones' reagent gives the diketone (**8-2**). The ylide prepared from that compound by means of potassium carbonate in aprotic media adds internally to the ring carbonyl group to give fused cylopentenone (**8-3**). Conjugate addition of a methyl group to the enone by means of the cuprate reagent from methyl lithium occurs predominantly on the open β face of the molecule to afford (**8-4**). The counterpart of the upper side chain is then added to the molecule by condensation with the ylide from triphenylphosphoniumpentanoic acid bromide. The product (**8-5**) is obtained as a mixture of E and Z isomers about the new olefin due to the absence of directing groups. Removal of the tetrahydropyran protecting groups with mild aqueous acid completes the synthesis of **ciprostene** (**8-6**) [13]. This compound has the same platelet aggregation inhibitory activity as PGI_2, though with greatly reduced potency.



An analogue in which a fused tetralin moiety replaces the furan and part of the side chain in prostacyclin is approved for use as a vasodilator for patients with pulmonary hypertension. The lengthy, complex synthesis starts with the protection of the hydroxyl group in benzyl alcohol (**9-1**) by reaction with *tert*-butyl dimethyl siliyl chloride (**9-2**). Alkylation of the anion from (**9-2**) (butyl lithium) with allyl bromide affords (**9-3**). The protecting group is then removed and the benzylic hydroxyl oxidized with oxalyl chloride in the presence of triethyl amine to give the benzaldehyde (**9-4**). The carbonyl group is then condensed with the organomagnesium derivative from treatment of chiral acetylene (**9-5**) with ethyl Grignard to afford (**9-6**) (the triple bond is not depicted in true linear form to simplify the scheme). The next few steps adjust the stereochemistry of the newly formed

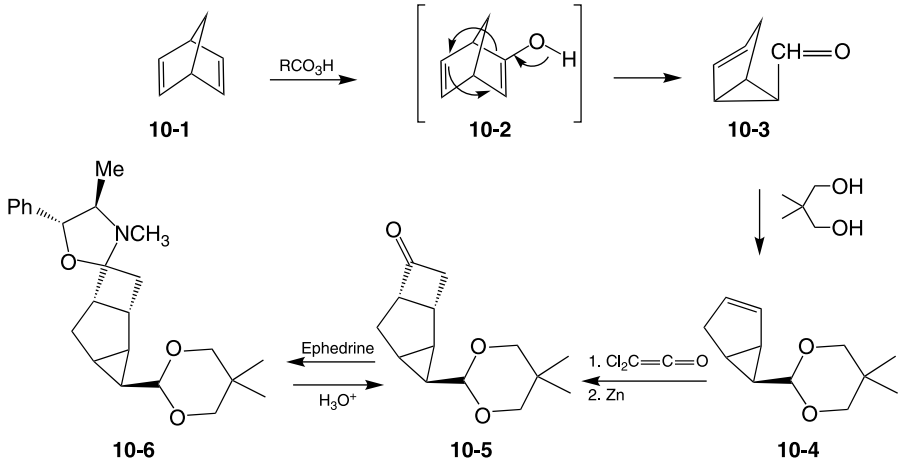
alcohol in (**9-6**). This group is first oxidized back to a ketone with pyridinium chlorochromate. Reduction with diborane in the presence of chiral 2-(hydroxydiphenylmethyl)pyrolidine affords the alcohol as a single enantiomer. This is then again protected as its *t*BDMS ether (**9-7**). Heating this compound with cobalt carbonyl leads to the formation of the tricyclic ring system. Mechanistic considerations aside, the overall sequence to the product (**9-8**) involves eletrocylic formation of the six-membered ring from the olefin and the acetylenic bond as well as insertion of the elements of carbon monoxide to form the five-membered ring. Catalytic hydrogenation of that product (**9-8**) leads to a reduction of the double bond in the enone as well as hydrogenolyis of the benzylic *t*BDMS ether on the six-membered ring (**9-9**). Reduction of the ketone then leads to the alcohol, apparently as a single enantiomer. Acid hydrolysis leads to the loss of the tetrahydropyrany protecting group to afford intermediate (**9-10**). The presence of labile groups in this compound precludes the usual methods such as hydrogen bromide or boron tribromide for cleaving the



methyl ether. Instead, in an unusual sequence, phenol (**9-11**) is obtained by treatment of (**9-10**) with butyl lithium and diphenyl phosphine. The product is then alkylated with 2-chloroacetonitrile. Hydrolysis of the cyano group to an acid finally affords the vasodilator **treprostinil** (**9-12**) [14–16].

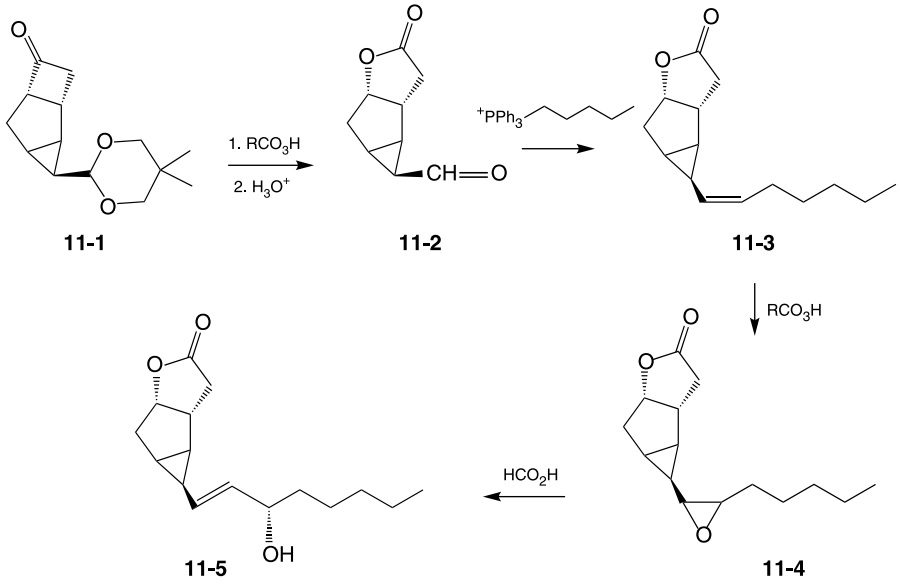
Dinoprost ($PGF_{2\alpha}$) was the first prostaglandin to be approved for clinical use. The specific indication comprised induction of labor. It has received some publicity recently as a result of its use as an adjunct in RU-486 (**mifepristone**; *see* Chapter 4) induced abortions. Though initial supplies of $PGF_{2\alpha}$ were obtained by partial synthesis from soft coral–derived starting materials, this was supplanted by a total-synthesis product. The reported synthesis, like those noted above, relies on a rigid fused bicyclic starting material for determining the relative configuration of the substituents on the cyclopentane ring.

The sequence starts by epoxidation of bicycloheptadiene (**10-1**) with peracid, a reaction that had been found earlier to proceed to aldehyde (**10-3**) rather than stopping at the epoxide. This rearrangement, which will control stereochemistry at positions 11, 12, and 15 in one fell swoop, is related conceptually to the *i*-steroid rearrangement discovered at least a decade earlier. The reaction relies in effect on the mobile equilibrium between a cyclopropylcarbinyl carbocation and its homoallyl partner: This rearrangement can be visualized as starting with the protonation of the initially formed epoxide to (**10-2**). This could then first ring open to an alcohol. The observed product (**10-3**) would be obtained by Wagner–Meerwin rearrangement of the resulting carbocation. The same product would be formed by the concerted reaction shown in the scheme below. The aldehyde is then protected as its acetal (**10-4**) with 2,2-dimethylpropylene glycol. The two carbon atoms that will form the upper side chain are then incorporated by electrocyclic addition of dichloroketene; the chlorine atoms are removed by reduction with zinc to give (**10-5**). Delaying the all-important resolution until a late step in the synthesis of chiral compounds invokes the penalty

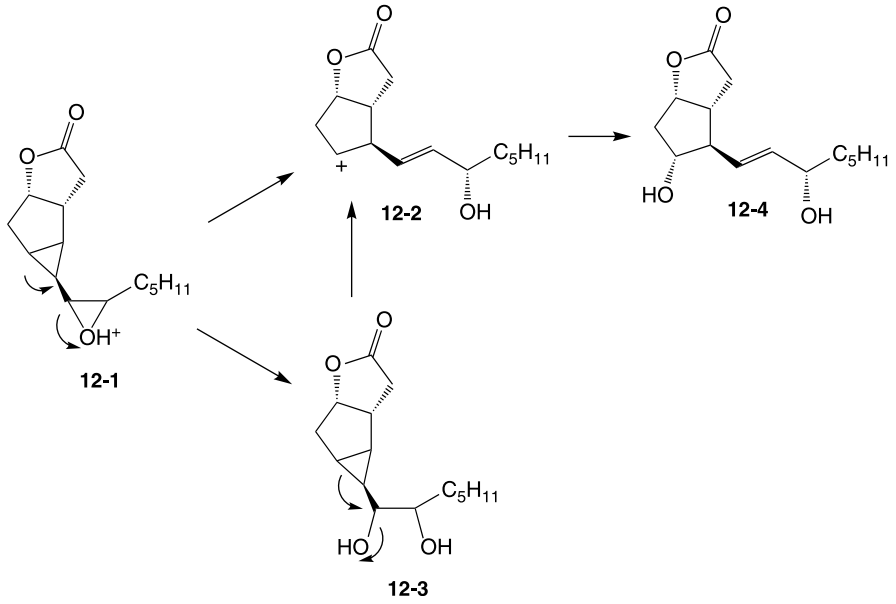


of carrying the useless inactive enantiomer through a large number of transformations. Efficient syntheses either incorporate the separation early or, better yet, start with chiral compounds. An unusual method is used to affect the resolution in the case at hand. Thus, condensation of fused cyclobutanone (**10-5**) with l-ephedrine affords a pair of diastereomeric oxazolidines (**10-6**); the higher melting of the pair providentially corresponds to the desired isomer. Separation followed by hydrolysis over silica gives (**10-5**) with the prostaglandin stereochemistry.

The cyclobutanone is then lactonized by means of Bayer–Villiger oxidation; treatment with dilute acid then serves to remove the acetal group to afford lactone-aldehyde (**11-2**). The next step comprises incorporating the remaining carbon atoms required for the lower side chain, Thus, Wittig condensation of the aldehyde with the ylide from triphenylphosphoniumhexyl bromide under salt-free conditions affords the *cis* olefin (**11-3**), which is converted to epoxide (**11-4**) by means of peracid. Solvolysis of this last intermediate in formic acid gives compound (**11-5**) accompanied by significant amounts of glycols; the mixture is recycled to give (**11-5**) in modest yield.



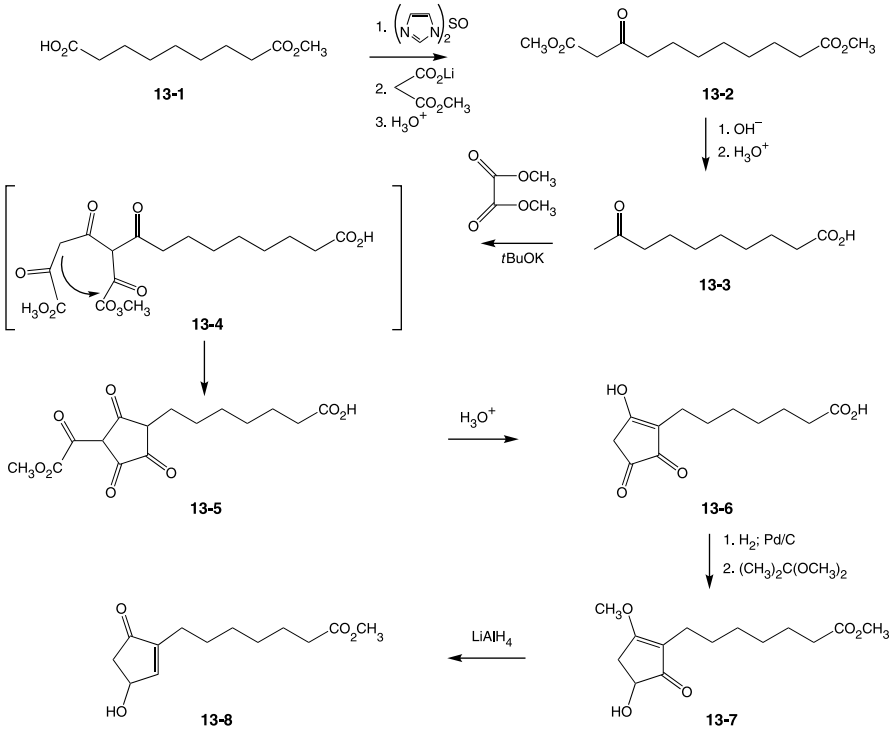
This rearrangement, which is in effect the reverse of that used to form the cyclopropyl ring in (**10-2**), can be visualized as starting with protonated epoxide (**12-1**); this can then go on to rearrange via a homoallyl ion (**12-2**); the observed stereoselective formation of the 11-hydroxyl argues for a concerted reaction. Solvolysis of the diol byproduct (**12-3**) may also go through carbocation (**12-2**) or through a more concerted transition state. The product (**12-4**) is finally taken on to $PGF_{2\alpha}$ by a sequence very similar to that used to first add the lower side chain to (**7-6**), and after suitable protection of the hydroxyls elaboration of the upper side chain [17,18].



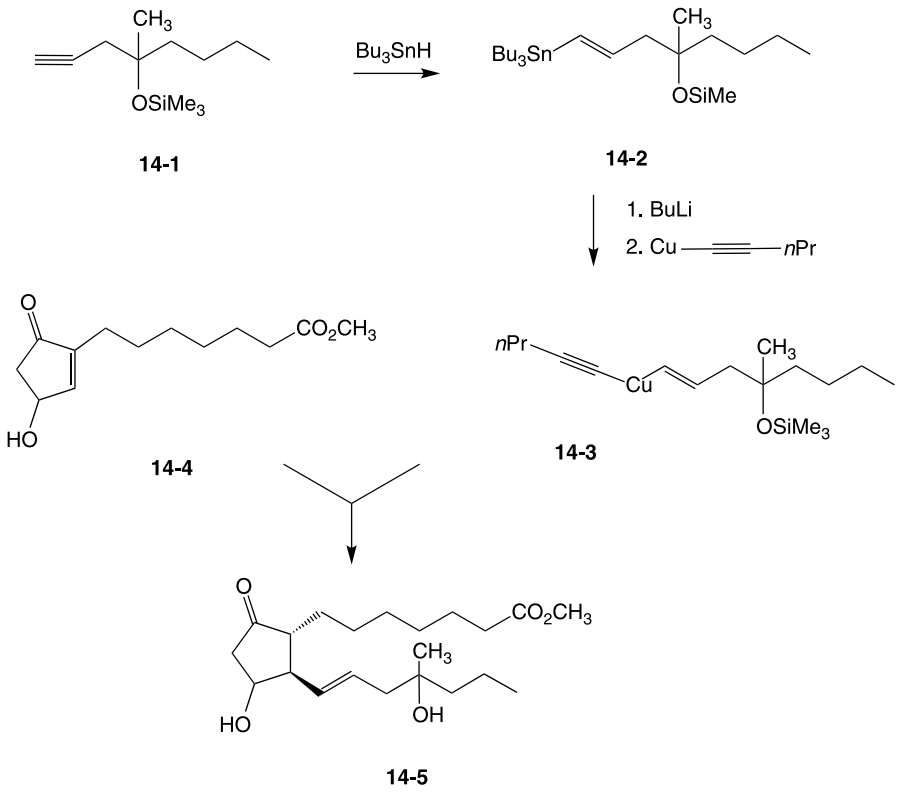
It has been known for some time that a mucus layer secreted by gastric cells protects the lining of the stomach from noxious agents, including its own digestive agents. Studies on the pharmacology of the prostaglandins revealed that these compounds had a cytoprotective effect on the gastric mucosa by maintaining the mucus layer. The recognition that aspirin and the pharmacologically related NSAIDs owed their action to the inhibition of cyclooxygenase, at the time thought to consist of a single enzyme, offered an explanation for their well-recognized injurious effect on gastric mucosa. Inhibition of that enzyme leads to a decrease in prostaglandin synthesis and a consequent increased vulnerability to irritants, including normal stomach acid. This prostaglandin deficit is difficult to remedy due to the manifold activity of most congeners, their very short biological half-life, and poor oral bioavailabilty. The finding that biological activity is retained when the side chain hydroxyl is moved from the prime site of metabolism, 15, to the 16 position eventually resulted in the development of misoprostol (**14-5**), a drug approved for the prevention of NSAID-induced ulcers.

The synthesis of this compound represents a notable departure from those discussed above. The presence of the carbonyl group at the 9 position of the cyclopentane ring, which classifies this compound as a PGE, removes one asymmetric center and thus somewhat reduces the stereochemical complexity of the synthesis. More importantly, this introduces the possibility of attaching the lower side chain by means of a 1,4-addition reaction; the *trans* relationship of the two side chains should be favored by thermodynamic considerations. The very unusual functionality of the required Michael acceptor, that of a cyclopent-2-en-4-ol-1-one, leads to a rather lengthy albeit straightforward synthesis for the requisite intermediate.

The scheme starts by activation of monomethylazeleiate (**13-1**) as its imidazole amide by means of thionyl bisimidazole. Condensation of that product with the *bis* anion from reaction lithium salt of monomethyl malonate gives acetoacetate (**13-2**); the first-formed tricarbonyl compound decarboxylates on workup. The two terminal methyl ester groups are then saponified to the corresponding acids; that β to the carbonyl group decarboxylates to a methyl ketone on acidification to afford (**13-3**). Acylation of this last intermediate with dimethyl oxalate leads to the addition of an oxalyl group to each carbon flanking the ketone to give an intermediate such as (**13-4**). (Both this and (**13-5**) are depicted as their unlikely all-ketone tautomers in the interest of clarity.) That intermediate cyclizes to the triketocyclopentane (**13-5**) under reaction conditions. Treatment with acid leads to a scission of the superfluous pendant oxalyl group. The product (**13-6**) probably exists as a mixture of the two possible enolates. Hydrogenation in the presence of palladium on charcoal interestingly leads to a reduction of the single carbonyl group not involved in that tautomerism to give the future prostaglandin 11 hydroxyl. Reaction of the product with acetone dimethyl acetal in the presence of acid leads initially to the formation of enol ethers; these can be forced to (**13-7**) because of its lower solubility in ether. Reduction of that (**13-7**) with lithium aluminum hydride or Vitride at -60°C leads on workup to the enone (**13-8**).



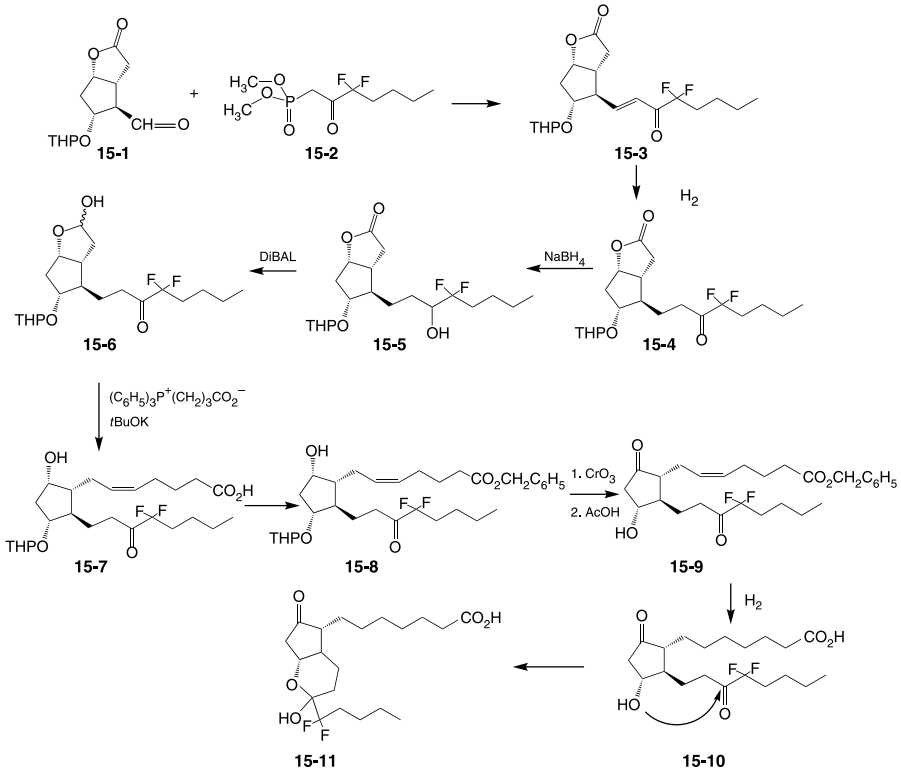
Preparation of the reagent required for adding the lower side chain involves a series of metal interchanges carried out as a one-pot reaction. The sequence starts by stereospecific stannylation of acetylene (**14-1**) by means of tributlytin hydride. Reaction of that with butyl lithium gives the corresponding vinyl lithio reagent, where the tin is replaced with retention of configuration. The lithium is then replaced by organocopper moiety by reaction with copper pentyne to give the cuprate reagent (**14-3**). The addition of (**14-3**) to the cyclopentenone as its silyl ether (**14-4**) gives the Michael product. Removal of the silyl protecting group affords **misoprostol** (**14-5**) as a mixture of enantiomers [19,20].



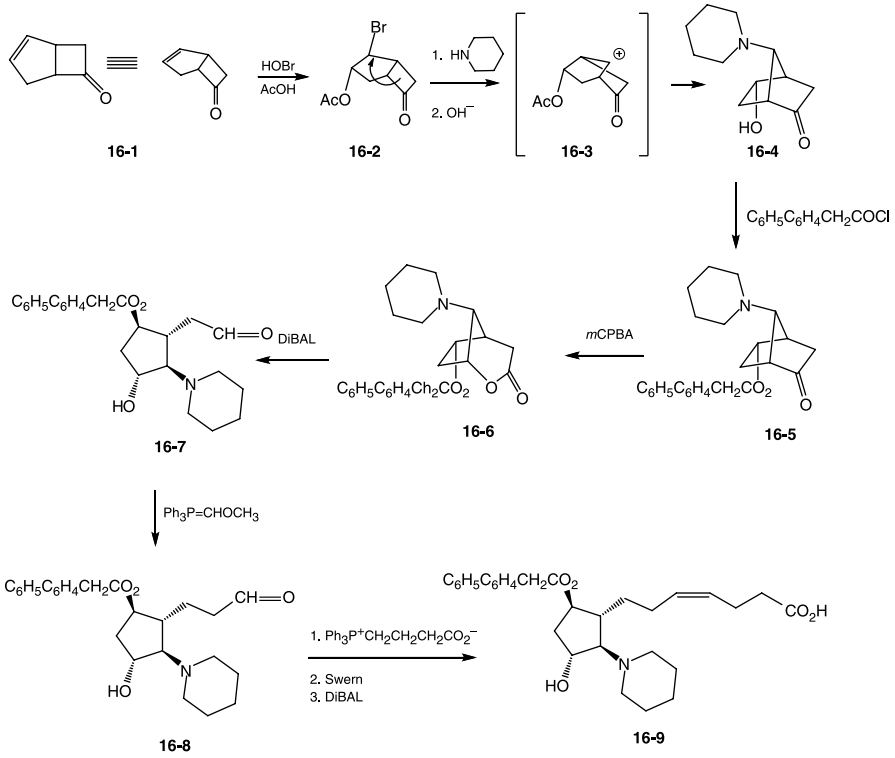
14-1 **14-2** **14-4** **14-3** **14-5**

Among their many other activities, prostaglandins have a direct effect on the gastrointestional (GI) tract. PGE_2, for example, regulates many physiological functions of the gut including mucosal protection, gastrointestinal secretion, and motility. A PGE-related compound, **lubiprostone** (**15-11**), for example, increases both intestinal fluid secretion and motility. This compound has been recently approved for the treatment of chronic constipation and is being investigated as a treatment of constipation-predominant irritable bowel syndrome. It has been ascertained that the drug interacts with specific ion channels in the GI tract, causing increased fluid output into the lumen. The starting material for the synthesis (**15-1**) comprises a variant

on the Corey lactone. Condensation of this aldehyde with the ylide from the difluorinated phosphonate (**15-2**) leads to the addition product (**15-3**). The double bond in the olefin has the expected *trans* geometry, though the next step, hydrogenation, makes this point moot. Sodium borohydride then reduces the side chain ketone function to give (**15-5**) as a mixture of isomers. The lactone is next reduced to the key lactol in the usual fashion, by means of diisobutyl aluminum hydride (**15-6**). The product is then condensed with the ylide obtained from the reaction of the zwitterion 4-triphenylphosphoniumbutyrate to give the chain extended olefin (**15-7**). The carboxylic acid in this intermediate is next protected as the benzyl ester by alkylation of its salt with benzyl chloride (**15-8**). Oxidation of the ring alcohol by means of chromium trioxide followed by exposure to mild acid to remove the tetrahydropyranyl group establishes the keto-alcohol PGE-like function in the five-membered ring (**15-9**). Catalytic hydrogenation of this last intermediate at the same time reduces the remaining double bond and removes the benzyl protecting group on the acid to give the open chain version (**15-10**) of the product. The electron-withdrawing power of the fluorine atoms adjacent to the side chain ketone causes the carbonyl carbon to become a reasonable electrophile. The electron-rich oxygen on the ring alcohol thus adds to this to give a cyclic hemiacetal. This form (**15-11**) greatly predominates in the product **lubiprostone** [21].



As noted previously, NSAIDs inhibit the inflammatory and, to some extent, the platelet-aggregating activities of products from the arachidonic cascade by inhibiting the enzyme, cylooxygenase, that catalyzes their formation. One of the few nitrogen-containing prostaglandin analogues, **vapiprost** (**16-9**), is reported to be an inhibitor of thromboxane A_2-induced platelet aggregation. This congener is potentially a more specific inhibitor of platelet aggregation, the prelude to thrombus formation, than NSAIDs in that it blocks thromboxane A_2 at the receptor site. Treatment of the chiral adduct (**16-1**) from ketene and cyclopentadiene with bromodimethylhydantoin in acetic acid results in the formation of bromoacetate (**16-2**), which results from the formal addition of hydrobromous acid. The stereochemistry of the product probably results from the formation of the initial bromonium ion on the more open face of the molecule. Treatment with piperidine leads to a rearrangement to a 2,2,1-bibycloheptane with the incorporation of nitrogen on the new one-carbon bridge. The structure of the product can be rationalized by postulating an intermediate, or transition, species such as (**16-3**) along the reaction pathway. Saponification of the initially formed product gives keto-alcohol (**16-4**). This is acylated to (**16-5**) by means of *para*-biphenylacetyl halide, a bulky group used in other prostaglandin syntheses for directing the stereochemistry of reductions. Bayer–Villiger oxidation with peracid gives a bridged version (**16-6**) of a Corey lactone; reduction with diisobutylaluminum hydride in the cold leads to hydroxyaldehyde (**16-7**), here



isolated in open form. The aldehyde is then first homologated by reaction with methoxymethyl phosphorane to give (**16-8**). A second Wittig condensation, with the ylide from triphenylphosphonium butyrate, completes the construction of the side chain that differs from that in natural prostaglandins in that the olefin is moved one atom closer to the terminal acid. The next two steps consist of inverting the stereochemistry of the 11 hydroxyl group to the unnatural β configuration. Thus, Swern oxidation of the initial product followed by reduction with diisobutylaluminum hydride gives **vapiprost** (**16-9**) [22]. The stereochemistry of the reduction is probably guided by the very bulky *para*-phenylbenzoyl group at the 9 position.

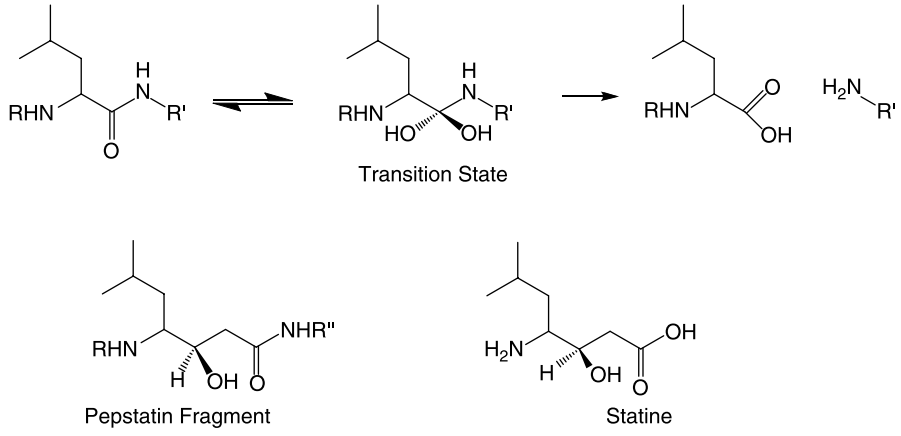
1.2. PEPTIDOMIMETIC COMPOUNDS

1.2.1. Protease Inhibitors

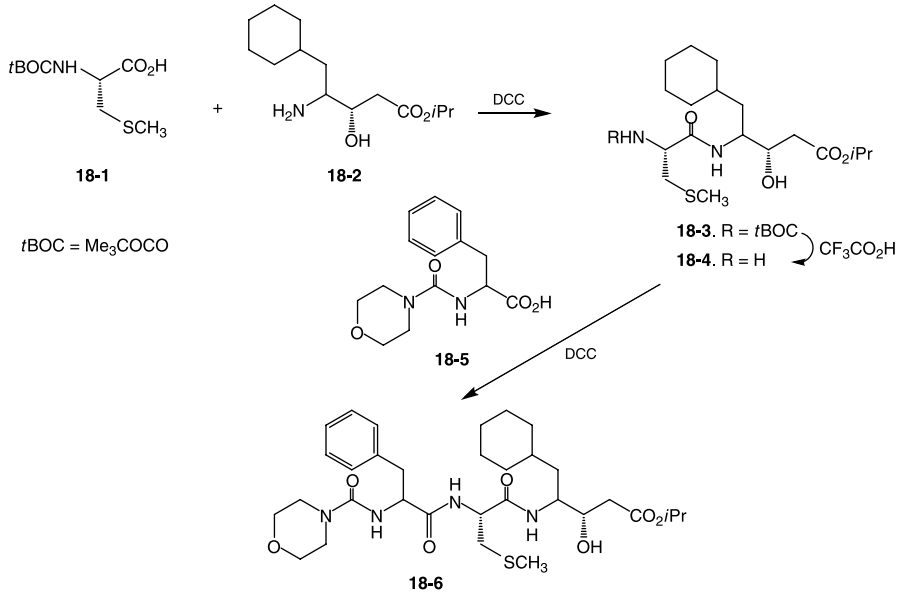
1.2.1.1. Introduction. The central role of polypeptides as regulators of life processes is of course very generally recognized. An important class of those regulators consists of enzymes, virtually all of which are made up of chains of amino acids. It is an interesting fact that these compounds, whose assembly is mediated by transcription of RNA, are quite frequently not synthesized directly in their final form. Instead, they quite often first appear as part of a much larger peptide; a specialized class of enzymes, dubbed proteases, cut the chain at specific locations so as to excise the enzyme in its active form. Renin was one of the first of the proteases to be investigated in some detail. This polypeptide specifically cleaves the large peptide angiotensinogen to excise therefrom the decapeptide angiotensin I. This last yields the potent vasoconstrictor octapeptide angiotensin II in reaction with yet another protease, an angiotensin-converting enzyme (ACE). A series of nonpeptide compounds that blunted the action of that enzyme, known as the ACE inhibitors, have proven useful in treating hypertension by decreasing levels of vasoconstricting angiotensin II by lowering levels of ACE. Considerable effort has been devoted to the search for drugs that block this cascade upstream at the level of renin in the search for antihypertensive agents that would avoid some of the shortcomings of the generally well-tolerated ACE inhibitors. This search has been rewarded with the development of several compounds that inhibit the cascade at its very inception by blocking the action of renin.

Proteases, like many enzymes, act by stabilizing a relatively high energy transition state; in this case the initial adduct of a hydroxyl group, or its functional equivalent, to the carbonyl carbon. This addition causes the geometry of that center to change from trigonal to tetrahedral. Known inhibitors consist of molecules that mimic an essential stretch of the protease recognition site and, most importantly, provide a sequence that duplicates the transition center sterically without, however, including a cleaveable bond. The fermentation product, pepstatin, a peptide-like inhibitor of pepsin, provided an early clue for the synthesis of protease inhibitors; the central portion of that molecule provides a 1,3-hydroxyamide sequence that is thought to act as a transition state analogue from a peptide bond; note that a methylene replaces one

amide nitrogen. The active moiety, statine, has been prepared by a total synthesis involving aldol-like condensation of isoleucylaldehyde with the lithio carbanion from acetate [23].

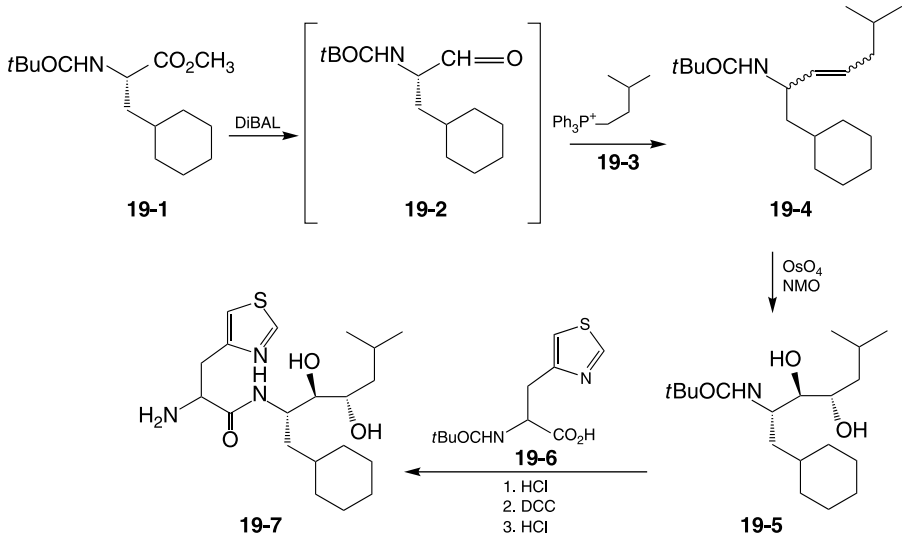


1.2.1.2. Renin Inhibitors. Preparation of the renin inhibitor **terlakiren** (**18-6**) starts with the reaction of the S-methyl ether of cysteine protected as its *tertiary*-butoxycarbonyl amide (BOC) (**18-1**) with the statine analogue (**18-2**), in which cyclohexyl replaces the isobutyl group; the coupling reaction is catalyzed by di-cyclohexylcarbodiimide (DCC). The amino group in product (**18-3**) is then



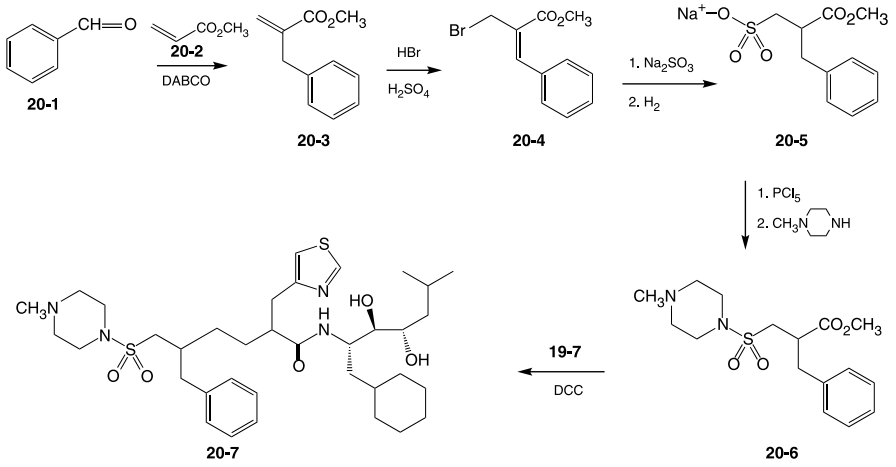
deprotected by treatment with trifluoroacetic acid; this reagent leads to the elimination of isobutylene from the BOC group followed by decarboxylation of the now-unstable free carbamic acid to afford free amine (**18-4**). The coupling sequence is now repeated using a phenyl alanine derivative (**18-5**) to yield the desired product (**18-6**) [24].

The enantioselective synthesis of a somewhat more complex renin inhibitor starts with the reduction of the ester group in the chiral amino-ester (**19-1**) by means of diisobutyl aluminum hydride in the cold. The aldehyde product (**19-2**) is then reacted with prior isolation with the ylide from phosphonium salt (**19-3**) and a strong base



to give the olefin (**19-4**) as a mixture of geometric isomers. Oxidation of the product with *N*-methylmorpholine oxide (NMO) in the presence of a catalytic amount of osmium tetroxide leads to the *trans* glycol (**19-5**). Treatment with hydrogen chloride then cleaves the protecting group to afford the free amine. That intermediate is then coupled in the presence of DCC with the chiral thiazoloalanine (**19-6**). A second round of hydrogen chloride leads to the dipeptide-like intermediate (**19-7**).

The reaction of benzaldehyde with methyl acrylate in the presence of the non-nucleophilic base DABCO results in an unusual aldol condensation in which the product (**20-3**) results from the addition of the anion from the unsaturated olefin carbon. A reaction with hydrogen bromide in strong acid results in rearrangement of the conjugated olefin with concomitant bromination on the new allylic methyl group (**20-4**). Treatment with sodium sulfite replaces halogen with sulfur to afford the sulfonic acid salt (**20-5**). The new functional group is then converted to the acid halide with phosphorus pentachloride. The reaction of that intermediate with *N*-methyl piperazine affords the remaining large moiety. The ester in (**20-6**) is then saponified to afford the free acid. Condensation of that last piece with the "dipeptide" (**19-7**) in the presence of DCC gives the renin antagonist **zankiren** (**20-7**) [25].



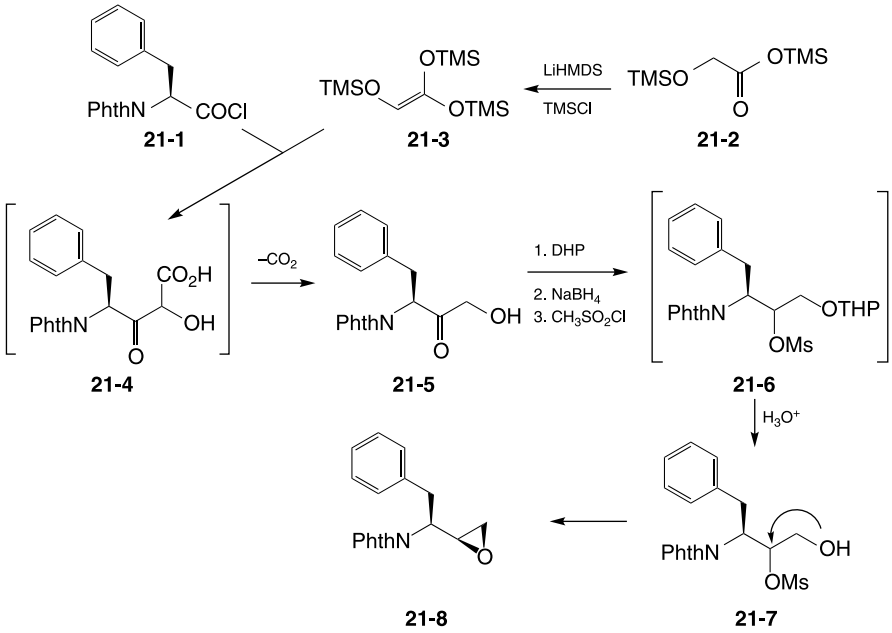
1.2.1.3. Antiviral Compounds

1.2.1.3.1. Human Immunodeficiency Virus. The functional simplicity of viruses combined with the fact that they require a living host for their replication has made them an unusually difficult therapeutic target. Human immunodeficiency virus (HIV), in common with most viruses, consists of a packet of genetic information encoded, in this case, in RNA and an outer protein coat. One of the final steps in viral replication involves synthesis of the coat peptide. Production of the coat peptide involves the scission of the initially produced, much larger protein by means of an aspartyl protease; a virus lacking the correct coat is not functional. The research that led to the HIV protease inhibitors detailed below represents a new era in drug development. The availability of a full three-dimensional structure of the protease, obtained by X-ray diffraction, made possible the use of computer-based modeling programs for designing inhibitors that best fit the target enzyme. This largely accounts for the fact that these inhibitors, which to some extent must mimic a polypeptide, include at the most only one of the naturally occurring amino acids.

The discovery that protease inhibitors were effective against HIV sparked intensive work in many laboratories on preparing proprietary compounds. Some nine discrete anti-HIV protease inhibitors have been approved by the Food and Drug Administration (FDA) as of this writing. The account that follows describes only a few from that large group.

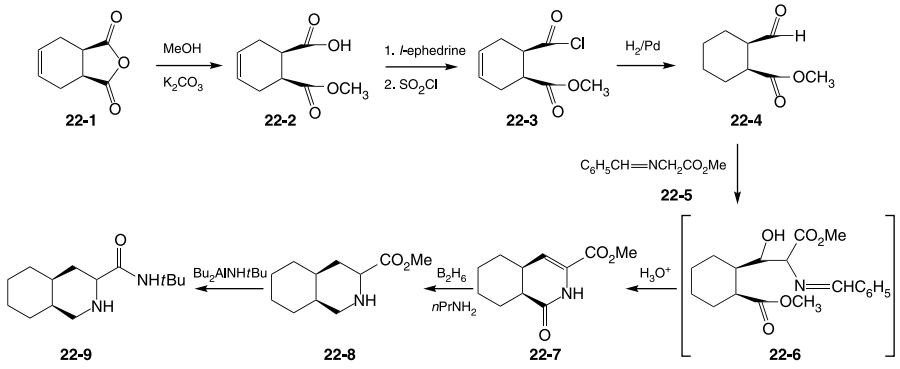
The statine-like moiety in one of the first drugs, **saquinovir** (**23-8**), comprises a transition state mimic for the cleavage of phenylalanylprolyl and tyrosylprolyl sequences. Construction starts with the protection of the amino group of phenylalanine as its phthaloyl derivative (Phth) by reaction with phthalic anhydride; this is then converted to acid chloride. The chain is then extended by one carbon using a Friedel–Crafts-like reaction. The required reagent (**21-2**) is prepared by reaction of the enolate obtained from the *bis*-silyl ether (**21-3**) of glyoxylic acid and lithio

hexamethyldisilazane (LiHMDS) with trimethylsilyl chloride [26]. The uncatalyzed reaction of acid chloride (**21-1**) with (**21-2**) gives the chain extended product (**21-5**) directly on acidification; the first formed β-carbonyl compound (**21-4**) apparently decarboxylates spontaneously. The terminal alcohol is then protected as a tetrahydropyranyl ether by adding it to dihydropyran; reduction of the ketone with sodium borohydride occurs enantioselectively due to the presence of the adjacent chiral center. Reaction with methanesulfonyl chloride then gives intermediate mesylate (**21-6**), which is not isolated. The pyranyl ether is then removed by acid catalyzed exchange with ethanol to give (**21-7**). The alkoxide formed from the terminal hydroxyl in this last compound on treatment with potassium *tert*-butoxide internally displaces the adjacent mesylate to form epoxide (**21-8**), in which the configuration of the former alcohol carbon is inverted [27].

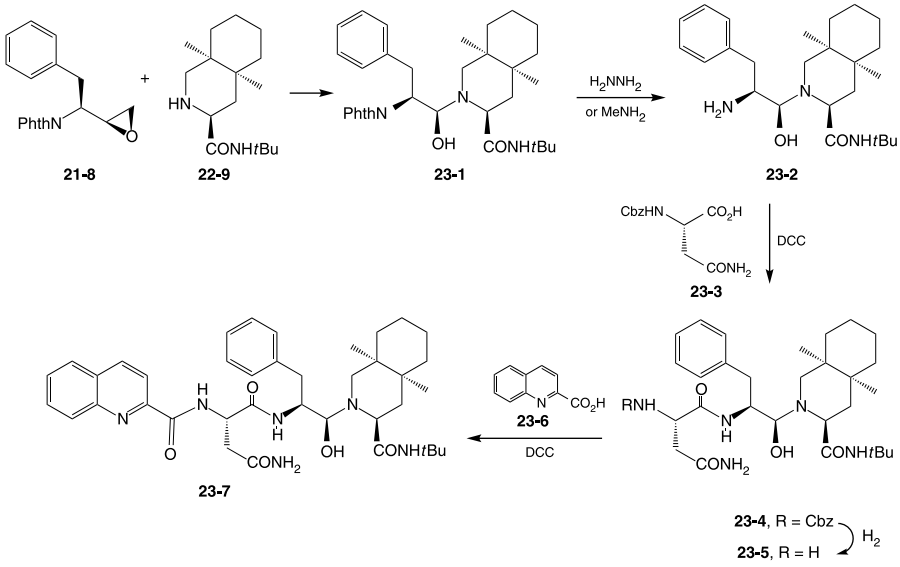


The other major fragment consists of a decahydroisoquinoline that may be viewed as a rigid analogue of an amino acid. Methanolysis of the adduct (**22-1**) from butadiene and maleic anhydride in basic methanol gives the half-ester (**22-2**); the obligate *cis* stereochemistry of the adduct determines that of the future perhydroisoquinoline ring fusion. The half-acid is then resolved as its salt with *l*-ephedrine. The desired enantiomer is next converted to the acid chloride (**22-3**); hydrogenation under Rosenmund conditions, and palladium in charcoal in the presence of quinoline, lead to the aldehyde (**22-4**). The next step involves essentially adding methyl glycinate to the aldehyde group. Conversion of that compound to its benzal derivative (**22-5**) serves to remove the more acidic amino protons and at the same time activates the protons on the methylene group. Condensation of the lithium salt from that

compound with aldehyde (**22-4**) may be envisaged as first forming an adduct such as (**22-6**). The acidic workup serves to dehydrate the β-hydroxyester, to hydrolyze the Schiff base, and to cyclize the ester with the newly revealed amine, though not necessarily in that order. The first product isolated is in fact the lactam (**22-7**). Reaction with diborane in the presence of propylamine serves to reduce both the lactam and the olefin conjugated with the ester to afford (**22-8**). Displacement of the ester methoxyl by means of dibutylaluminum-*tert*-butylamide gives the decahydroquinoline (**22-9**) [27].

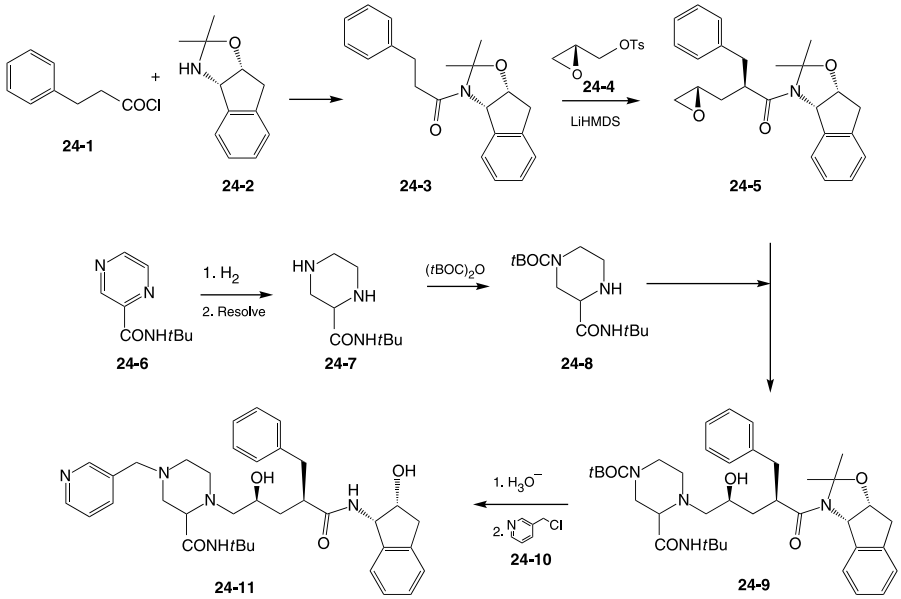


The last stage in this convergent synthesis comprises the connection of the individual units. The ring opening of epoxide (**21-8**) by the secondary amino group on perhydroisoquinoline (**22-9**) gives the alcohol (**23-1**). The phthaloyl protecting



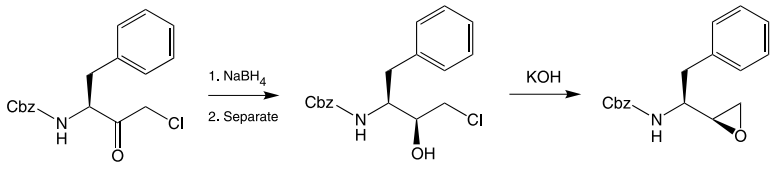
group is then removed by traditional treatment with hydrazine or, alternatively, with methylamine, the latter being more suitable to large scale work (**23-2**). The free amino group is then condensed with the Cbz derivative (**23-3**) of the monoamide from aspartic acid to give amide (**23-4**). Hydrogenation over palladium on charcoal reductively removes the benzyl group from the Cbz derivative; the unstable carbamic amide that remains decarboxylates to afford the amine (**23-5**). Condensation with quinoline-2-carboxylic acid (**23-6**) catalyzed by DCC forms the last amide bond [28]. There is thus obtained the HIV protease inhibitor **saquinovir** (**23-7**).

The HIV protease inhibitor **indinavir** (**24-11**) differs markedly in its structural components and is notable for the fact that it does not include a single natural α-amino acid [29]. Construction of this compound starts with reaction of resolved 1-amino-2-indanol with acetone to afford the cyclic carbinolamine derivative (**24-2**) that will act as a protecting group for both the amine and the alcohol. Acylation of this intermediate with hydrocinnamyl chloride (**24-1**) gives the amide (**24-3**). One of the key transformations in the sequence involves the alkylation of the carbanion obtained on treatment of (**24-3**) with LiHMDS with the toluenesulfonate derivative (**24-4**) from chiral glycidol. The enantioselective course of the alkylation reaction leading to (**24-5**) can be attributed to the proximity of the two chiral centers on the indan. In the other arm of the converging scheme, the catalytic reduction of the *tert*-butylamide (**24-6**) of pyrazine carboxylic acid gives the corresponding piperazine (**24-7**). This is then resolved as its camphorsulfonate salt. The amine at the 4 position is next selectively protected as its *tert*-butoxycarbonyl derivative (**24-8**) using BOC anhydride. The lesser steric bulk about that amino group as well as the possible hydrogen bonding of the amine at 1 with the adjacent carbonyl



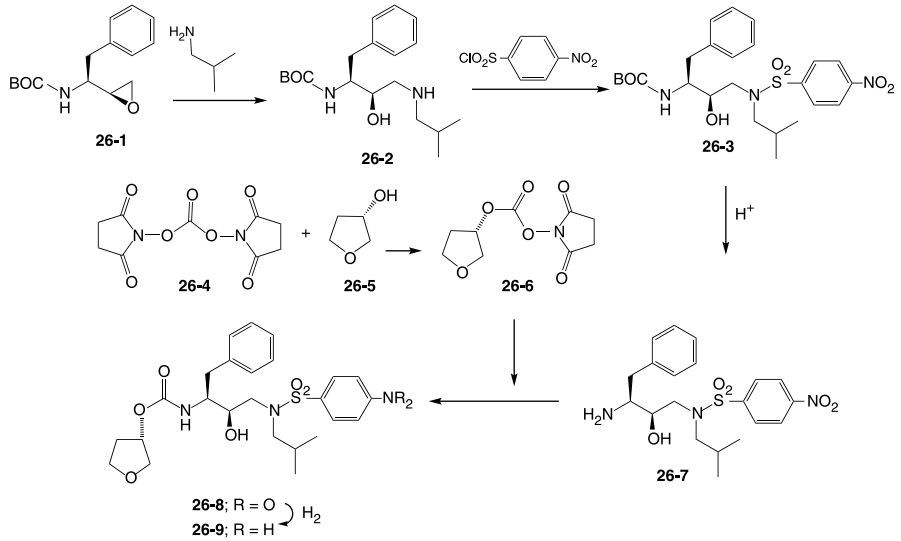
group contribute to the selectivity of this acylation step. Condensation of intermediate (**24-8**) with the large fragment (**24-5**) leads to an attack of the free amino group of the piperazine on the epoxide with consequent ring opening and formation of the alcohol (**24-9**); this reaction proceeds with the expected retention of configuration of the chiral center bearing the hydroxyl group. The *tert*-butoxycarbonyl protecting group is then removed by exposure of the intermediate to acid; the carbinolamine hydrolyzes under reaction conditions. Alkylation of the newly revealed piperazine nitrogen with 3-chloromethylpyridine (**24-10**) affords the protease inhibitor **indinavir** (**24-11**) [30].

One scheme for preparing a key intermediate for incorporating the statine-like fragment in the protease inhibitor **amprenvir** (**26-9**) begins with the chloromethyl ketone (**25-1**) derived from phenylalanine in which the amine is protected as a Cb group. Reduction of the carbonyl group by means of borohydride affords a mixture of aminoalcohols. The major *syn* isomer (**25-2**) is then isolated. Treatment of that compound with a base leads to the internal displacement of halogen and the formation of the epoxide (**25-3**) [31].



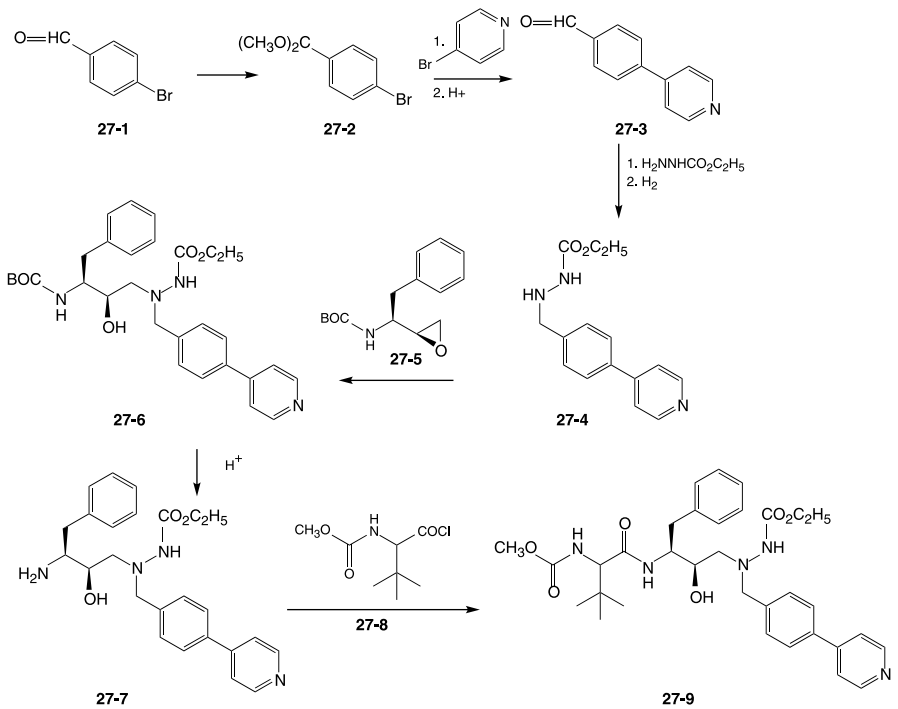
25-1 **25-2** **25-3**

The corresponding analogue (**26-1**), in which the amine is protected as a *t*-butyloxycarbonyl function rather than Cbz, is used for preparing the HIV protease



inhibitor **amprenavir** (**26-9**). Reaction of (**26-1**) with isobutyl amine leads to a ring opening of the oxirane and the formation of the aminoalcohol (**26-2**). The thus-formed secondary amine in the product is then converted to the sulfonamide (**26-3**) by treatment with *p*-nitrobenzenesulfonyl chloride. The BOC protecting group is then removed by exposure to acid, leading to primary amine (**26-7**). In a convergent scheme, chiral 3-hydroxytetrahydrofuran (**26-5**) is allowed to react with *bis*(*N*-sucinimidooxy)carbonate (**26-4**). The hydroxyl displaces one of the *N*-hydroxysuccinimide groups to afford the tetrahydrofuran derivative (**26-6**) equipped with a highly activated leaving group. Reaction of this intermediate with the amine (**26-7**) leads to the displacement of the remaining *N*-hydroxysuccinimide and the incorporation of the tetrahydrofuryl moiety as a urethane (**26-8**). Reduction of the nitro group then affords the protease inhibitor **amprenavir** (**26-9**) [32].

The protease inhibitor **atazanivir** includes some significant structural differences from the preceding examples, though it shares a similar central aminoalcohol sequence that is presumably the pharmacophore. Construction of one end of the molecule begins with the protection of the carbonyl function in *p*-bromobenzaldehyde (**27-1**) as its methyl acetal (**27-2**) by treatment with methanol in the presence of acid. The reaction of that intermediate with the Grignard reagent from 4-bromopyridine leads to an unusual displacement of bromine from the protected benzaldehyde and the formation of the coupling product. Mild aqueous acid restores the aldehyde function to afford (**27-3**). This is then condensed with *t*-butyloxycarbonyl hydrazine

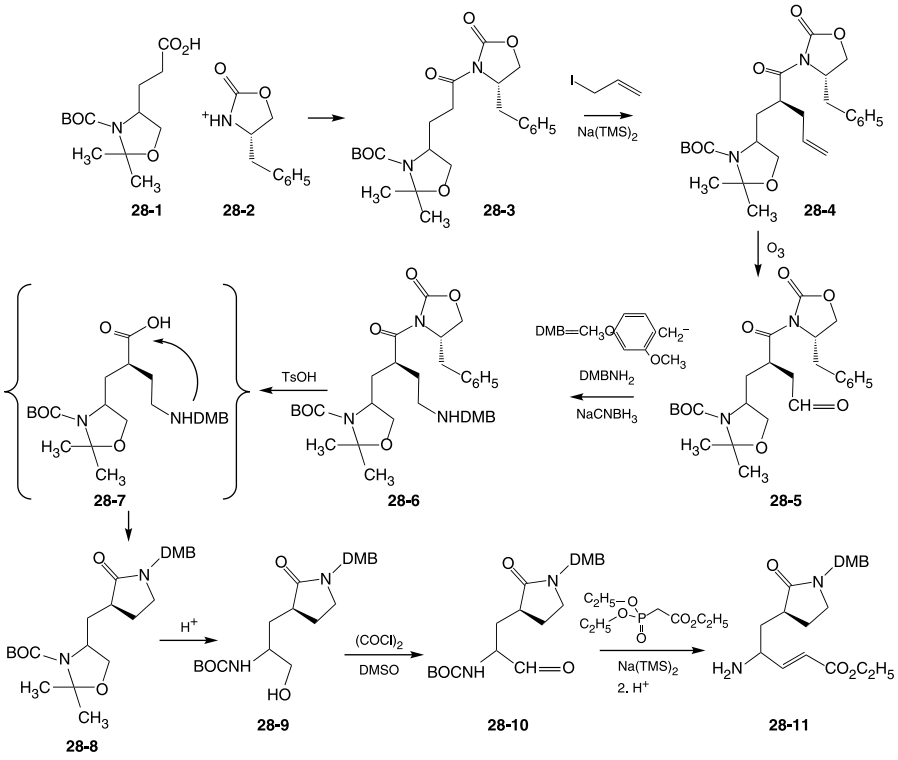


to form the respective hydrazone. Reduction of the imine function leads to the substituted hydrazine (**27-4**). The reaction of this last intermediate with the amino-epoxide (**26-1**), also used for amprenavir, results in an oxirane opening by attacking the basic nitrogen in hydrazine (**27-4**) and the consequent formation of the addition product (**27-6**). The BOC protecting group is then removed by treatment with acid. The final step comprises the acylation of the free primary amine in (**27-7**) with the acid chloride from the *O*-methyl urethane (**27-8**). This is a protected version of an unnatural α-aminoacid that can be viewed as valine with an additional methyl group on what had been the side chain secondary carbon atom. There is thus obtained the protease inhibitor **atazanavir** [33] (**27-9**).

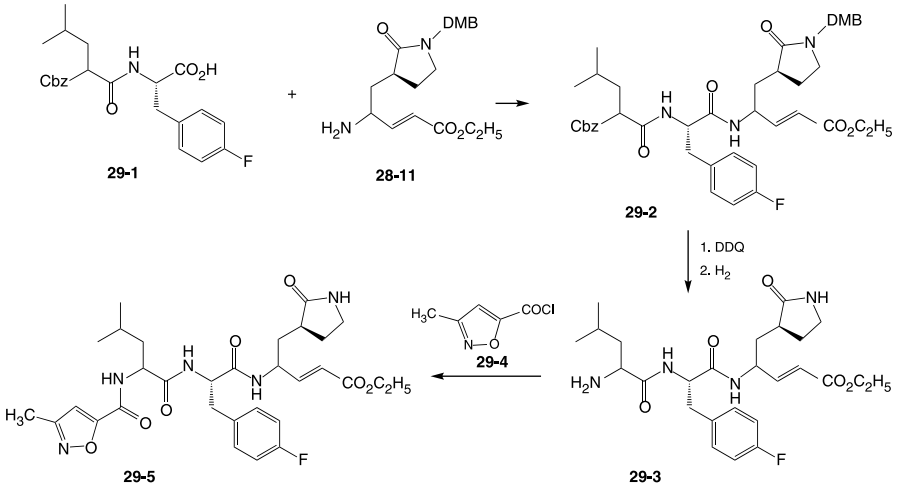
1.2.1.3.2. Human Rhinovirus. Human rhinoviruses are one of the most frequent causes of the affliction that accompanies cooling weather, the common cold. These viruses, too, consist of a small strand of RNA enveloped in a peptide coat. Fresh virions in this case also depend on the excision of that peptide from the larger initially produced protein. The statine-based HIV drugs act by occupying the scission site of the protease enzyme and consequently preventing access by the HIV-related substrate. That binding is, however, reversible in the absence of the formation of a covalent bond between the drug and the enzyme. A different strategy was employed in the research that led to the rhinovirus protease inhibitor **rupinavir** (**29-5**). The molecule as a whole is again designed to fit the protease enzyme, as in the case of the anti-HIV compounds. In contrast to the latter, however, this agent incorporates a moiety that will form a covalent bond with the enzyme, in effect inactivating it with finality.

The main part of the somewhat lengthy convergent synthesis consists of the construction of a Michael acceptor for a thiol group on a cysteine residue known to be present at the active site of viral proteiase. The preparation of that key fragment starts with the protected form of chiral 3-amino-4-hydroxybutyric acid (**28-1**); note that the oxazolidine protecting group simply comprises a cyclic hemiaminal of the aminoalcohol with acetone. The first step involves the incorporation of a chiral auxiliary to guide the introduction of an additional carbon atom. The carboxylic acid is thus converted to the corresponding acid chloride and is then reacted with the S isomer of the by-now classic oxazolidinone (**28-2**) to give the derivative (**28-3**). Alkylation of the enolate from (**28-3**) with allyl iodide gives the corresponding allyl derivative (**28-4**) as a single enantiomer. The double bond is then cleaved with ozone; reductive workup of the ozonide affords the aldehyde (**28-5**). Reductive amination of the carbonyl group with 2,6-dimethoxybenzylamine in the presence of cyanoborohydride proceeds to the corresponding amine (**28-6**). This last step in effect introduces a protected primary amino group at that position. The chiral auxiliary grouping is next removed by mild hydrolysis. The initially formed amino acid (**28-7**) then cyclizes to give the five-membered lactam (**28-8**). Treatment under stronger hydrolytic conditions subsequently serves to open the cyclic hemiaminal grouping to reveal the free aminoalcohol (**28-9**). Swern-type oxidation of the terminal hydroxyl group in this last product affords an intermediate (**28-10**) that now incorporates the aldehyde group required for building the Michael acceptor function. Thus the reaction of

that compound with the ylide from ethyl 2-diethoxyphosphonoacetate adds two carbon atoms and gives the acrylic ester (**28-11**).



The remaining part of the target molecule is prepared by the condensation of *N*-carbobenzyloxyleucine with *p*-fluorophenylalanine to give the protected dipeptide

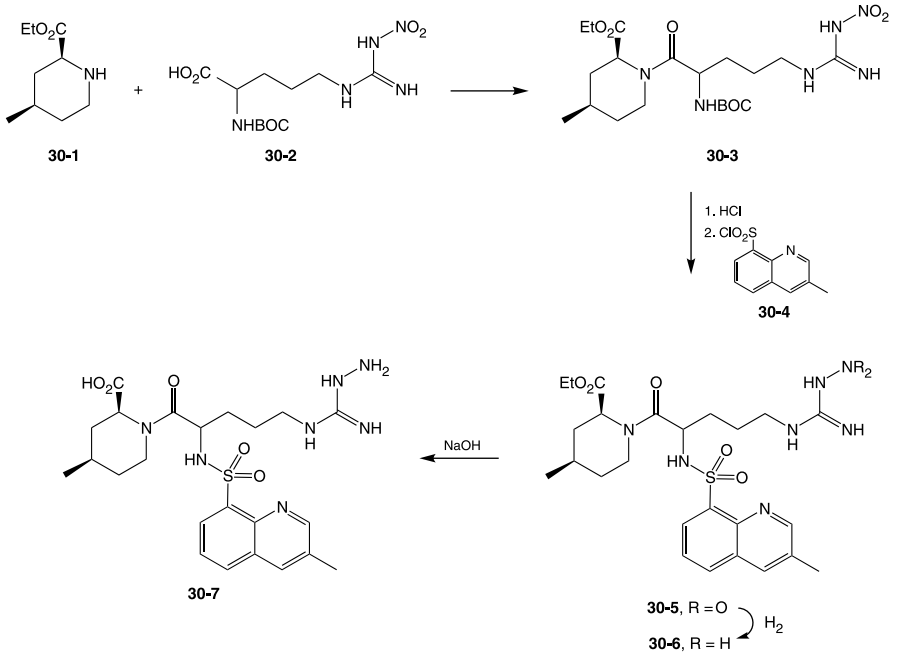


(**29-1**). Condensation of that intermediate with the Michael acceptor fragment (**28-11**) under standard peptide-forming conditions leads to the dipetide-like compound (**29-2**). The reaction of that with dichlorodicyanoquinone (DDQ) leads to the unmasking of the amide group by oxidative loss of the DMB protecting group; hydrogenation then removes the carbobenzyloxy protecting group on the terminal amine (**29-3**). Acylation of that function with isoxazole (**29-4**) finally affords the rhinovirus protease inhibitor **rupinavir** (**29-5**) [34].

1.2.2. Fibrinogen Receptor Antagonists

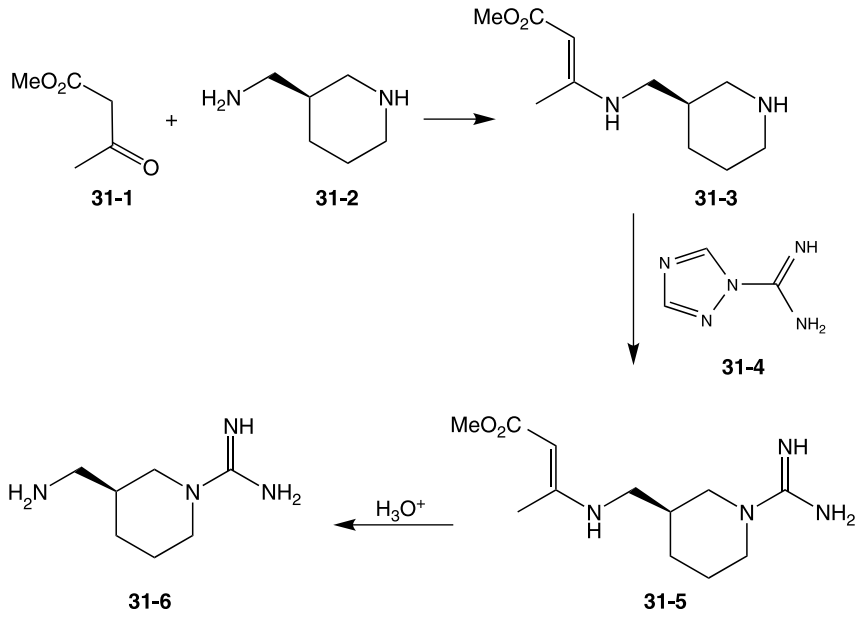
Formation of the clots that seal off broken blood vessels begins with the aggregation of platelets at the site of injury. This event sets off the long cascade that leads to the formation of fibrin. Inappropriate aggregation of platelets leads to the formation of clots that lead to thromboses or even strokes. The aggregation of platelets depends on the binding of fibrinogen to specific sites on platelet membranes. The presence of two arginine–glycine–aspartic sequences in the structure of fibrinogen has led to the development of several antagonists, parts of whose structures mimic that sequence. No fewer than eight fibrinogen antagonists have been granted USAN as of this writing.

The key starting material of one of the first antagonists, **argatroban** (**30-6**), comprises a derivative of arginine itself in which the amine is protected as its *tert*-butoxycarbonyl derivative and an *N*-nitro group moderates the basic nature of the guanidine group (**30-2**). That intermediate is first condensed with the piperidine



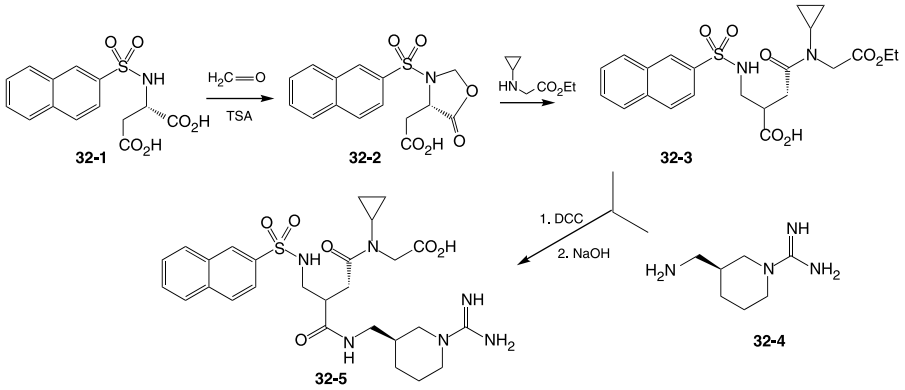
(**30-1**). The BOC protecting group is the removed by treatment with acid. The newly revealed primary amine is next acylated using quinoline sulfonyl chloride (**30-4**). Catalytic hydrogenation of the product (**30-5**) from this last reaction serves to reduce the nitro group to form an *N*-amino guanidine (**30-6**). Saponification of the ester completes the synthesis of **argatroban** (**30-7**) [35].

A somewhat more complex compound features a guanidine function in which one of the nitrogen atoms forms part of a piperidine ring. Construction of that function begins with catalytic hydrogenation on 3-aminomethylpyridine to give the corresponding piperidine; that product is then resolved by way of its tartrate salt to afford (**31-2**) as a single enantiomer. The reaction of (**31-2**) with methyl acetoacetate (**31-1**) discriminates between the primary and secondary amino groups in the compound since the former more readily form an enamine with the β-ketoester. The reaction of the thus-protected intermediate (**31-3**) with triazolo amidine (**31-4**) leads to the transfer of the amidine to the more basic amine on the piperidine and the formation of guanidine (**31-5**). Trreatment of that product with aqueous acid leads to hydrolysis of the enamine to afford the synthon (**31-6**).

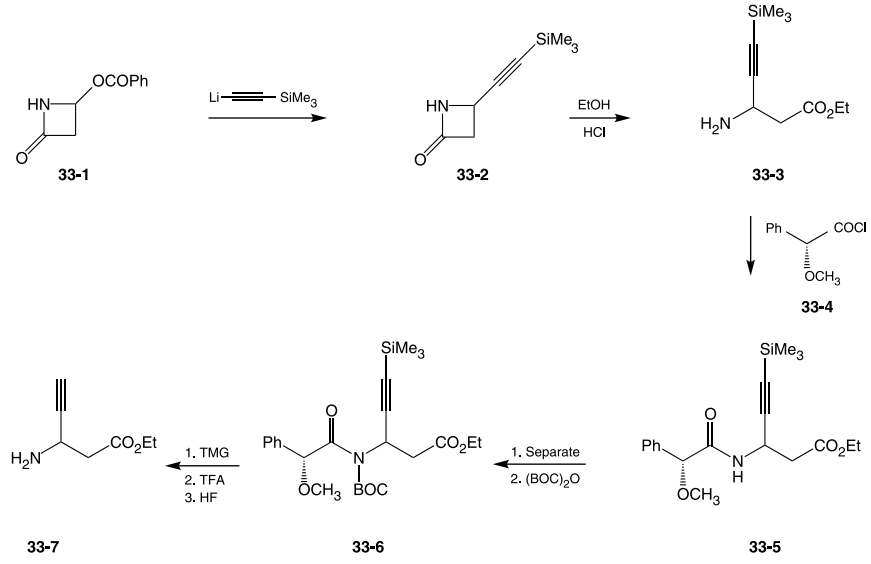


The naphthyl sulfonamide derivative (**32-1**) of glutamic acid comprises the starting material for the other part of **napsagatran**. The reaction of the sulfonamide with formaldehyde in the presence of acid probably starts by the formation of a carbinolmine by addition to amide nitrogen. This intermediate cyclizes to oxazolidine (**32-2**) under reaction conditions. This newly formed ring activates the ring carbonyl ring toward displacement by providing a good leaving group. Reaction of that compound with *N*-cyclopropyl glycine, itself obtained from displacement by bromine in ethyl

bromoacetate by cyclopropyl amine, leads to the amide (**32-3**). The carbinolamine that results from the ring opening reverts to the sulfonamide under reaction conditions. Condensation of the carboxylic acid in (**32-3**) with primary amine (**33-4**) followed by saponification of the terminal ester afford the fibrinogen antagonist **napsagatran** (**32-5**) [36].



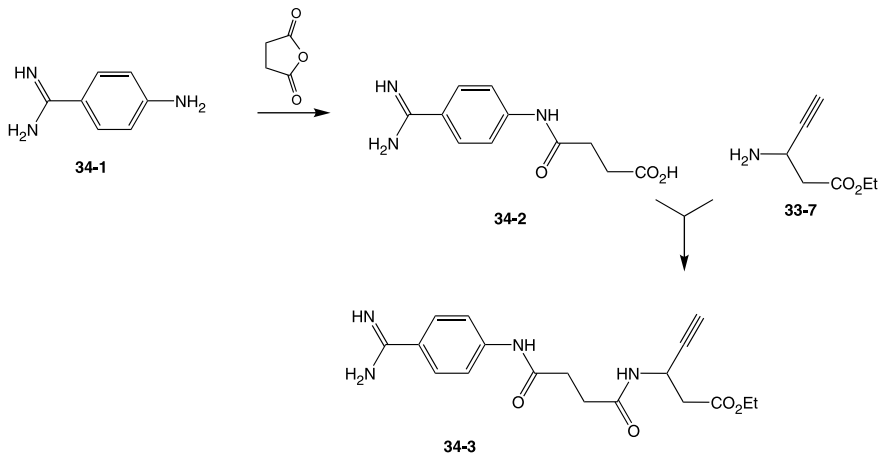
The observation that activity is retained when the guanidine is replaced by an amidine group points to the considerable degree of freedom that exists in this series for receptor recognition. This also applies for the rest of the chain since naturally occurring amino acids can be replaced by other groups. The resulting compounds should also be less likely to be metabolized by proteolytic enzymes



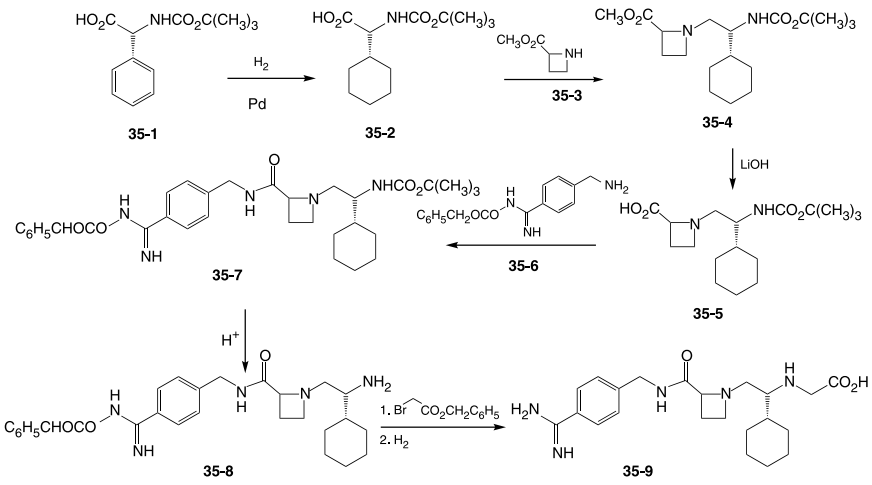
TMG = tetramethylgunidine

than the peptide based drugs. The synthesis of **xemilofiban** (**34-4**) starts with the preparation of an "unnatural" β amino acid. Displacement of the benzoate ester in azetidone (**33-1**) by the lithio anion from trimethylsilyl acetylene affords the C-alkyne derivative (**33-2**). The azetidone may exist as its enolate under reaction conditions, protecting the ring carbonyl group from attack by the acetylide. Fisher esterification in ethanol opens the ring to give the ethyl glycinate (**33-3**) as a mixture of enantiomers. This is then acylated with chiral *O*-methyl mandelic chloride. The resulting mixture of diastereomers is then separated by chromatography. The desired isomer (**33-5**) is next converted to its *tert*-butoxycarbonyl derivative by exposure to BOC anhydride. Tetramethylguanidine then serves to cleave the amide bond, releasing the chiral auxiliary mandelate. Succesive reaction with trifluoroacetic acid and hydrogen fluoride removes the remaining protective group to afford the β-amino ester (**33-7**) as a single enantiomer.

In a convergent sequence amidine (**34-1**) is allowed to react with succinic anhydride to afford the amide (**34-2**). The resulting acid is then condensed with the amino acid (**33-7**). The fibrinogen **xemilofiban** (**34-3**) is thus obtained [37].



The synthesis of yet another fibrinogen antagonist starts with the hydrogenation of phenylglycine BOC amide (**35-1**) to the corresponding cyclohexyl derivative (**35-2**). The free carboxyl group is then coupled with the azetidine (**35-3**) to afford the amide (**35-4**). Saponification with lithium hydroxide then gives the free acid (**35-5**). The carboxyl group in that product is then coupled with the benzylamine (**35-6**), in which the amidine group at the *para* position is protected as the benzyloxycarbonyl derivative to give intermediate (**35-7**). The protecting group on the terminal amino group is then removed by hydrolysis with acid (**35-8**). The primary amine in this last intermediate is then alkylated with benzyl bromoacetate. Hydrogenolysis removes the protecting groups on the terminal functions in this molecule to afford **melagartan** (**35-9**) [38].

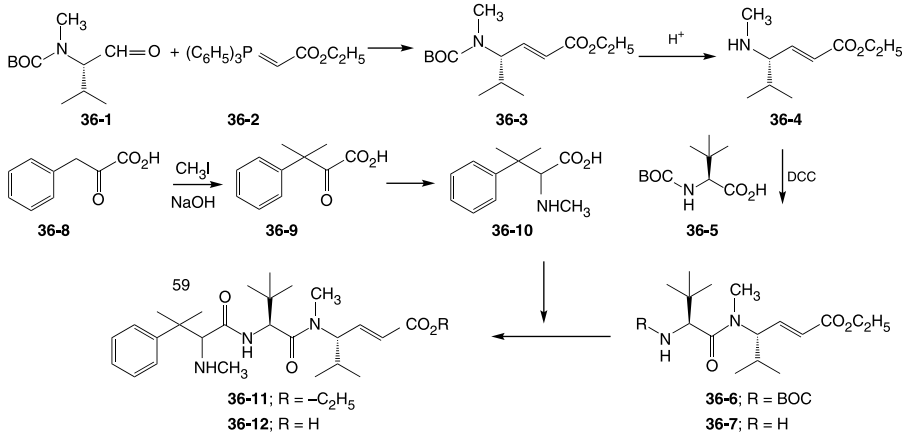


1.2.3. Antitumor Peptidomimetic

The microskeleton of cells consists of structures called microtubules that consist of polymers of the peptide tubulin. During cell division these filaments pull apart the nascent newly formed pair of nuclei. Compounds that interfere with tubulin function and thus block this process, such as, for example, the vinca alkaloid drugs vincristine and vinblastine, block the self-assembly of tubulin into those filaments. Paclitaxel, more familiarly known as Taxol®, on the other hand stabilizes tubulin and in effect freezes cells into mid-division. Screening of marine natural products uncovered the cytotoxic tripeptide-like compound hemiasterlin that owes its activity to the inhibition of tubulin formation. A synthetic program based on that led to the identification of **taltobulin** (**36-12**). The conjugated unsaturated ester in this molecule suggests that it may act as a nonreversible inhibitor by binding to its site by covalent bonds.

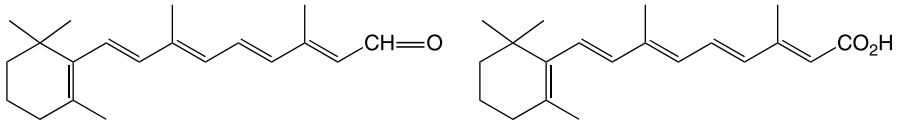
One arm of the convergent synthesis begins with the construction of that acrylate-containing moiety. Thus, condensation of the BOC protected α-aminoaldehyle (**36-1**) derived from valine with the cabethoxymethylene phosporane (**36-2**) gives the corresponding chain extended amino ester (**36-3**). Exposure to acid serves to remove the protecting group to reveal the primary amine (**36-4**). Condensation of that intermediate with the tertiary butyl-substituted aminoacid (**36-5**) leads to the protected amide (**36-6**); the BOC group in this is again removed with acid to unmask the primary amino group in (**36-7**). Construction of the other major fragment involves, first, the addition of a pair of methyl groups to the benzylic position of pyruvate (**36-8**). This transform is accomplished under surprisingly mild conditions by simply treating the keto-acid with methyl iodide in the presence of hydroxide. Treatment of the product (**36-9**) with methylamine and diborane results in reductive amination of the carbonyl group and thus the formation of α-aminoacid (**36-10**) as a mixture of the two isomers. Condensation of that with the dipeptide-like moiety (**36-7**) under standard peptide-forming conditions gives the amide (**36-11**) as a mixture of diastereomers. The

isomers are then separated by chromatography; saponification of the terminal ester function of the desired *SSS* isomer affords the antitumor agent **taltobulin** (**36-12**) [39] .



1.3. RETINOIDS

Vitamin A consists of a mixture of two polyene diterpenes, retinol and its biologically active oxidation product, retinal, shown as its *trans* isomer (**37-1**). Retinal forms a crucial link in vision; light-induced isomerization of the double bond adjacent to the carbonyl, conjugated with vision proteins as a Schiff base, from *cis* to *trans* plays a key role in the transduction of light to visual perception. The metabolite from oxidation of retinal, retinoic acid (**37-2**), has potent biological activity in its own right. The compound is a ligand for receptors involved in epithelial differentiation. All-*trans* retinoic acid, under the USAN **tretinoin**, has, as a result of that activity, found clinical use in the treatment of skin diseases such as acne. Considerable research has been prompted by data suggesting that the agent may have an effect on cancer progression.

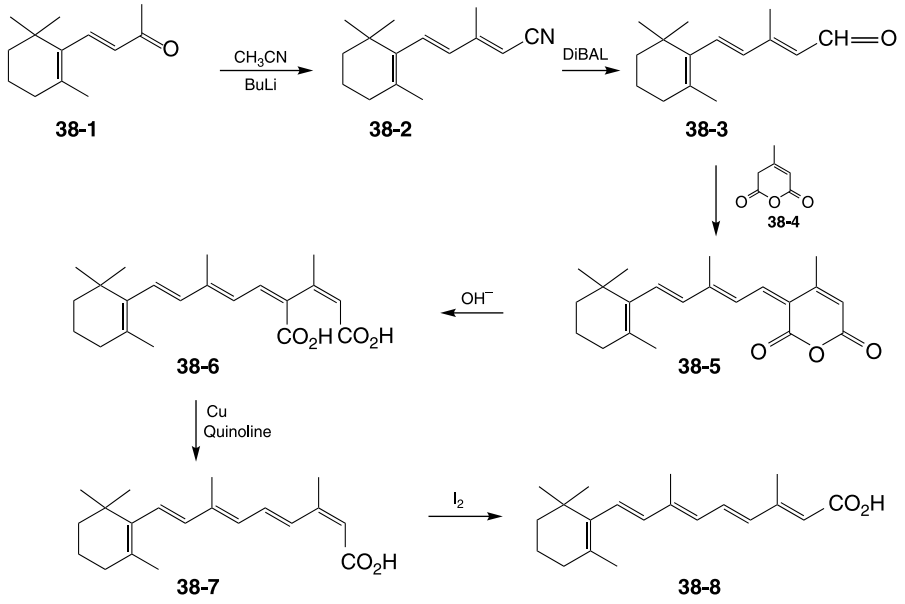


37-1
Retinal

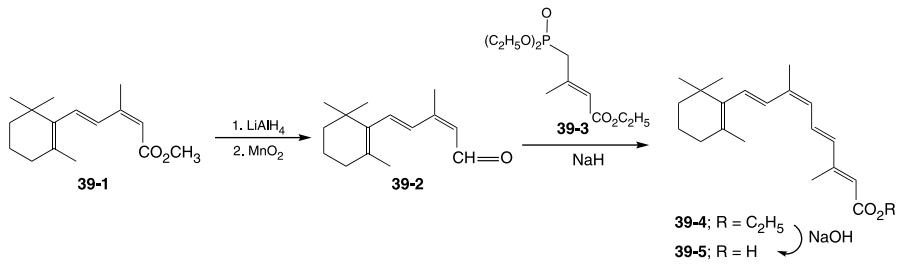
37-2
Retinoic Acid

The majority of published syntheses of **tretinoin** start with readily available β-ionone (**38-1**), a compound that already incorporates the highly substituted cyclohexene ring as well as four of the side chain atoms. Condensation with the carbanion from acetonitrile followed by dehydration of the initially formed carbinol gives the intermediate (**38-2**). Reduction of the cyano group by diisobutylaluminum hydride leads to the

corresponding imine; this hydrolyzes to aldehyde (**38-3**) during the acid workup [40]. Base-catalyzed aldol condensation of that aldehyde with β-methylglutaconic anhydride (**38-4**) involves condensation with the activated methylene group of the anhydride and leads to the product (**38-5**) in which the remainder of the side chain has been added. The anhydride is then hydrolyzed to the vinylogous β-dicarboxylic acid (**38-6**). The superfluous carboxyl group is removed by heating the compound in quinoline in the presence of copper to afford acid (**38-7**). The terminal double bond is then isomerized by any of several methods to give **tretinoin** (**38-8**) [41].

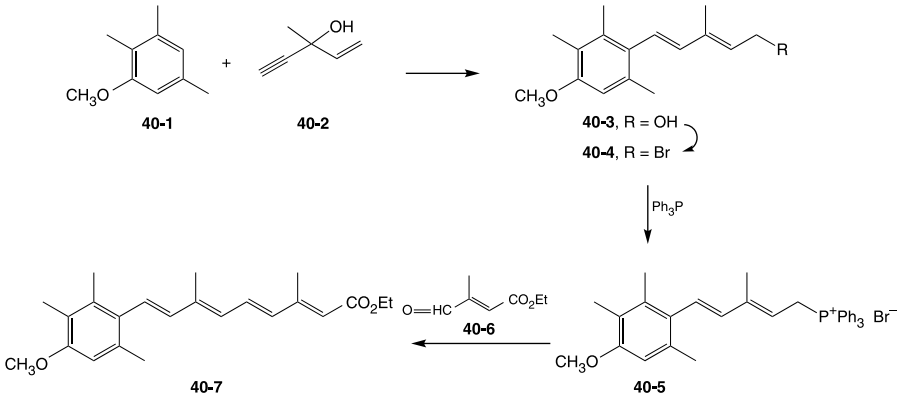


The closely related 9-*cis* isomer of retinoic acid binds to a different set of receptors involved in skin cell growth and has been found to control the proliferation of some cancer cells. The drug is thus indicated for topical use in controlling the spread of Kaposi sarcoma lesions. Reduction of the ester group in compound (**39-1**), which incorporates the requisite future 9-*cis* linkage, with lithium aluminum hydride leads to the corresponding alcohol. This is then oxidized to aldehyde (**38-2**) by means of manganese dioxide. Condensation of the carbonyl group with the ylide derived by treatment of the complex phosphonate (**38-3**) adds the rest of the

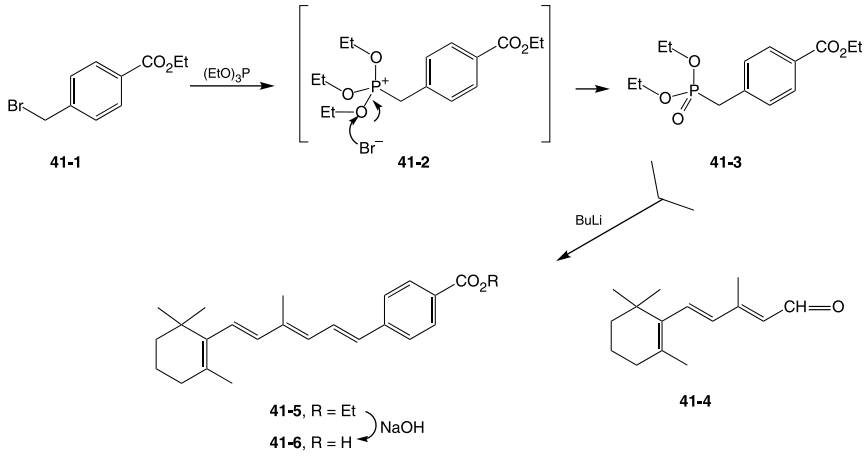


carbon skeleton (**39-4**). Saponification of the ester then gives the corresponding acid, **alitretinoin** (**39-5**) [42].

Replacement of the cylohexene ring by an aromatic moiety is interestingly still consistent with retinoid-type activity. Construction of this analogue starts by reaction of 2,3,5-trimethyl anisole (**40-1**) with acetylene (**40-2**), itself obtainable from acetylene and methylvinyl ketone, with a strong Lewis acid under Friedel–Crafts conditions. The ambident carbocation from (**40-2**), where the charge is smeared over the entire chain, reacts with the aromatic ring at the end of the acetylene moiety. The alkylated intermediate then adds back the hydroxyl at the terminal position to give the terpene-like intermediate (**40-3**); the resulting allylic alcohol is then converted to its bromide (**40-4**). Displacement of halogen by means of triphenylphosphine leads to phosphonium salt (**40-5**). Wittig condensation of the ylide from this last intermediate with the half-aldehyde derivative of α-methylfumaric ester (**40-6**) adds the remainder of the retinoid side chain. Saponification of the ester then affords **etretinate** (**40-7**) [43].



Activity is largely retained in a compound in which one of the terminal double bonds in the side chain of **tretinoin** is replaced by an aromatic ring. The key reaction in the construction of this compound consists in Wittig condensation of the ylide from

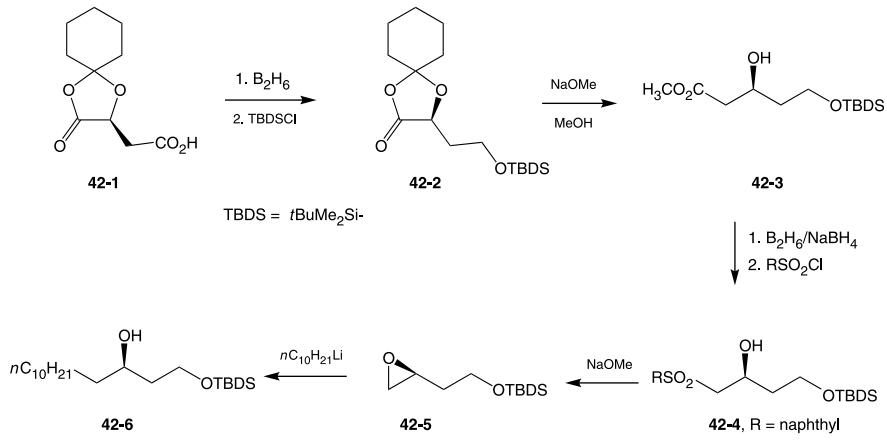


phosphonate (**41-3**) with the chain extended aldehyde (**38-3**) used in the synthesis of **tretinoin** itself. The Arbuzov rearrangement provides ready access to the phosphonate. Reaction of ethyl *para*-bromomethylbenzoate (**41-1**) with triethyl phosphite probably proceeds by initial displacement of halogen by phosphorus to give a transient intermediate charged species such as (**41-2**). Displacement of one of the ethyl groups on phosphorus by a bromide ion from the first displacement followed by bond reorganization leads to phosphonate (**41-3**) and ethyl bromide as a by-product. Reaction of the ylide from that product with aldehyde (**38-3**) affords the extended polyene (**40-5**). Saponification then yields **pelretin** (**41-6**) [44].

1.4. A MISCELLANEOUS DRUG

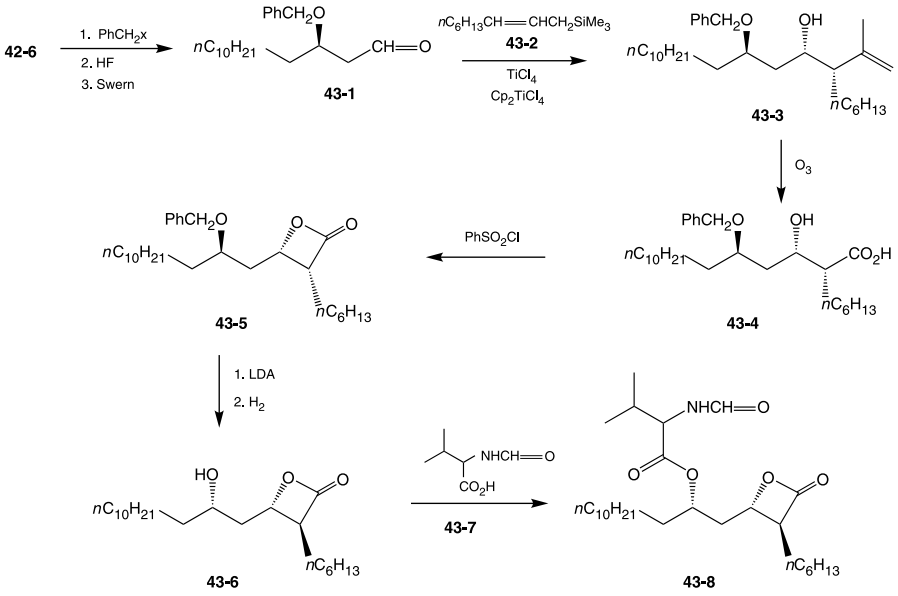
Fermentation broths have proven to be a very rich source for leads for antibiotics, a circumstance helped significantly by bioassays against bacteria that are sensitive to very low levels of active agents in the broths. The development of high turnover in *in vitro* screens against other endpoints provided leads for compounds in other therapeutic targets. The original lead for the enormously popular statins came from just this sort of program. Another program turned up a compound that inhibited pancrealipase, the enzyme responsible for the hydrolysis of dietary triglycerides to circulating fatty acids. The drug that came out of this program, **orlistat** (**43-8**), known in the press as a "fat blocker," offers dieters the ability to control caloric intake without foregoing fatty delicacies.

The structure of this agent in essence comprises a propiolactone that bears two long fatty acid-like side chains. Construction of one of the side chains in this somewhat lengthy synthesis begins with the cyclohexanone acetal of L-mallic acid (**42-1**). The carboxylic acid is first reduced to the carbinol by means of diborane, and that is then protected as its *tert*-butyldimethylsilyl ether (**42-2**). The acetal ring is then opened by means of sodium methoxide in methanol (**42-3**). The resulting ester is then reduced, and the resulting hydroxyl is converted to a leaving group by reaction



with naphthylsulfonyl chloride (**42-4**). Treatment with a strong base leads to internal displacement and thus the formation of the oxirane (**42-5**). The ring is then opened with the lithium reagent from the exchange of *n*-bromodecane with butyllithium to afford the long chain product (**42-6**) [42].

Addition of the second part of the molecule starts by first protecting the free hydroxyl group as its benzyl ether by exchange with *O*-benzyliminitrifloroacetamide. The silyl protecting group on the other hydroxyl is then removed by means of hydrogen fluoride. Swern oxidation then converts that to an aldehyde group (**43-1**). the titanium tetrachloride catalyzed addition of a carbocation to the aldehyde group serves to add the second fatty side chain. Thus the addition of the ambident carbocation from the allylic silyl reagent (**43-2**) in the presence of *bis*-cyclopentyldienyltitanium dichloride gives the condensation product (**43-3**). Asymmetric induction by the adjacent chiral ether leads to the stereoselective formation of the new chiral center. Ozonization of the terminal olefin followed by an oxidative workup leads to the loss of the two terminal carbon atoms and the formation of the carboxylic acid (**43-4**). Treatment of the hydroxyl acid with benzenesulfonyl chloride in pyridine leads those functional groups to cyclize to the propiolactone (**43-5**), likely though the intermediacy of the sulfonate. The configuration of the hexyl side chain is next inverted to match that of the natural product via its enolate by treatment with a strong base. Hydrogenolysis of the benzyl ether affords the intermediate (**43-6**). The last fragment, formyl leucine (**43-7**), is added by means of a version of the Mitsonobu reaction. Thus the reaction of (**43-6**) with the acid in the presence of diethyldiazo dicarboxylate (DEAD) and triphenyl phosphine leads to the ester (**43-8**) and thus **orlistat** [45]. The inversion of configuration at oxygen indicates that this last reaction involves SN_2-like displacement rather than esterification.



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