Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs

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Received January 9, 1993 (Revised Manuscript Received March 27, 1993)

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I. Introduction

Prostaglandins (PGs) and prostacyclin (PGI_2) are naturally occurring substances found in animals and man and are biosynthesized from C_{20} polyunsaturated fatty acids via a cyclooxygenase enzyme system widely distributed in mammalian tissues (Figure 1). A specific synthase with more limited tissue distribution is required for the conversion of the endoperoxide intermediate (PGH_2) to PGI_2. PGs and PGI_2 play important regulatory roles in many normal cellular functions. In contrast to hormones, PGs and PGIs do not circulate nor are they stored in tissues. Rather, they are synthesized locally on demand, perform a tissue-specific function, and then are rapidly inactivated by metabolic enzymes. Given extrinsically, they can exert a host of pharmacological effects and have been the subject of extensive research and chemical modification by pharmaceutical companies in the quest for drug candidates.

PGs, of which there are several types (Figure 2), were discovered in the 1930s by von Euler[1] but not until 1957 were they isolated and their structures determined.[2,3] By the mid-1960s, there was widespread belief that PGs would be useful therapeutic agents in a large number of diseases and efforts to synthesize the natural compounds and structurally modified analogs became intense in both academic and industrial laboratories. The road to therapeutic utility, however, was impeded by three major problems with natural PGs: (1) chemical instability, (2) rapid metabolism, and (3) incidence of numerous side effects.[4] The chemical instability of PGs resides largely in the E types which readily undergo acid- or base-catalyzed elimination of the 11-hydroxy substituent to give the biologically less active or inactive PGA form. PGs are attacked metabolically by enzymes prevalent in most cells. The major foci of metabolism of PGs, in order to rapidity, are oxidation of the 15-hydroxy group to a ketone, β-oxidation of the α-chain (upper side chain) to generate acetic acid and the dinor-PG acid, and ω-oxidation at C-20 to produce the 20-hydroxy and carboxylic acid analogs. The products of these metabolic pathways are all biologically inert. The side effects observed with PGs are due to their multiple pharmacological and physiological activities all of which may be manifested when the body is exposed to them systemically. In general, modification strategies employed by medicinal chemists have been directed at

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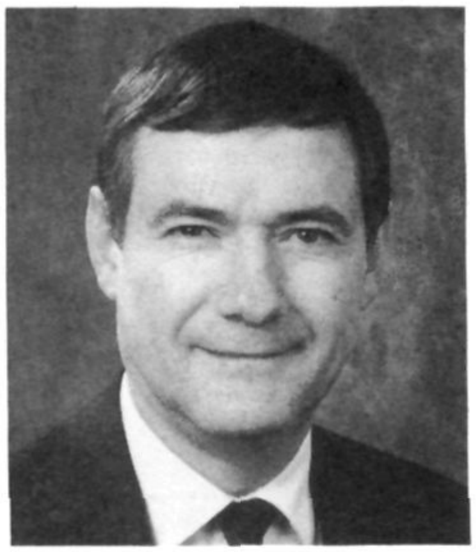
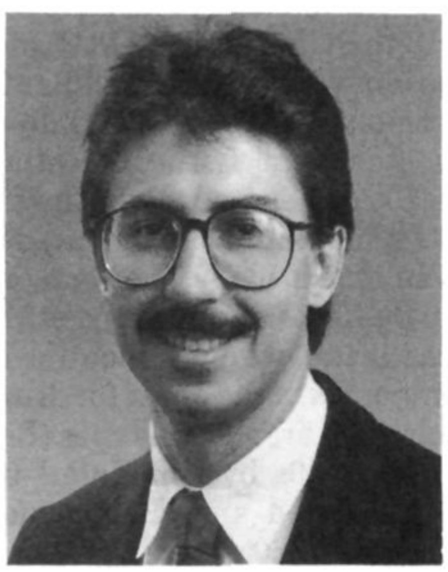


Paul W. Collins received a B.S. in Pharmacy from the University of South Carolina in 1962 and a Ph.D. in Medicinal Chemistry from the Medical College of Virginia in 1966. After postdoctoral study with Professor Alfred Burger at the University of Virginia, he joined G.D. Searle in 1967 where he is presently Senior Research Fellow in the Department of Chemistry. Dr. Collins's career at Searle has been largely devoted to the modification of naturally occurring prostanoids for antiulcer and other therapeutic applications. He is the co-inventor of misoprostol, enisoprost, and remiprostol. Dr. Collins has published and lectured extensively on prostaglandins, holds 30 U.S. Patents, and is a former member of the editorial advisory board of the *Journal of Medicinal Chemistry*. He was a co-recipient of the 1990 Monsanto Edgar M. Queeny Award given for the discovery of misoprostol.



Stevan W. Djuric was born in Leicester, U.K., in 1954. He obtained a B.Sc. degree (1st class honors) in Chemistry from the University of Leeds in 1976 and completed his doctoral studies at the same institution in 1979. After a postdoctoral fellowship at The Ohio State University in the laboratories of Professor Philip D. Magnus, he joined Searle in 1981 where he is presently Research Fellow in the Department of Chemistry. His research interests are in the design and development of novel therapeutic agents for the treatment of inflammatory diseases and, in particular, agents that inhibit or antagonize the actions of lipoxygenase derived products of arachidonic acid such as leukotriene B_4.

one or more of these problems. Success in finding acceptable drug candidates has been difficult and has also been compounded by poor clinical efficacy in many therapeutic areas.

Prostacyclin was discovered in the mid-1970s and, like the PGs, was originally thought to be a revolutionary find for therapeutics, especially in the cardiovascular arena. But, due to similar problems of instability (the $t_{1/2}$ for PGI_2 at pH 7.4 and 37 °C is 3 min), metabolism and lack of selectivity, PGI_2 and its analogs have also experienced a difficult path to therapeutic success.

This review[5] will focus on the synthesis of therapeutically useful analogs of PGs and PGI_2. Where appropriate, recent synthetic improvements as well as the initially reported synthesis will be described. Due to the large number of such compounds, discussion for the most part will be limited to those which have reached some stage of clinical evaluation. The prostaglandin analogs are listed in Table 1 along with their primary therapeutic indication and, where possible, their clinical or market status. Similar information for prostacyclin analogs is given in Table 2.

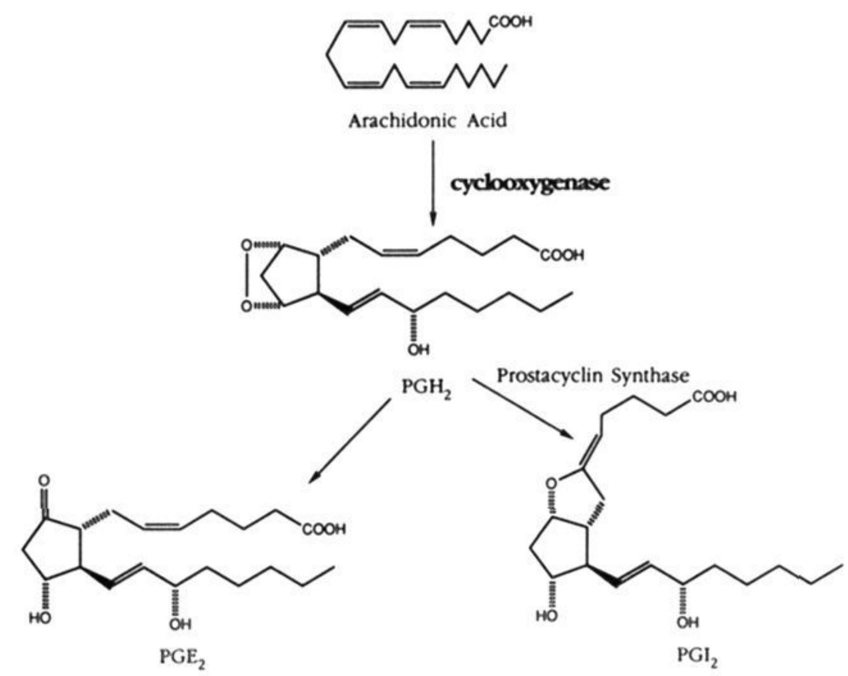


Figure 1. Biosynthesis of prostaglandins and prostacyclin.

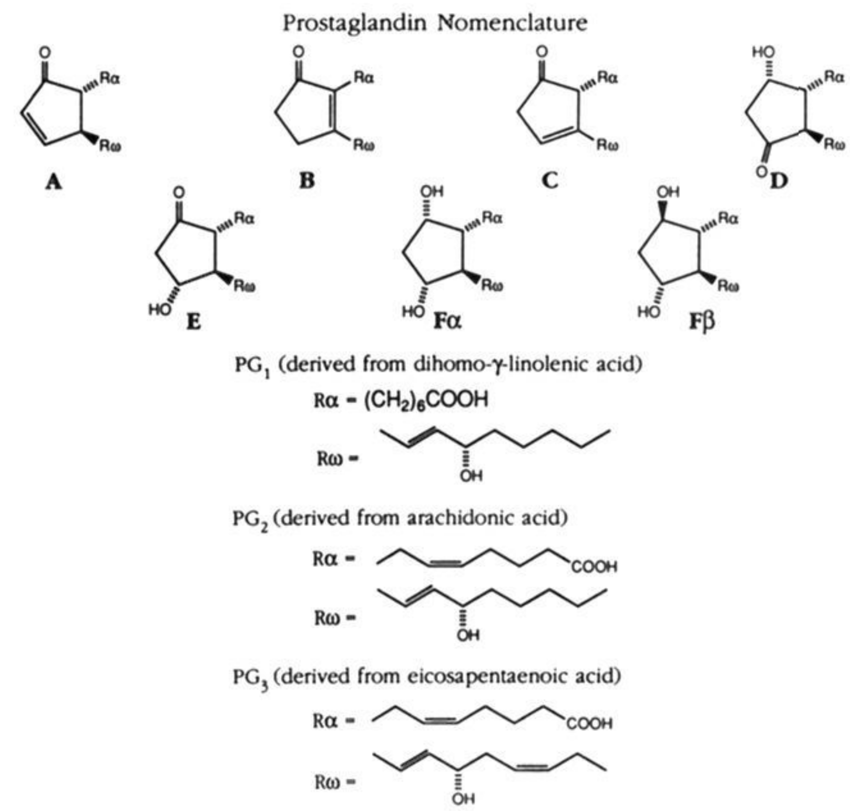


Figure 2. Prostaglandin nomenclature.

II. Prostaglandin Analogs

A. Background

Although PGs have been examined for a variety of clinical indications, the predominant use of E type PGs has been for peptic ulcer and cardiovascular diseases and F type PGs for gynecological or fertility control applications. To date, the only widely marketed PGE analog is misoprostol (for prevention of gastroduodenal ulcers caused by nonsteroidal antiinflammatory drugs); but several others are approved in some countries and others are in late phase clinical study (Table 1). PGF compounds have found limited utility in human reproductive indications and are more extensively used for farm animal estrus synchronization.

The synthesis of prostaglandins has occurred over a period of about 25 years beginning in the 1960s with the natural compounds and extending into this decade. The evolution of synthetic methodology will be apparent as the newer analogs and improved routes to older compounds are described.

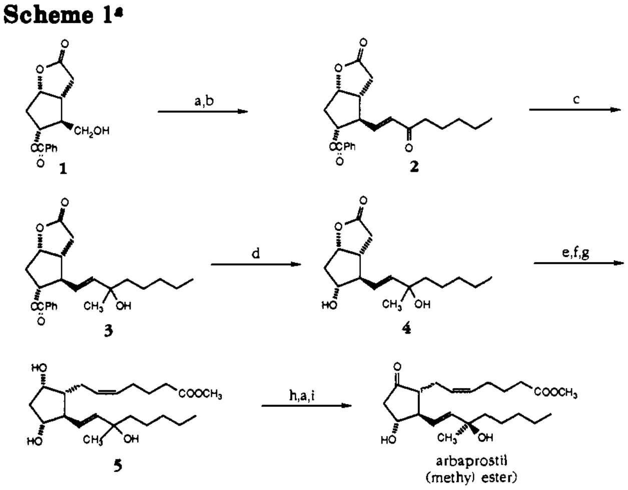
B. Synthesis

1. Arbaprostil

In the late 1960s and early 1970s, researchers at Upjohn reported[6,7] two clever approaches to the problem of rapid metabolism of the 15-hydroxy group of natural PGs. By placing a methyl group at C-15 or two methyl groups at C-16 of PGE_2, oxidative metabolism of the hydroxy group was prevented, and the resulting compounds, 15-methyl-PGE_2 and 16,16-dimethyl-PGE_2, were orally active and pharmacologically more potent and longer lasting than PGE_2 itself. Unfortunately, the side effects of these two compounds have severely restricted their clinical utility. 16,16-Dimethyl-PGE_2 has become widely used as a pharmacological tool and standard while 15-methyl-PGE_2 has been pursued as a clinical candidate for ulcer disease in its (15*R*)-epimer form. Arbaprostil, (15*R*)-15-methyl-PGE_2, is the unnaturally configured and biologically inert diastereomer. It is active by oral administration, however, because the tertiary allylic alcohol at C-15 readily epimerizes under the acidic conditions of the stomach to a mixture of isomers. This strategy was utilized because the side effects observed with arbaprostil were less than those experienced with the (15*S*)-isomer.

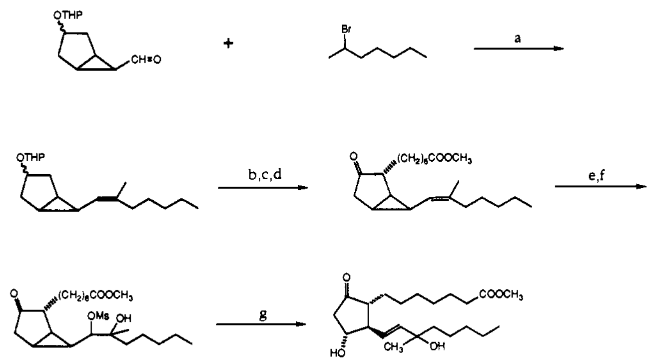
The total synthesis of 15-methyl-PGE_2 was reported in 1974.[8] This original synthesis (Scheme 1) was analogous to the popular Corey route.[9] Oxidation of the benzoate 1 (rather than the *p*-phenyl benzoate commonly known as Corey's lactone) with Collins reagent (CrO_3–pyridine) gave the unstable aldehyde which was reacted in unpurified form with dimethyl (2-oxoheptyl)phosphonate to give **2**. The tertiary methyl group was introduced by treatment with either methyl magnesium bromide at −78 °C or trimethylaluminum in benzene at room temperature. Attack

Scheme 1[a]



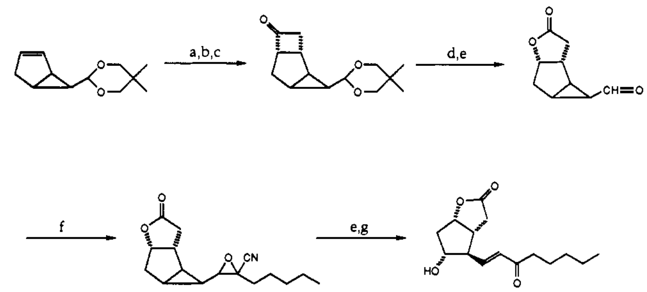
[a] (a) CrO_3/pyridine. (b) $(MeO)_2P{=}CHC(O)C_5H_{11}$. (c) MeMgBr. (d) CH_3ONa. (e) DIBAL. (f) $Ph_3P{=}CH(CH_2)_3COOH$. (g) CH_2N_2. (h) $Me_3SiN(Et)_2$. (i) H_3^+O.

Scheme 2[a]



[a] (a) Ylide reaction. (b) H_3^+O. (c) [O]. (d) $I(CH_2)_6COOCH_3$/base. (e) OsO_4. (f) MsCl/pyridine. (g) H_2O/acetone solvolysis.

Scheme 3[a]



[a] (a) $Cl_2C{=}C{=}O$. (b) Zn, NH_4Cl. (c) Resolution with (−)-ephedrine. (d) m-$ClC_6H_4CO_3H$. (e) HCOOH. (f) $C_5H_{11}C(Br_2)CN$, $P[N(Me)_2]_3$. (g) H_2SO_4.

at the lactone or benzoate was avoided by control of reaction conditions. The resulting mixture of epimeric alcohols **3** was treated with sodium methoxide in methanol to cleave the benzoate ester and provide the diol 4 again as an inseparable mixture of C-15 epimers. Reduction of the lactone with diisobutylaluminum hydride (DIBAL) at −78 °C and treatment of the resulting lactol with the ylide of (4-carboxybutyl)-triphenylphosphonium bromide followed by esterification with diazomethane gave the PGF analogs **5** as a separable mixture of 15-epimers. The assignment of configuration at C-15 was originally based on biological activities but was confirmed by X-ray crystallography of the *p*-bromophenacyl ester of (15*S*)-**5**. Selective monosilylation of (15*R*)-**5** at C-11 followed by oxidation with Collin's reagent and subsequent removal of the silyl protecting group gave the methyl ester of arbaprostil. Interestingly, the conditions used to remove the trimethylsilyl group (methanol, water, trace of acetic acid, room temperature) did not cause epimerization at C-15 while conditions traditionally used to remove tetrahydropyranyl (THP) groups (acetic acid, water, THF, 40 °C) caused complete epimerization within 3 h. Arbaprostil has also been synthesized by the early Upjohn bicyclohexane mesylate approach[6] (Scheme 2) and by a commercial-scale process[10] (Scheme 3) developed at Upjohn which uses a modification of the bicyclohexane chemistry to produce the intermediate to compound 2 in Scheme 1.

The synthesis of Corey's lactone was one of the first reported routes to classical PGs. The original process was modified and improved by Corey and others[9] and is the basis for the large-scale preparation of several PGs. Further improvements in this process have recently been reported.[11] Corey[11a] described a catalytic

Table 1

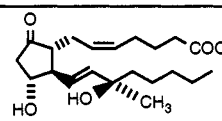
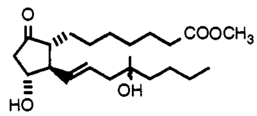
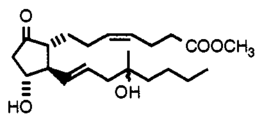
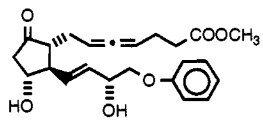
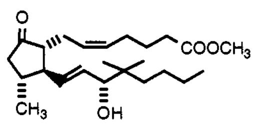
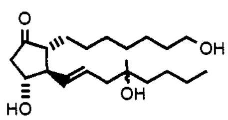
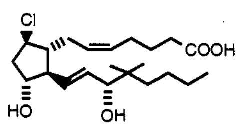
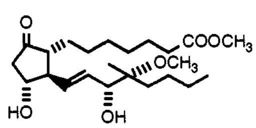
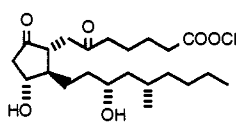
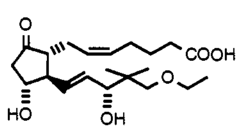
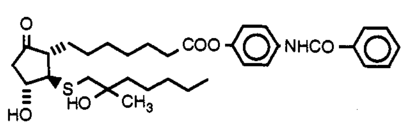
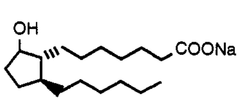
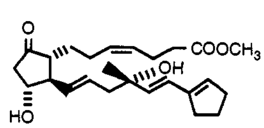
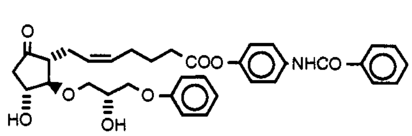
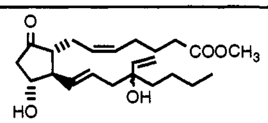
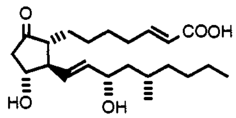
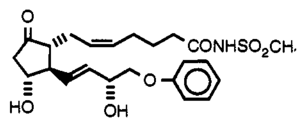
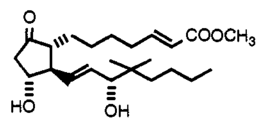
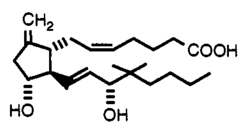
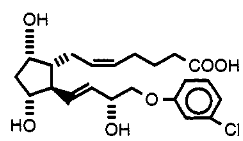
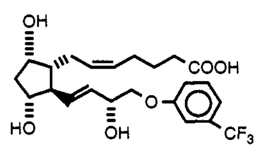
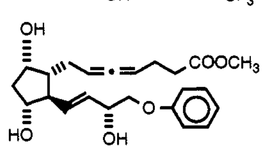
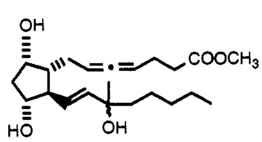
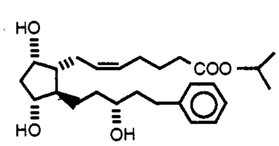
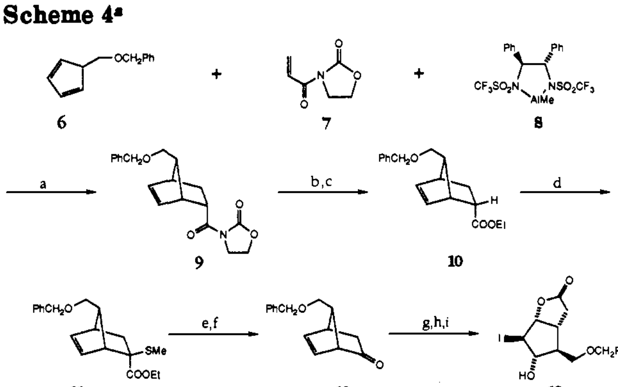
compound	structure	company	code no.	therapeutic indication	clinical/ market status
arbaprostil		Upjohn		antiulcer	phase III: Arbacet
misoprostol		Searle	SC-29333	antiulcer	marketed: Cytotec
enisoprost		Searle	SC-34301	antiulcer	dropped
enprostil		Syntex	RS-84,135	antiulcer	marketed: Gardrin
trimoprostil		Roche	RO-21,6937	antiulcer	phase III/ dropped
rioprostol		Miles/Ortho and Bayer AG	TR-4698	antiulcer	marketed
nocloprost		Schering AG	ZK-94726	antiulcer	phase III
mexiprostil		Lepetit	MDL-646	antiulcer	phase II
ornoprostol		ONO	ONO-1308	antiulcer	marketed: Ronak
dimoxaprost		Hoechst-Roussel	HR-260	antiulcer	phase II/III
tiprostanide		Merck AG	EMD-33290	antiulcer antihypertensive	phase II
rosaprostol		IBI		antiulcer	marketed: Rosal
remiprostol		Searle	SC-46275/SC-48334	antiulcer	dropped
		Glaxo	GR-63779X	antiulcer	phase I/II

Table 1 (Continued)

compound	structure	company	code no.	therapeutic indication	clinical/ market status
viprostol		Lederle	CL-115,347	antihypertensive	phase II/ dropped
limaprost		ONO	ONO-1206	antihypertensive	marketed: Opalmon
sulprostone		Pfizer Schering AG	CP-34089	fertility control	marketed: Nalador
gemeprost		ONO	ONO-802	fertility control	marketed: Cervagem
meteneprost		Upjohn		fertility control	phase III/ dropped
cloprostenol		ICI	ICI 80,996	veterinary use	marketed
fluprostenol		ICI	ICI 80,008	veterinary use	marketed
fenprostalene		Syntex	RS-84043	veterinary use	marketed
prostalene		Syntex	RS-9390	veterinary use	marketed: Synchrocept
latanoprost		Kabi Phanmacia	PhXA41	antiglaucoma	phase II

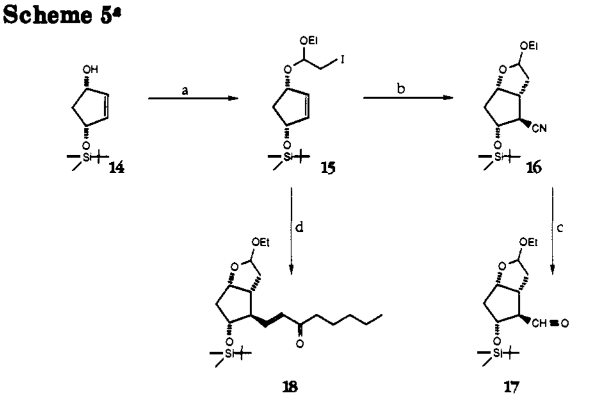
enantioselective Diels–Alder reaction between 6 and 7 in the presence of 10 mol % of the (*S*,*S*) catalyst 8 which gave the adduct 9 in greater than 95% ee (Scheme 4). The adduct 9 was then converted to enantiopure iodolactone 13 by a sequence of high yield steps. Treatment of 9 with aqueous lithium hydroxide–hydrogen peroxide followed by esterification with ethanol gave 10 which was transformed to the methyl thio derivative 11 by deprotonation with LDA (lithium diisopropylamide) and quenching with dimethyl disulfide. Base cleavage of the ester and oxidative decarboxylation provided 12. Baeyer–Villiger oxidation of 12, hydrolysis of the resulting lactone, and iodolactonization produced, after recrystallization, the iodolactone 13 in 100% ee. Deiodination with tributyltin hydride and protecting group manipulation provided the traditional Corey lactone alcohol.[9] Stork[11b] applied a radical cyclization trapping methodology to the preparation in a single step of the lactol intermediates 17 and 18 (Scheme 5). The mixed iodoacetal 15 was obtained by treatment of 14 with ethyl vinyl ether and *N*-iodosuccinimide. Reaction of 15 with tributyltin chloride, sodium cyanoborohydride, a catalytic amount of AIBN and *tert*-butyl isocyanide as the radical trap produced the lactol 16. The nitrile could be readily converted to the aldehyde 17 by reduction with DIBAL. Alternatively, use of 2-(trimethylsilyl)-1-octen-3-one as the radical trap provided the vinyl ketone 18 directly.

Scheme 4[a]



[a] (a) CH_2Cl_2, −78 °C, 18 h. (b) $LiOH/H_2O_2$. (c) $EtOH/HC(OEt)_3$, H^+. (d) LDA/MeSSMe. (e) KO-*t*-Bu/DMSO. (f) [O]. (g) Baeyer–Villiger. (h) OH^-. (i) I_2.

Scheme 5[a]

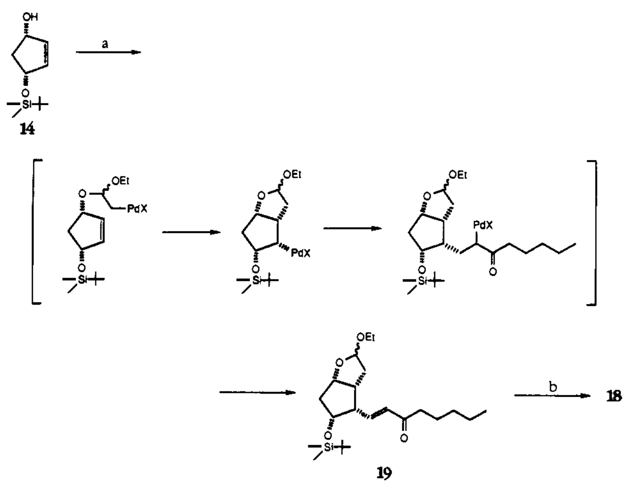


[a] (a) Ethyl vinyl ether, NIS, −20 °C. (b) Bu_3SnCl, $NaCNBH_3$, *t*-BuNC, AIBN. (c) DIBAL. (d) Bu_3SnCl, $NaCNBH_3$, $h\nu$ (254 nm), 2-(trimethylsilyl)-1-octen-3-one.

Keck[12] has also reported a variation of this latter reaction using a vinyl stannyl enone (Scheme 5) radical trap.

Larock[11c] employed an ingenious one-step palladium-promoted intermolecular coupling of three different alkenes to produce the 12-epi lactol intermediate **19** (Scheme 6). The alcohol **14** was treated with ethyl vinyl ether and 1-octen-3-one in the presence of palladium acetate, sodium acetate, and a catalytic amount of sodium iodide at room temperature for 3 h (no solvent) to generate **19** directly in 72% yield as a 2–3:1 mixture of exo and endo lactol isomers. Inversion of C-12 of **19** was cleanly achieved by heating with a mixture of acetic acid and morpholine (3:1) in dimethoxyethane–water at 70–75 °C for 72 h to give **18**.[13] (*S*)-BINAL-H was used to stereoselectively reduce the ω-chain (lower side chain) ketone of **18** to the (*S*)-alcohol.

Scheme 6[a]



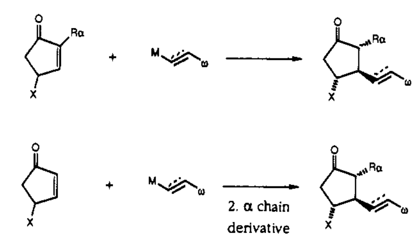
[a] (a) $EtOCH{=}CH_2$, $H_2C{=}CHCOC_5H_{11}$, $Pd(OAc)_2$, NaOAc, NaI. (b) AcOH, morpholine, 70–75 °C.

2. Misoprostol

Misoprostol is a 15-deoxy-16-methyl-16-hydroxy analog of PGE_1. It is currently marketed worldwide as Cytotec for the prevention of gastroduodenal ulcers induced by nonsteroidal antiinflammatory drugs (NSAIDs) and was the first PG analog approved for antiulcer therapy. Misoprostol's discovery was prompted by the observation that translocation of the pivotal 15-hydroxy group of PGE_1 to C-16 did not affect gastric antisecretory activity but did significantly reduce side effects.[14] Addition of a methyl group to C-16 to block oxidative metabolism produced misoprostol.

Misoprostol is synthesized via a conjugate addition route.[14,15] This approach, which has been widely researched, involves the conjugate addition of organometallic derivatives of the ω-chain to cyclopentenones which generally already contain the appropriate α-chain. An alternative three-component coupling procedure, in which the α-chain is incorporated by reaction with the enolate arising from the initial conjugate addition reaction, has been elegantly researched and refined by Noyori *et al.*[16] These general approaches are illustrated in Scheme 7. The advantages of this strategy is the versatility in preparing analogs and the stereoselectivity obtained in the addition reaction. Other variations of this route have been reported.[17-21]

Scheme 7

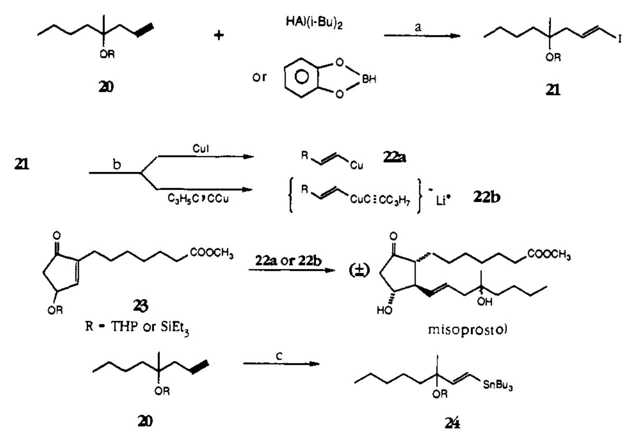


X = H or OR; R = protecting group

With misoprostol, which was first prepared in the early 1970s, the initial organometallic reagent was resourced from a vinyl iodide obtained by derivatization of the protected racemic homopropargylic alcohol **20** with either DIBAL or catechol borane followed by treatment with iodine (Scheme 8). The vinyl iodide **21** was then converted to a vinyl copper species **22a** or a cuprate reagent **22b** by treatment with *n*-butyllithium (*n*-BuLi) followed by cuprous iodide or copper pentyne, respectively.[22a] Conjugate addition of either of these reagents to the protected racemic hydroxycyclopentenone **23** provided misoprostol in good yield after protecting group removal.

A superior cuprate precursor is the vinylstannane **24**. A simple 2–4-h sunlamp irradiation of a mixture of **20** and tributyltin hydride in ordinary pyrex glassware gave the (*E*)-vinylstannane **24** plus about 15% of the corresponding (*Z*)-isomer. Conversion of **24** to a vinyllithium species with *n*-BuLi at −60 °C and addition

Scheme 8[a]



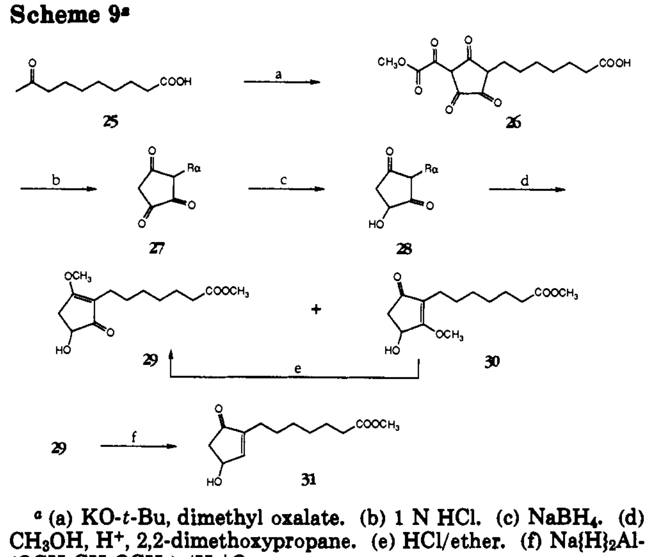
[a] (a) I_2. (b) *n*-BuLi. (c) $HSnBu_3/h\nu$.

of copper pentyne provided the requisite cuprate reagent. The presence of the (*Z*)-vinylstannane is a minor inconvenience on a laboratory scale because the (13*Z*)-misoprostol generated can be easily separated by chromatography. Furthermore, the conversion of the (*Z*)-vinylstannane to the vinyllithium species can be limited by reducing the amount of *n*-BuLi because the (*Z*)-isomer reacts appreciably less rapidly with *n*-BuLi than does the desired (*E*)-isomer.

On a manufacturing scale, however, the isomeric mixture of vinylstannanes is detrimental to production efficiency. A concerted effort to circumvent this problem as well as improve the overall process has been carried out at Searle. This work, as well as the early research on the vinylstannane technology and the conjugate addition process, was recently reviewed.[22b]

The racemic hydroxycyclopentenone precursor (**31**) to misoprostol was prepared by a laborious multistep procedure[15] beginning with keto acid **25** (Scheme 9). Condensation of **25** with dimethyl oxalate in the presence of excess potassium *tert*-butoxide in refluxing *tert*-butyl alcohol gave the glyoxalate derivative **26**. The glyoxalate appendage was removed by refluxing **26** in 1 N HCl to afford the triketone **27**. Reduction of **27** with sodium borohydride in ethanol and water at 0 °C cleanly yielded the hydroxydione **28**. Esterification of **28** to a mixture of isomeric enol ethers **29** and **30** was

Scheme 9[a]



[a] (a) KO-*t*-Bu, dimethyl oxalate. (b) 1 N HCl. (c) $NaBH_4$. (d) CH_3OH, H^+, 2,2-dimethoxypropane. (e) HCl/ether. (f) $Na\{H\}_2Al(OCH_2CH_2OCH_3)_2/H_3^+O$.

carried out in methanol containing HCl and the water scavenger 2,2-dimethoxypropane. The desired isomer **29** is crystalline while **30** is not. A reasonable yield of **29** was obtained by inducing its crystallization from acidic ether, thereby driving the solution equilibrium toward **29**. This step has been greatly improved by use of hindered alcohols[23] or acids such as triisopropylbenzenesulfonic acid[24] to form selectively the enol ether or ester corresponding to **29**. Reduction of **29** with sodium dihydrobis(2-methoxyethoxy)aluminate in toluene at −60 °C, followed by an acidic workup gave the desired enone **31**. Although a THP protecting group was originally used in the synthesis of misoprostol, the preferred and currently used one is triethylsilyl because of its ease of attachment and removal.

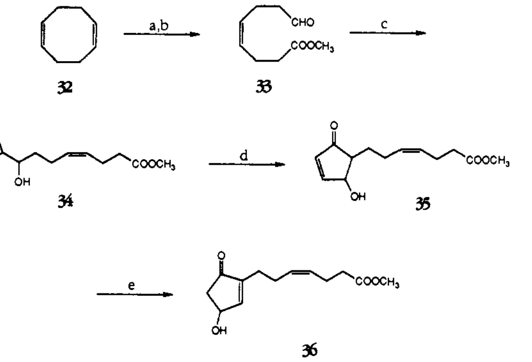
As indicated in Scheme 8, misoprostol is a mixture of two racemates or four stereoisomers and is marketed as such. The mixture is created by the use of racemic enone and ω-chain; however, the stereospecificity of the cuprate reaction avoids the formation of other ring isomers. Although the naturally configured (11*R*,16*S*) isomer is the only bioactive component of misoprostol, the practical limitations of efficiently producing a single isomer during the time of misoprostol's development necessitated selection of the mixture as the drug candidate. Preparation and absolute configurational assignments of the isomers of misoprostol have been described.[25]

3. Enisoprost

Enisoprost is the Δ^4-*Z*-analog of misoprostol and was originally targeted as a second generation back up candidate for misoprostol in the antiulcer market. The rationale for its preparation was that insertion of a cis double bond at the unnatural (PGE_2 contains a cis double bond at C_{5-6}) C-4,5 position would impede metabolic degradation of the α-chain and thus provide a long-acting compound;[26] and indeed, in animals, enisoprost is more potent and longer acting as a gastric antisecretory agent than misoprostol. However, in clinical studies enisoprost failed to show any appreciable advantage over misoprostol and was dropped for this indication. More recently, enisoprost has been studied clinically as an immunosuppressive agent in organ transplantation.

Enisoprost, a mixture of four stereoisomers just as misoprostol, was prepared via similar chemistry.[26] An improved synthesis for this compound has been developed at Searle.[27] The improvements consist of a much more direct route to the enone as well as modifications in the cuprate reaction. Preparation of the racemic enone is shown in Scheme 10. (*Z*,*Z*)-1,5-Cyclooctadiene (**32**) in a methanol/methylene chloride slurry containing sodium bicarbonate was ozonolyzed to about 65–70% of completion and quenched with triethylamine and acetic anhydride to give the aldehyde ester **33** in 40–50% yield along with about 2–5% of the corresponding dialdehyde. Reaction of crude **33** with 2-furanylmagnesium chloride provided the furanylcarbinol **34** which was refluxed in aqueous dioxane with zinc chloride for 18–24 h to produce **35**. Treatment of **35** with a catalytic amount of anhydrous chloral in the presence of triethylamine gave the desired enone **36** which was protected as a triethylsilyl ether.

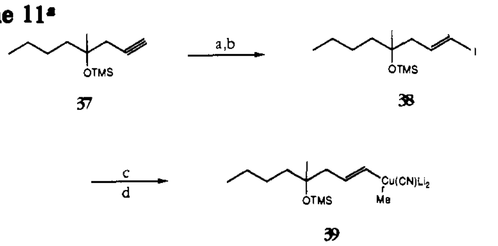
Scheme 10[a]



[a] (a) Ozone, $NaHCO_3$. (b) Ac_2O, Et_3N. (c) Furanyl MgCl. (d) $ZnCl_2$. (e) Chloral, Et_3N.

To avoid the isomeric mixtures encountered with tin hydride functionalization of the ω-chain, zirconocene chloride hydride followed by iodine was used to generate exclusively the (*E*)-vinyl iodide **38** from **37** (Scheme 11). Treatment of **38** with *n*-BuLi generated the vinyllithium species which was then converted to a dilithio cyanocuprate reagent **39** by addition of lithium methylcyanocuprate (prepared freshly from MeLi and copper cyanide).

Scheme 11[a]



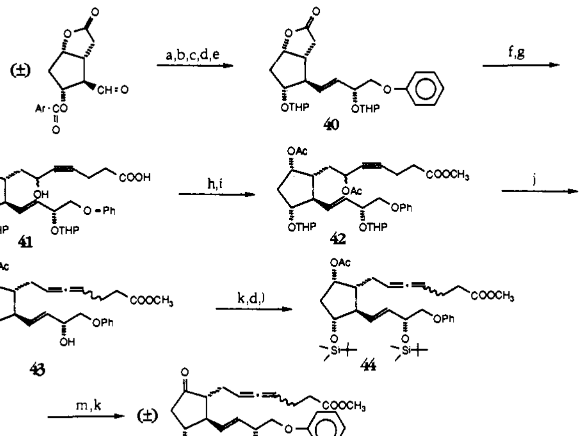
[a] (a) $Cp_2Zr(H)Cl$. (b) I_2. (c) *n*-BuLi. (d) LiMeCuCN.

A further improvement in the cuprate-based methodology for producing misoprostol, enisoprost, and related compounds was recently reported simultaneously by Searle researchers[28] and Lipschutz *et al.*[29] In the one-pot Searle procedure, the ω-chain precursor **37** was first functionalized with zirconocene chloride hydride in THF. The vinylzirconium intermediate was transmetalated directly by treatment with 2 equiv of *n*-BuLi or MeLi at −30 to −70 °C. Sequential addition of copper cyanide and MeLi elicited the *in situ* generation of the higher order cyanocuprate which was then reacted with the appropriate enone to give the PG.

4. Enprostil

Enprostil is a racemic C-4,5-dehydro-PGE_2 analog developed by Syntex and is currently marketed in several countries for the prevention/treatment of gastric and duodenal ulcers. It contains a unique allene moiety at C-4–6 which is unresolved. Thus, enprostil is a racemic mixture of four stereoisomers, consisting of a pair of diastereoisomers that are epimeric about the allene center, together with the corresponding enantiomers.[30] Both the allene and the ω-chain phenoxy groups were installed in the molecule to decrease metabolic susceptibility.[31] Interestingly, either modification alone has a relatively modest effect on the antisecretory potency of PGE_2 while enprostil itself is 600 times as potent as its parent in inhibiting gastric acid secretion in rats.[31]

Scheme 12[a]

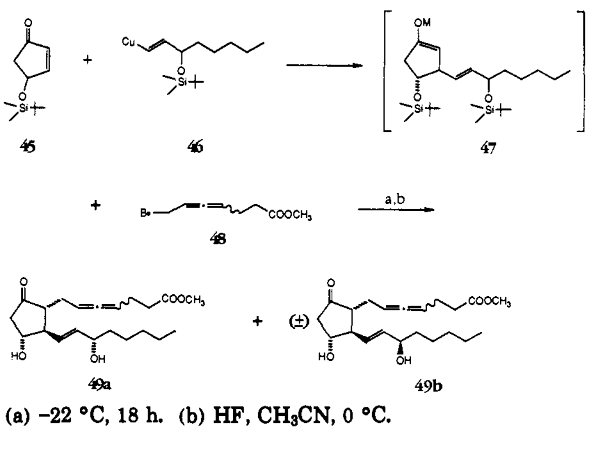


[a] (a) $PhOCH_2C(O)CH_2 P(O)(OCH_3)_2$/NaH. (b) $Zn(BH_4)_2$. (c) Chromatography. (d) K_2CO_3. (e) Dihydropyran/H^+. (f) DIBAL. (g) LiC≡C$(CH_2)_2$COOLi. (h) CH_2N_2. (i) Ac_2O. (j) Me_2CuLi. (k) AcOH/H_2O. (l) *t*-$BuMe_2SiCl$. (m) CrO_3, pyridine.

Enprostil was first prepared[5] via racemic Corey lactone (Scheme 12). After incorporation of the aryloxy ω-chain by Horner–Wadsworth–Emmons chemistry, reduction, and separation of 15-epimeric alcohols and manipulation of protecting groups, the lactone of **40** was reduced with DIBAL and the resulting lactol opened with the dilithio salt of 4-pentynoic acid to give **41**. Esterification with diazomethane and diacetylation produced **42** which was converted to the allene **43** by treatment with dimethylcuprate[32] and subsequent acidic cleavage of the THP ethers. Removal of the C-9 acetate followed by selective protection of the C-11- and C-15-hydroxy groups with *tert*-butyldimethylsilyl chloride provided **44** which was oxidized and subsequently deprotected to give enprostil.

This procedure is quite long and some of the steps gave less than desirable yields. Thus, it is not surprising that other strategies have been investigated including several conjugate addition approaches.[33-35] Two of these involve addition of the ω-chain to a cyclopentenone with a truncated α-chain followed by elaboration of the allenic moiety. Perhaps the most direct procedure is a tandem alkylation sequence recently reported by Patterson[35] (Scheme 13). The enolate **47** formed by reaction of the racemic ω-chain organocopper derivative

Scheme 13[a]

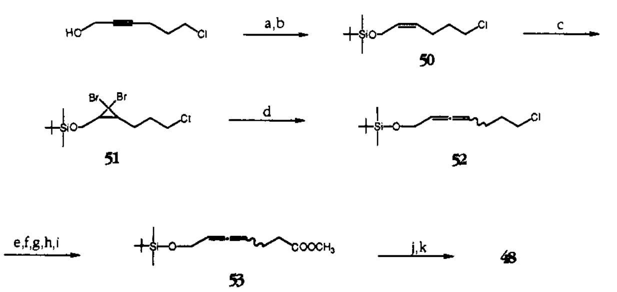


[a] (a) −22 °C, 18 h. (b) HF, CH_3CN, 0 °C.

46 and the racemic cyclopentenone 45 was quenched with the α-chain derivative 48 to give, after protecting group removal and purification, a separable epimeric mixture of products **49a** and **49b** although in low yield (28%). The cause of the low yield in the cuprate/alkylation reaction was attributed to slow enolate alkylation with subsequent destruction of the enolate. This problem is often experienced in the tandem alkylation approach, but can be overcome by using more reactive alkylating reagents.[36]

The allenic bromide 48 was prepared as shown in Scheme 14. 6-Chloro-2-hexyn-1-ol was hydrogenated to the (*Z*)-olefin and subsequently protected as a silyl ether to give 50. Cyclopropanation with bromoform and aqueous potassium hydroxide gave the dibromocyclopropane 51 which was opened directly to the racemic allene 52 by treatment with *n*-BuLi. Conversion of the chloride to the alcohol which was oxidized sequentially to the aldehyde under Swern conditions and then to the acid with *m*-chloroperbenzoic acid, and finally diazomethane treatment gave the silyl ether ester 53.

Scheme 14[a]



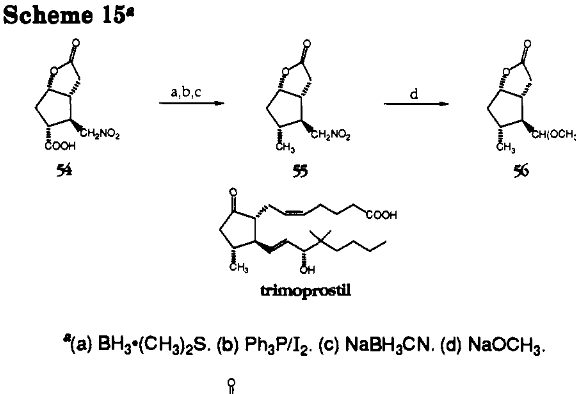
[a] (a) {H}. (b) *t*-$BuMe_2SiCl$. (c) $CHBr_3$/KOH. (d) *n*-BuLi. (e) NaI/Me_4NAc. (f) K_2CO_3. (g) DMSO/oxalyl Cl. (h) Peracid. (i) CH_2N_2. (j) AcOH, H_2O. (k) MsCl/LiBr.

The silyl ether was cleaved with aqueous acetic acid and the resulting alcohol was converted to 48 via its mesylate with lithium bromide in acetone.

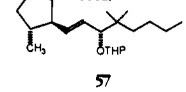
5. Trimoprostil

Trimoprostil (Scheme 15) is a single isomer analog of 16,16-dimethyl-PGE_2 in which the 11-hydroxy group has been replaced by a methyl group. This modification removes the instability inherent in E type PGs but it also reduces potency. Trimoprostil has undergone clinical trials for the treatment of peptic ulcer disease,

Scheme 15[a]



[a] (a) $BH_3{\bullet}(CH_3)_2S$. (b) Ph_3P/I_2. (c) $NaBH_3CN$. (d) $NaOCH_3$.



57

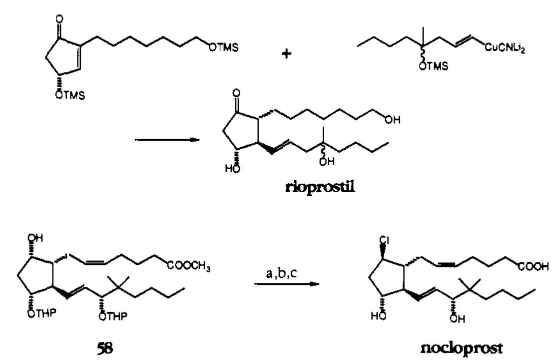
but reportedly, development has been terminated, presumably because of low efficacy and side effects.

Trimoprostil is another analog prepared by the Corey route or a combination of the conjugate addition and Corey approaches. Initially trimoprostil was prepared[37] starting with the optically active nitro compound 54 (Scheme 15). Reduction with borane gave the alcohol which was treated with iodine and triphenylphosphine and subsequently reduced with sodium cyanoborohydride to give the key 11-methyl substituent in 55. Conversion of the nitro group to the aldehyde was effected by treatment with sodium methoxide to give protected aldehyde 56. Exposure of the aldehyde by acid hydrolysis was followed by introduction of the ω- and α-chains by the standard Corey methodology. An alternate approach[36] developed for large-scale synthesis involved the conjugate addition of a resolved vinyl zirconium reagent to a resolved cyclopentenone having a truncated α-chain. The intermediate 57 was then converted to trimoprostil by standard ylide chemistry.

6. Rioprostil

Structurally, rioprostil is simply the 1-alcohol analog of misoprostol. However, it consists of only two isomers rather than four due to the use of resolved enone in its synthesis. Rioprostil is less potent than misoprostol as an inhibitor of gastric acid secretion but may have certain advantages because of reduced side effects. This compound has been extensively studied clinically as an antiulcer agent but is marketed in only a few countries. The synthesis[39] of rioprostil is analogous to that for misoprostol and involves conjugate addition of a cyanocuprate reagent of the ω-chain to a bis-silyl derivative of the resolved enone (Scheme 16) followed by hydrolysis of protecting groups.

Scheme 16[a]



[a] (a) CCl_4/Ph_3P. (b) CH_3COOH. (c) KOH.

7. Nocloprost

Nocloprost is the 9-β-chloro analog of 16,16-dimethyl-PGE_2 and is the result of another strategy to remove the chemical instability of E-type PGs. It is chemically stable and was selected for development as an antiulcer agent because of its high cytoprotective activity and low side effects. Nocloprost is in phase III clinical study and is licensed to Marion Merrell Dow for the United States and Canadian markets.

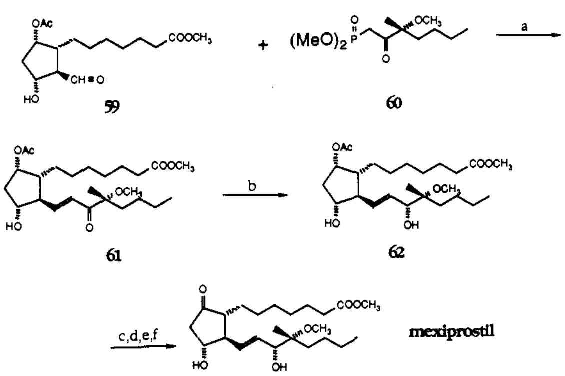
The only reported synthesis[40] of nocloprost is from the protected form of 16,16-dimethyl-$PGF_{2\alpha}$ 58 (Scheme 16) which was generated from the Corey lactone. Treatment of 58 with carbon tetrachloride and triphenylphosphine gave the β-chloro intermediate which was converted to nocloprost by protecting group removal and ester hydrolysis.

8. Mexiprostil

This compound, 16(*R*)-methoxy-16-methoxy-PGE_1 methyl ester, was first reported in 1986[41] and is a derivative of 16,16-dimethyl-PGE_2 in which one of the C-16 methyl groups has been replaced by a methoxy group. The goal of this work was to determine if the electronic demands of a methoxy group might alter the side-effect profile. Phase I clinical studies have shown mexiprostil to be a well tolerated and moderately active antisecretory and cytoprotective compound.[42] Mexiprostil is licensed to Marion Merrill Dow in the United States.

The presence of the methoxy group at C-16 imposes additional stereochemical complexity to the molecule, but this has been handled well in both the original synthesis and a recent improvement. In the original work[41] (Scheme 17) the aldehyde **59** was condensed with the resolved ω-chain phosphonate **60** to give the 15-keto analog **61**. Reduction of **61** with sodium borohydride provided a separable mixture of **62** and its 15-epimer. The configurations of the C-15 epimers were assigned on the basis of their chromatographic behavior and NMR analysis. Mexiprostil was obtained by protecting the C-11 and C-15 alcohols and THP ethers, removal of the C-9 acetate with potassium carbonate, oxidation with Collins reagent, and removal of the THP protecting groups.

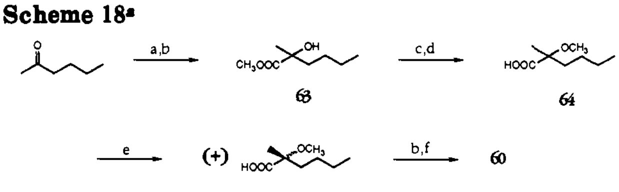
Scheme 17[a]



[a] (a) NaH. (b) $NaBH_4$. (c) DHP/PTSA. (d) K_2CO_3. (e) CrO_3/pyridine. (f) H_3O^+.

The synthesis of the resolved phosphonate (Scheme 18) started with 2-hexanone which was reacted with sodium cyanide, solvolyzed, and esterified to give **63** which was alkylated and hydrolyzed to provide **64**. Resolution of **64** with (+)-amphetamine provided the (+)-acid **65**. Absolute configuration was established by comparing the circular dichroism curves with a similar compound (saturated atrolactic acid) of known configuration. The phosphonate was prepared by reaction of the ester of **65** with the lithium salt of dimethyl methylphosphonate.

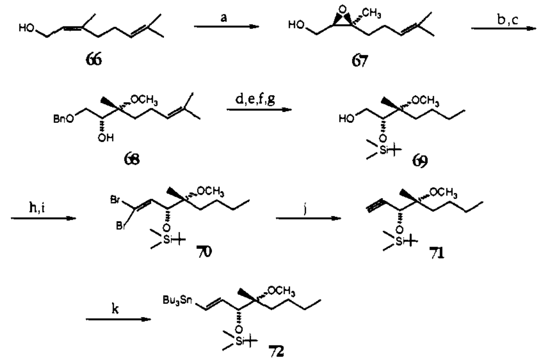
Scheme 18[a]



[a] (a) NaCN. (b) HCl/MeOH. (c) NaH/MeI. (d) NaOH. (e) Amphetamine/recrystallization. (f) $(MeO)_2P(O)CH_2Li$.

More recently, a three-component process[43] has been developed for the preparation of mexiprostil (Scheme 19). The ω-chain component was prepared from nerol (**66**) by Sharpless epoxidation to give the epoxide **67** in 70% optical purity. Benzylation of **67** followed by stereo- and regioselective cleavage of the epoxide in methanol provided the methoxy hydroxy derivative **68**, having the required configuration for mexiprostil. The propylidene function in **68** was converted to the aliphatic chain derivative **69** by a sequence consisting of ozonolysis, methylenation of the resulting aldehyde, protection of the alcohol, and hydrogenation to saturated the double bond and remove the benzyl group.

Scheme 19[a]

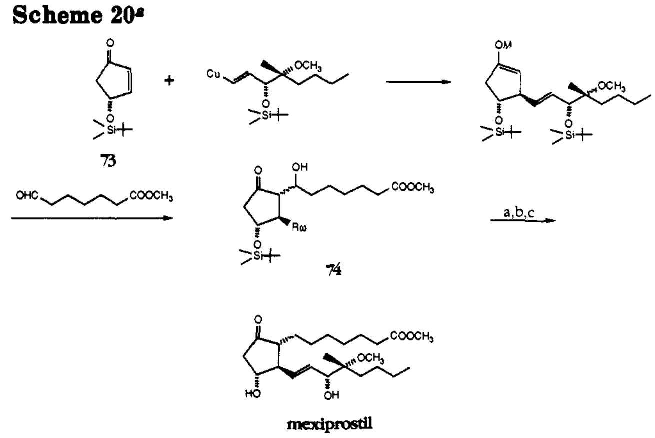


[a] (a) (−)-DET, $Ti(O\text{-}i\text{-}Pr)_4$, *t*-BuOOH, C_7H_8 −15 °C. (b) BnBr, KO-*t*-Bu. (c) MeOH, Dowex 50, H^+. (d) O_3. (e) $Ph_3P{=}CH_2$. (f) *t*-BuMe_2SiCl. (g) $Pd(OH)_2/H_2$. (h) DMSO, $(COCl)_2$. (i) CBr_4, Ph_3P. (j) *n*-BuLi. (k) $HSnBu_3$, AIBN, 130 °C.

The alcohol **69** was oxidized under Swern conditions to the aldehyde and converted with carbon tetrabromide and triphenylphosphine to the dibromo olefin **70**. The acetylene **71** was produced by treatment of **70** with *n*-BuLi at −78 °C. The vinylstannane **72** (90% (*E*)-isomer) was obtained by AIBN and heat-catalyzed hydrostannation of **71** with tributyltin hydride. The organocopper reagent from **72** was prepared by sequential treatment with *n*-BuLi, cuprous iodide, and tri-*n*-butylphosphine.

Treatment (Scheme 20) of the enone **73** with the cuprate followed by enolate quenching with the α-chain aldehyde gave a mixture of diastereoisomers of the

Scheme 20[a]



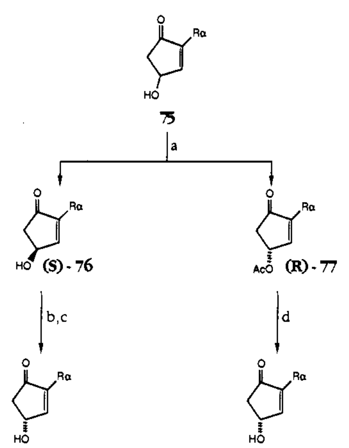
[a] (a) MsCl, DMAP. (b) Bu_3SnH, $(t\text{-}BuO)_2$. (c) AcOH, THF, H_2O, 25 °C, 48 h.

hydroxy PG derivatives **74** in 42% yield. Dehydration of the 7-hydroxy group (60% after chromatography) followed by reduction with tributyltin hydride, chromatographic purification, and deprotection gave mexiprostil in isomerically pure form.

The tradeoffs of using the often superficially elegant three-component process versus the more traditional two-component process (where the α-chain is already incorporated into the enone) are readily apparent in this synthesis. Although the authors claim high efficiency for their synthesis, in fact the yield of mexiprostil from the enone is only 20% and requires three steps and two chromatographic purifications after the cuprate reaction. In contrast, the two-component process routinely provides yields of 80% of final PG from the enone and requires only a simple deprotection step and one chromatographic purification after the cuprate reaction. Given improved methods for preparing[44] (such as the furan route described for enisoprost) and resolving α-chain-substituted enones, one has to question the indiscriminate preference for the three-component strategy.

A recently reported[45] enzymatic resolution of such enones is illustrative. Treatment of the racemic hydroxy enone **75** with commercially available porcine pancreatic lipase (PPL) in vinyl acetate at room temperature for 4 days gave a separable mixture of (*S*)-**76** and acetate (*R*)-**77** with ee's of 90% or better (Scheme 21). Furthermore, (*S*)-**76** could be inverted via Mitsunobu chemistry to the desired (*R*)-isomer without loss of stereochemical integrity. The (*R*)-**77** was readily cleaved to the (*R*)-alcohol with guanidine in methanol. The (*R*)-alcohol could also be recycled to improve its enantiomeric purity. The overall process is efficient, general, and adaptable to large scale.

Scheme 21[a]



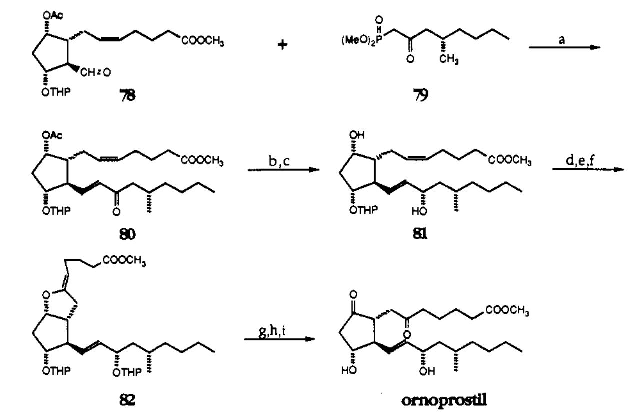
[a] (a) Lipase, vinyl acetate. (b) $N_2(COOEt)_2$, Ph_3P, HCOOH. (c) Al_2O_3; MeOH. (d) Guanidine, MeOH.

9. Ornoprostil

Ornoprostil was developed by Ono Pharmaceutical and is currently marketed as an antiulcer drug in Japan by Ono and Upjohn. It is a single isomer and differs from PGE_1 by having a 6-keto substituent, a 17(*S*)-methyl group and an elongated ω-chain.

The synthesis of ornoprostil has not been published in detail in English; thus the sequence outlined in Scheme 22 was gathered from synopsis reports.[46] The aldehyde **78** (presumably prepared from the Corey lactone) was reacted with the ω-chain phosphonate **79** to give **80**. Stereoselective reduction of the 15-keto group was performed with (*S*)-BINAL-H[47] (derived by treatment of LAH with 1 equiv each of ethanol and (*S*)-1,1′-bi-2-naphthol) to give **81** after acetate removal with potassium carbonate. The 6-keto functionality was installed by iodocyclization with iodine in aqueous bicarbonate, protection of the C-15-hydroxy group as a THP ether, dehydroiodination with DBU in toluene to give the prostacyclin derivative **82**, and acid hydrolysis to give the C-9-hydroxy-6-keto derivative. Oxidation of the C-9-hydroxy group with Jones reagent and protecting group removal provided ornoprostil. The phosphonate **79** was prepared from (*S*)-3-methylheptanoic acid ethyl ester by reaction with the lithium salt of dimethyl methylphosphonate.

Scheme 22[a]



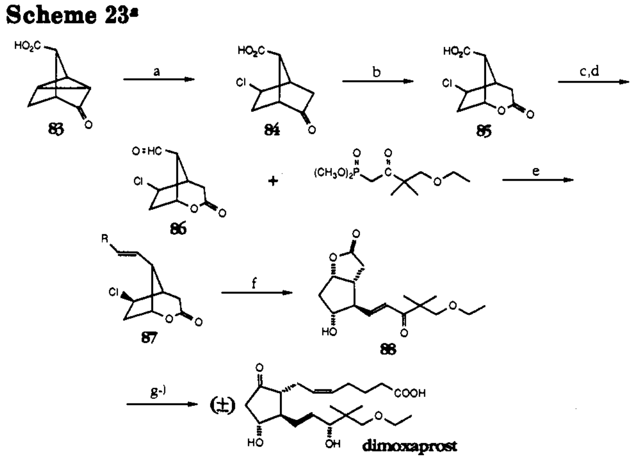
[a] (a) NaH. (b) (*S*)-BINAL-H. (c) K_2CO_3. (d) I_2, $NaHCO_3$. (e) DHP, H^+. (f) DBU. (g) 1 N HCl. (h) CrO_3, H_2SO_4, H_2O.

10. Dimoxaprost

Dimoxaprost is the racemic 18-oxa analog of 16,16-dimethyl-PGE_2 and was prepared in an attempt to improve selectivity between antiulcer activity and side effects. Although the modification reduced gastric antisecretory/mucosal protective activity relative to 16,16-dimethyl-PGE_2, it appears to have improved selectivity, especially with respect to diarrheagenic potency.[48]

Dimoxaprost is prepared through a modification of the Corey lactone procedure (Scheme 23). The tricyclic keto acid **83** was treated with HCl to give the chloro

Scheme 23[a]



[a] (a) HCl. (b) CH_3CO_3H. (c) $SOCl_2$. (d) H_2/Pd. (e) NaH. (f) *p*-Toluenesulfonic acid, H_2O. (g) Diisobutylaluminum/2-6-di-*tert*-butyl-4-methyl phenolate. (h) DHP, H^+. (i) DIBAL. (j) Ylide chemistry. (k) CrO_3. (l) H^+_3O.

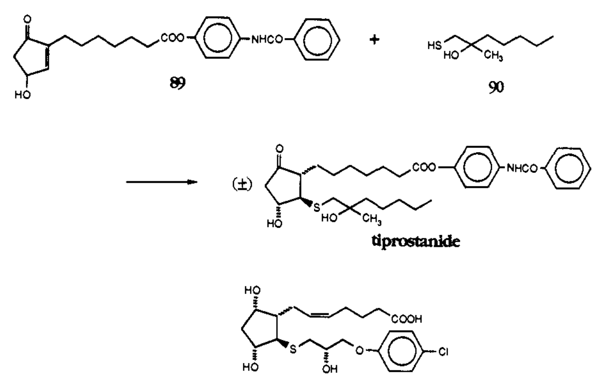
compound 84. Oxidation with peracetic acid provided the lactone 85 which was converted to the aldehyde 86 by catalytic reduction of the acid chloride of 85. Condensation of 86 with the ω-chain phosphonate gave the intermediate 87.[49] Treatment of 87 with p-toluene sulfonic acid in aqueous THF effected hydrolysis of the lactone and was followed by nucleophilic displacement of the chloride with the carboxylate anion to give the key Corey lactone derivative 88. The remainder of the synthesis is straightforward.[50]

11. Tiprostanide

This compound is a 13-thia-PGE_1 analog which also contains a p-benzamidophenyl ester, presumably to enhance crystallinity and stability.[51] Although originally targeted and evaluated as an antihypertensive agent, emphasis was switched to an antiulcer indication because of disappointing clinical results.

The synthesis[52] (Scheme 24) of tiprostanide involves a straightforward Michael addition reaction of the thiol ω-chain component 90 to the enone 89 (both racemic), in the presence of a hindered amine. The major product was tiprostanide along with a minor amount of the 11-epimer. The synthesis and rearrangement chemistry of similar 13-thia-PGs have been reported by other workers.[53]

Scheme 24



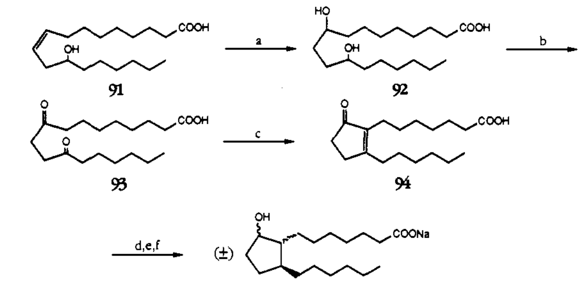
A relative of tiprostanide is luprostiol (Scheme 24) which is marketed by Merck AG in Germany for estrus synchronization in horses and cattle.

12. Rosaprostol

Rosaprostol[54] is a sparsely functionalized prostanoid developed by IBI in Italy. While it is devoid of the undesirable side effects of natural PGs, rosaprostol is an extremely weak antiulcer agent requiring gram quantity doses in humans. It is marketed exclusively in Italy as Rosal.

The synthesis[55] of rosaprostol (Scheme 25) began with ricinoleic acid 91 which was treated with mercuric acetate in aqueous NaOH to give 92. Oxidation to 93 followed by cyclization with sodium hydroxide in ethanol provided 94. Catalytic hydrogenation of the C-8,12 double bond, reduction of the C-9 ketone with sodium borohydride, and treatment with sodium hydroxide produced rosaprostol.

Scheme 25[a]



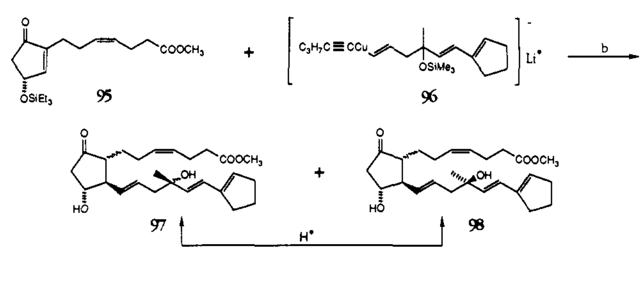
rosaprostol

[a] (a) $Hg(OAc)_2$. (b) CrO_3, H_2SO_4. (c) NaOH, EtOH. (d) H_2, PtO_2, AcOH. (e) $NaBH_4$. (f) NaOH.

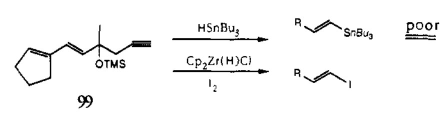
13. Remiprostol

Remiprostol is an ω-chain cyclopentenyl analog of enisoprost. In animal studies, it exerted extremely potent and prolonged gastric antisecretory and mucosal protective effects while displaying weak diarrheagenic side effects.[56] It also shows remarkable affinity and selectivity for the parietal cell (acid secreting cell) receptor. Remiprostol is a mixture of two C-16 diastereomers 97 and 98 and was developed as such because in acidic media (stomach pH), the bioactive isomer 97 rapidly epimerizes to the mixture (Scheme 26).

Scheme 26



b) PPTS, acetone



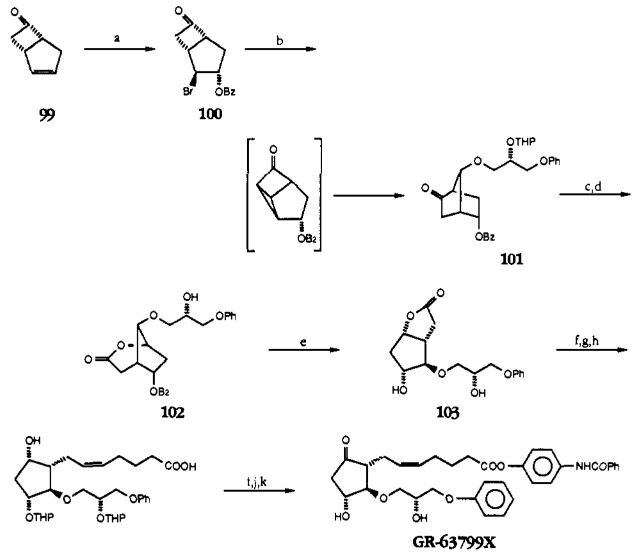
This compound was synthesized[57] by the cuprate process routinely used at Searle. Addition of the racemic ω-chain cuprate reagent 96 to (R)-enone 95 gave the separable diastereomers 97 and 98 after gentle (pyridinium p-toluenesulfonate) acid hydrolysis of protecting groups. Stronger acids (e.g., acetic acid) promoted allylic rearrangement and dehydration of the C-16 hydroxy group.

The traditional light-catalyzed hydrostannation methodology to derivatize the acetylenic ω-chain precursor proved to be extremely difficult with this and other conjugated diene analogs.[58] The reaction was very sluggish and numerous side products were observed. These difficulties prompted the development of the alternative hydrozirconation–iodination approach[59] to produce the (E)-vinyl iodide.

14. GR-63799X

GR-63799X is another new generation analog developed with improved selectivity as a goal. It can be considered, in a sense, an analog of tiprostanide because it contains a 13-oxa moiety and is a p-benzamidophenyl

Scheme 27[a]



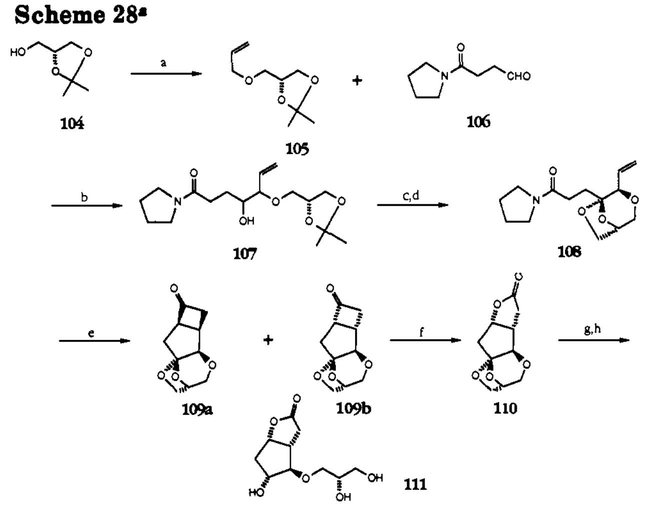
[a] (a) $PhCH_2OH$, NBS. (b) (2*R*)-$PhOCH_2CH(OTHP)CH_2OH$, Na. (c) MeOH, HCl. (d) CH_3CO_3H. (e) Pd, H_2. (f) DHP, H^+. (g) DIBAL. (h) *t*-BuOK, $Ph_3P(CH_2)_4COOH$. (i) {O}. (j) $PhCONHC_6H_4OH$. (k) $H^+{}_3O$.

ester. This compound is an effective antisecretory/mucosal protective agent without the diarrheagenic and uterine side effects associated with earlier compounds.[60]

The original synthesis[61] of GR-63799X started with the known resolved intermediate **99** of Scheme 27. Treatment of **99** with *N*-bromosuccinimide and benzyl alcohol generated the bromo benzyl ether **100**. Reaction of the alkoxide of the resolved ω-chain alcohol converted **100** to **101** through the intermediacy[62] of a tricyclic compound. Removal of the ω-chain THP ether was followed by treatment with peracetic acid to form the lactone **102**. Reductive removal of the benzyl protecting group caused a spontaneous rearrangement to generate a Corey lactone intermediate **103**. The remainder of the synthesis is straightforward. The phenolic ester was formed by either a mixed anhydride or carbodiimide procedure.

A second, more elegant approach to the key intermediate **103** has recently been described (Scheme 28).[63] Allylation of (*R*)-alcohol **104** gave the ether **105** which

Scheme 28[a]

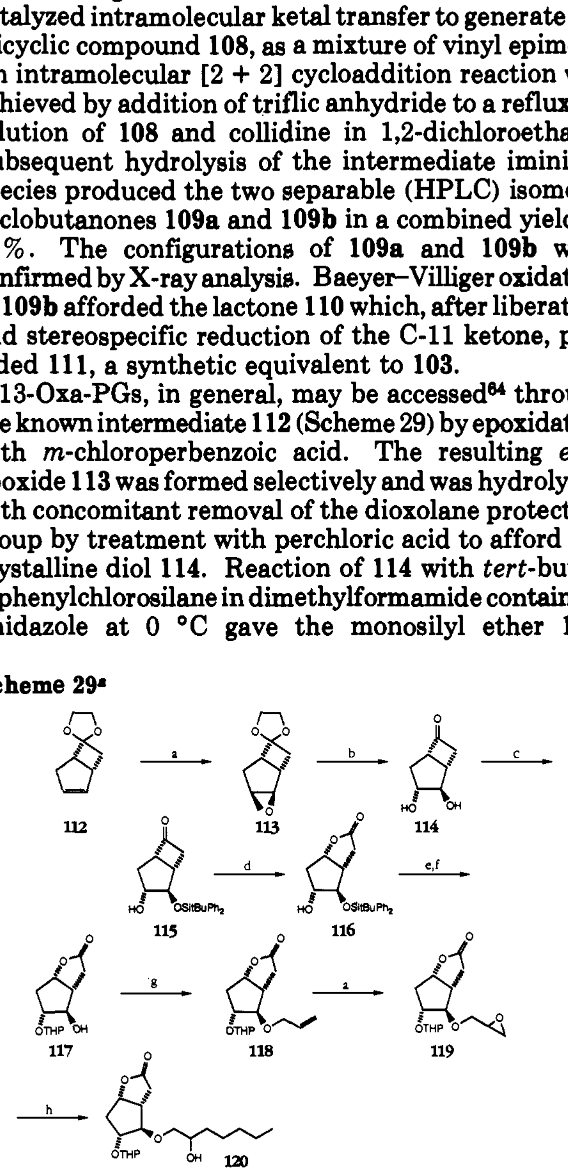


[a] (a) NaH, allyl bromide. (b) *sec*-BuLi, $ZnCl_2$. (c) $(COCl)_2$, DMSO, *N*-methylmorpholine. (d) *p*-toluenesulfonic acid. (e) $(CF_3SO_2)_2O$, collidine. (f) Baeyer–Villiger. (g) $H_3{}^+O$. (h) reduction.

was deprotonated with *sec*-butyl lithium, converted to the zinc salt with a zinc chloride solution and added to aldehyde **106** to give **107** as a mixture of diastereomeric alcohols. Oxidation of **107** under modified Swern conditions gave the ketone which underwent acid-catalyzed intramolecular ketal transfer to generate the tricyclic compound **108**, as a mixture of vinyl epimers. An intramolecular [2 + 2] cycloaddition reaction was achieved by addition of triflic anhydride to a refluxing solution of **108** and collidine in 1,2-dichloroethane. Subsequent hydrolysis of the intermediate iminium species produced the two separable (HPLC) isomeric cyclobutanones **109a** and **109b** in a combined yield of 40%. The configurations of **109a** and **109b** were confirmed by X-ray analysis. Baeyer–Villiger oxidation of **109b** afforded the lactone **110** which, after liberation and stereospecific reduction of the C-11 ketone, provided **111**, a synthetic equivalent to **103**.

13-Oxa-PGs, in general, may be accessed[64] through the known intermediate **112** (Scheme 29) by epoxidation with *m*-chloroperbenzoic acid. The resulting *exo*-epoxide **113** was formed selectively and was hydrolyzed with concomitant removal of the dioxolane protecting group by treatment with perchloric acid to afford the crystalline diol **114**. Reaction of **114** with *tert*-butyldiphenylchlorosilane in dimethylformamide containing imidazole at 0 °C gave the monosilyl ether **115**.

Scheme 29[a]



[a] (a) *m*-$ClPhCO_3H$. (b) Perchloric acid. (c) *t*-$BuPh_2SiCl$. (d) Peracetic acid, −20 °C. (e) DHP, H^+. (f) TBAF. (g) Ag_2O. (h) $LiCuBu_2$.

Interestingly, excess silylating reagent did not result in reaction of the adjacent hindered alcohol but, in contrast, both alcohols could be silylated with *tert*-butyldimethylchlorosilane. Baeyer–Villiger oxidation of **115** under mild conditions gave the lactone **116**. Protecting group manipulation followed by etherification of the free alcohol of **118** with silver oxide and allyl bromide gave the allyl ether **118**. Oxidation with *m*-chloroperbenzoic acid to give the epoxide **119** was followed by reaction with lithium dibutylcuprate to provide the alcohol **120**. Conventional chemistry was used to convert **120** to a PG.

15. Viprostol

Viprostol is an E_2 analog of misoprostol in which the C-16 methyl group has been replaced by a vinyl moiety. This analog is also a mixture of four stereoisomers.

Viprostol is effective in lowering blood pressure by both oral and transdermal administration and reached phase II clinical studies as an antihypertensive agent, and later, for the reversal of male pattern baldness.

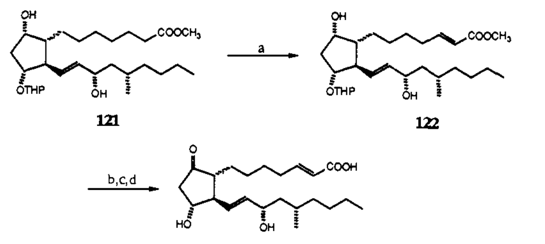
The synthesis of viprostol was carried out by conventional conjugate addition of the ω-chain cuprate to a (5*Z*)-enone.[65]

16. Limaprost

Limaprost is a relative of ornoprostil, having the same ω-chain but a different α-chain. Clinical trials with limaprost have indicated its usefulness in treating essential hypertension, acute myocardial infarction, and deep vein thrombosis.[66] Success in treating Raynaud's phenomenon with limaprost has also been reported.[67] It is comarketed in Japan by Ono and Dainippon.

Limaprost is synthesized, similarly to ornoprostol, utilizing Corey methodology. The C-2 (*E*)-double bond was introduced by treatment of **121** (Scheme 30) with LDA, quenching with diphenyl diselenide, and hydrogen peroxide oxidation to generate **122**. Ester hydrolysis, Jones oxidation at C-9, and deprotection led to limaprost.[68] A series of α-chain diene analogs of misoprostol was also prepared by selenide chemistry on 9-silyl enol ethers obtained by cuprate enolate capture with *tert*-butyldimethylchlorosilane.[24,69]

Scheme 30[a]



121, 122, limaprost

[a] (a) LDA, PhSeSePh, H_2O_2. (b) KOH. (c) Jones' reagent. (d) $AcOH/H_2O$.

17. Sulprostone

Sulprostone, an E2 analog containing an ω-chain phenoxy group and derivatized at C-1 as a sulfonimide, was the result of a concerted effort to improve both metabolic stability and selectivity of PGE_2.[70] It exerts potent uterine stimulant/abortifacient activity and is 30 times more selective than PGE_2 *in vivo* with respect to diarrheagenic side effects. Sulprostone is marketed in several countries including France for early pregnancy termination and has been used in conjunction with Roussel's RU-486.

Sulprostone was synthesized from the Corey lactone–aldehyde by conventional chemistry.[70] Interestingly, the sulfonimide could be introduced into the Wittig α-chain precursor prior to condensation with the lactol.

18. Gemeprost

Gemeprost is the C-2 (*E*)-analog of 16,16-dimethyl-PGE_2 and was synthesized by conventional methods via the Corey lactone. This compound is also marketed in several countries for gynecological purposes.[71]

19. Meteneprost

This compound, a 9-methylene analog of 16,16-dimethyl-PGE_2, is another example of efforts to eliminate the chemical instability of PGE-type structures. Meteneprost is an effective abortifacient for early pregnancy and appeared to be particularly well-tolerated in clinical studies.[72] The methylene functionality was introduced via Johnson's sulfoximine chemistry.[73]

20. Cloprostenol/Fluprostenol

These two $PGF_{2\alpha}$ analogs are relatives, varying only in the ω-chain aromatic substituent (see Table 1 for structure). Cloprostenol is used for estrus synchronization in cattle while fluprostenol is used to treat persistent luteal function in horses.[74a] Both compounds were prepared via Corey methodology.

21. Fenprostalene/Prostalene

These compounds are α-chain allenic analogs developed by Syntex for veterinary use. Fenprostalene, the $F_{2\alpha}$ analog of enprostil, is used to synchronize estrus in cattle while prostalene, a 15-methyl aliphatic ω-chain analog, is used in mares. The role of these and other PG analogs in swine production has been reviewed.[74b]

The synthesis of both analogs proceeds via the Corey lactone and institution of the allene unit via dimethyl cuprate reaction with acetylenic acetates.[75]

22. Latanoprost

Latanoprost is a $PGF_{2\alpha}$ analog and is structurally characterized by the substitution of a phenyl group for carbons 18–20, saturation of the C-13–14 double bond, and the presence of an isopropyl ester at C-1. Latanoprost is a pure, naturally configured isomer whose stereochemistry at C-15 is designated "*R*" because of a reversal of substituent priorities relative to $PGF_{2\alpha}$. Latanoprost is a new drug candidate for the treatment of glaucoma and reduces intraocular pressure (IOP) by increasing uveoscleral outflow.[76] This compound, while no more potent than the isopropyl ester of $PGF_{2\alpha}$ in reducing IOP, was selected for clinical study because of its reduced ocular side effects such as irritation and conjunctival hyperemia.

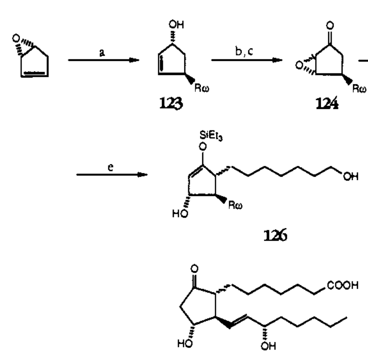
Latanoprost was synthesized from the Corey lactone using conventional methodology.[76] The C-13–14 double bond was reduced by hydrogenation with palladium on carbon as catalyst in the presence of sodium nitrate and was performed prior to institution of the α-chain.

C. Recent Advances in Synthetic Methodologies

1. Cyclopentene Epoxides

Marino[77] described a versatile entry to PG structures which utilizes the readily available cyclopentyl epoxide as starting material (Scheme 31). Cuprate addition of the ω-chain provided the alcohol **123** which was epoxidized with *tert*-butyl hydroperoxide and vanadyl acetylacetonate to generate the *cis*-epoxycyclopentanol (hydroxy-directed epoxidation) which was then oxidized with Collins reagent to give the epoxy ketone **124**. The silyl enol ether **125** was formed by treatment with LDA in THF at −78 °C followed by enolate trapping with triethylchlorosilane. Cuprate addition of the α-chain, followed by fluoride-induced hydrolysis of the enolate and C-1 alcohol silyl groups, chromatography to separate C-15 diastereomers, oxidation with oxygen and platinum of the C-1 alcohol, and deprotection of the

Scheme 31[a]



[a] (a) Li (RωCuCN), Rω = $(CH_2)_5CH(OTBDMS)CH{=}CH_2$. (b) t-BuOOH, $V(acac)_2$. (c) CrO_3–pyridine. (d) LDA, Et_3SiCl. (e) Li(RαCuCN), Rα = $(CH_2)_6CH_2OTMS$. (f) KF. (g) HPLC. (h) O_2, Pt. (i) HF, CH_3CN.

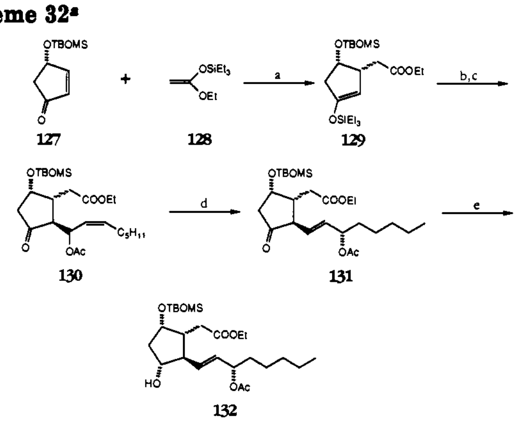
C-15 alcohol with hydrofluoric acid in acetonitrile provided PGE_1.

2. Three-Component Coupling

Noyori[78] has reported that the reagent formed by mixing dimethylzinc with the (*E*)-vinyllithium species of the ω-chain undergoes selective vinyl transfer to an enone, and that enolate trapping with the propargyl bromide of the α-chain (5 equiv, 10 equiv of HMPA, −78 to 40 °C, 24 h) gives the desired PGE structure in 71% yield. The process is a considerable improvement over the cuprate/triphenyltin chloride methodology.[16] A similar vinylzincate approach was independently described by Takahashi.[79]

Danishefsky[80] disclosed a clever "inverse" three-component strategy involving an electrophilic version of the ω-chain and a nucleophilic version of the α-chain to the (*S*)-enone **127** (Scheme 32). Reaction of **127** with

Scheme 32[a]

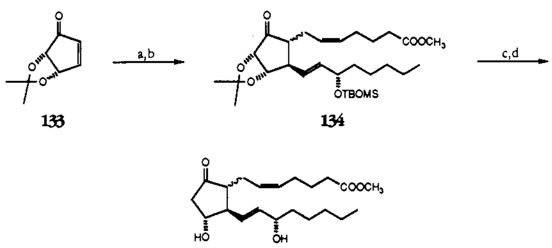


[a] (a) HgI_2. (b) (*E*)-Octenal, $TiCl_4$. (c) Ac_2O, pyridine, DMAP. (d) $Pd(MeCN)_2Cl_2$. (e) $NaBH_4$.

the silyl ketene acetal **128** in the presence of mercuric iodide produced the *cis*-silyl enol **129** exclusively. Reaction of **129** with (*E*)-octenal and titanium tetrachloride as catalyst provided the adduct **130**, after acetylation. Allylic transposition of the acetate was effected by treatment with $Pd(MeCN)_2Cl_2$ to provide **131**. Reduction of the C-11 ketone with sodium borohydride to give **132** stereospecifically set the stage for conversion to PGE_2 by conventional Corey lactone methodology.

Another approach to circumvent the low yields associated with the three-component coupling strategy

Scheme 33[a]

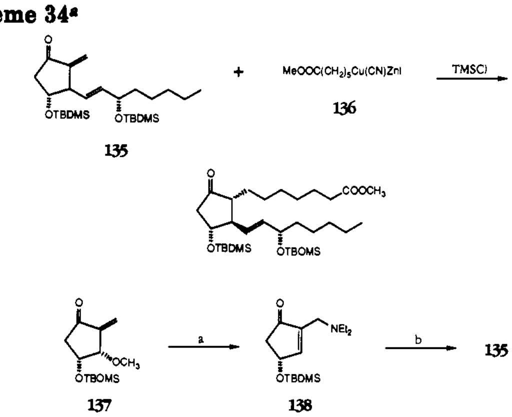


[a] (a) CuCH=CHCH(OTBDMS)C_5H_{11}. (b) Methyl 7-iodohept-5-enoate. (c) HF/pyridine. (d) Al(Hg).

when less reactive α-chain electrophiles are used as been developed by Johnson.[17] Use of the acetonide **133** (Scheme 33) suppresses enolate equilibration and resultant elimination of the C-11 alkoxide. Thus, organocopper addition of the ω-chain followed by alkylation with the appropriate α-chain allyl iodide provided the protected PG **134** in good to excellent yield. After deprotection of the C-15 hydroxyl, the acetonide was treated with aluminum amalgam to generate PGE_2 methyl ester cleanly. Additional advances in this methodology have been recently described.[81]

A variation combining the original Stork[82] strategy with zinc–copper α-chain reagents has been researched by Sato.[83] The enone **135** (Scheme 34), obtained by

Scheme 34[a]



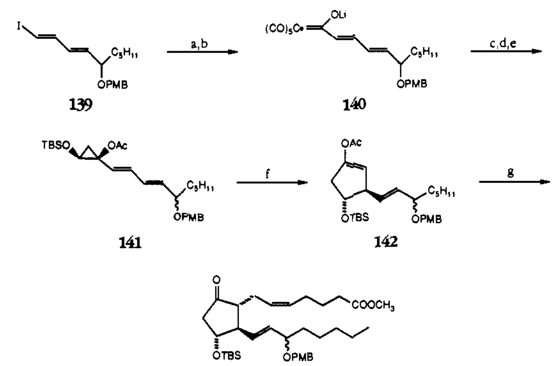
[a] (a) Et_2NH. (b) Rω cuprate.

quenching the cuprate enolate with formaldehyde followed by dehydration,[82] was treated successively with the cuprate reagent **136**, derived from the corresponding organozinc species and copper cyanide, and trimethylchlorosilane to generate the protected PG. The enone **135** was also accessible by treatment of **137** with diethylamine to generate **138** followed by cuprate addition of the ω-chain. Utility of **138** also has been demonstrated for preparation of 13,14-acetylenic PGs via conjugate addition of alkynyl aluminum reagents.[84]

3. Chromium Carbenes

Wulff[85] has devised an approach to PGs based on acyloxy chromium carbene complexes (Scheme 35). The dienyl iodide **139** (PMB = *p*-methoxybenzyl chloride) was treated with 2 equiv of *tert*-butyllithium followed by chromium hexacarbonyl to generate the lithium acylate **140**. Sequential treatment of **140** with tetrabutylammonium fluoride, acetyl bromide, and the *tert*-butyldimethylsilyl (TBS) enol ether of acetaldehyde provided the racemic cyclopropane intermediate

Scheme 35[a]



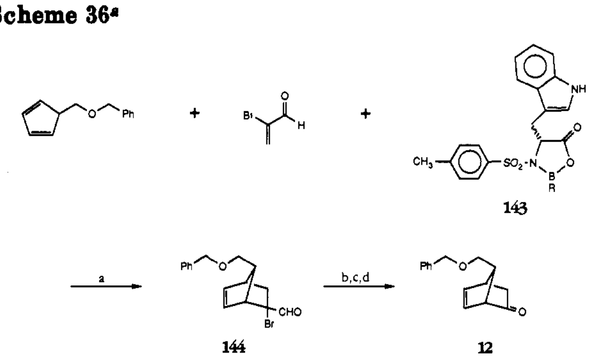
[a] (a) *t*-BuLi, Et_2O. (b) $Cr(CO)_6$. (c) Bu_4NF. (d) MeCOBr. (e) (f) *n*-Bu_2O, 190 °C, 2 h. (g) *n*-BuLi, HMPA, Ph_3SnCl, methyl 7-iodohept-5-enoate, 35 h.

141. Thermolytic ring expansion of 141 in *n*-butyl ether at 190 °C efficiently (85%) generated the *trans*-vinylcyclopentenyl ether 142. Installation of the α-chain was accomplished by treatment of the enolate of 142 with the appropriate allyl iodide.

4. Catalytic Enantioselective Diels–Alder Reactions

Furthering his work on catalytic enantioselective Diels–Alder reactions and their application to PG synthesis, Corey has recently reported[88] a highly efficient synthesis of key intermediate 12 (Scheme 4) in 92% ee (Scheme 36). Diels–Alder reaction of

Scheme 36[a]



[a] (a) −78 °C, 8 h, CH_2Cl_2. (b) NH_2OH. (c) TsCl, pyridine. (d) Aqueous NaOH.

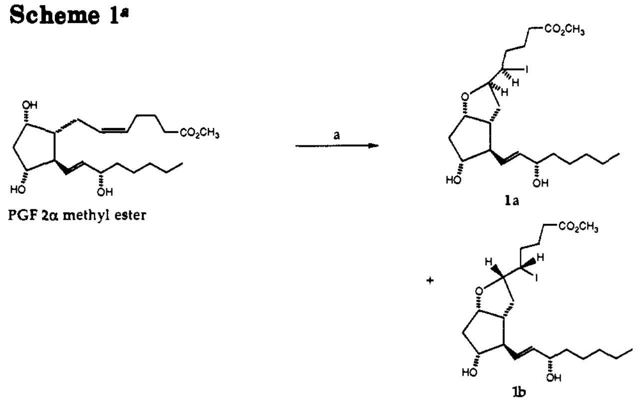
2-bromoacrolein and 5-[(benzyloxy)methyl]cyclopentadiene in the presence of 5 molar % of the catalyst 143 afforded the adduct 144 in 83–85% yield, 95:5 exo/endo aldehyde, and greater than 96:4 enantioselectivity. The minor endo aldehyde was removed by treatment with silver nitrate and then silica gel chromatography. The major aldehyde 144 was transformed into 12 by a two-flask sequence involving oxime formation and bromide solvolysis with aqueous hydroxylamine, tosylation and elimination to the cyanohydrin and base hydrolysis. The catalyst was prepared from *N*-(*p*-tolylsulfonyl)-(*R*)-tryptophan and either butylboronic acid (143, R = Bu) or borane in THF (143, R = H).

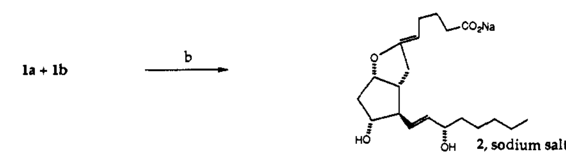
III. Prostacyclin Analogs

A. Background

Prostacyclin (2, Scheme 1) was discovered by Vane and co-workers in 1976 while examining the biochemical conversion of prostaglandin H_2 (PGH_2) by hog aorta

Scheme 1[a]





PGI$_2$ sodium salt

[a] (a) 1.1 equiv, I_2, $NaHCO_3$, Et_2O, room temperature. (b) NaOMe, MeOH, then 1 N NaOH.

microsomes.[87] The structure of 2 was subsequently characterized by Johnson and co-workers at Upjohn in collaboration with the Vane group.[88] 2 is an extremely potent vasodilator and inhibitor of platelet aggregation and has been implicated in the regulation of vascular tone and haemostasis.[89] Once discovered, it was clear that 2 might well have many clinical applications for the management of thromboembolic disorders, including cardiopulmonary bypass, Raynaud's phenomenon and heart failure, and the last 10 years have witnessed the evaluation of 2 in numerous clinical trials. The data from these trials has been recently and thoroughly reviewed.[90]

Due to the inherent chemical instability of crystalline PGI_2 sodium salt[91] and the difficulties associated with the clinical application of highly alkaline solutions (pH = 10.5)[92] necessary to ensure some degree of chemical stability, it seems likely that prostacyclin will not find widespread clinical usage. This perception presaged a veritable torrent of activity within the pharmaceutical industry toward the identification of chemically and metabolically stable analogs of 2 for development as clinically effective antithrombotic agents. This part of the review will focus on a select number of analogs of 2 (Table 2) that have received considerable pharmacologic scrutiny and describe the synthetic routes developed to access these novel agents. As much as possible, overlap with the excellent reviews of Aristoff[93] and Vorbrüggen[94] will be avoided. For organizational purposes the material will be divided into two sections: (A) drugs that are/or have been in clinical trials; (B) drugs in preclinical development. For the reader's convenience, the schemes and compounds have been numbered separately from the prostaglandin portion of this review.

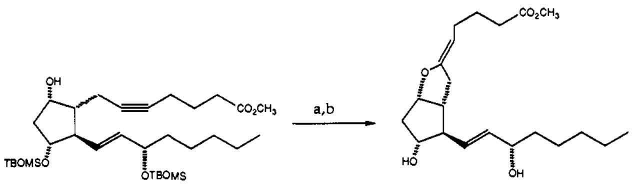
B. Synthesis

1. Epoprostenol

PGI_2 2, a.k.a. epoprostenol, has been launched in Great Britain as "Flolan" by the Wellcome group. Flolan is an injectable form of 2 for applications as an adjunct in renal dialysis, charcoal hemoperfusion, and cardiopulmonary bypass.

The original syntheses of 2 were described by an Upjohn group[95] and Whittaker[96] at Wellcome. The Whittaker synthesis is shown in Scheme 1. The key features of the synthesis were, of course, the iodocyclization reaction to produce diastereoisomeric pair **1a** and **1b** and their subsequent base-induced dehydrohalogenation to afford exclusively the desired (*Z*)-olefin present in PGI_2. Conversion to the sodium salt 2 was achieved by sodium hydroxide mediated hydrolysis. Noteworthy is the fact that the dehydrohalogenation step and the hydrolysis steps were achieved in one pot. Prepared in this manner, 2 can be dried and stored for at least 2 months at −30 °C. A more recent access to 2 was reported by the Noyori group[97] and is illustrated in Scheme 2.

Scheme 2[a]



TBDMS = tert - butyldimethylsilyl

[a] (a) $Hg(OCOCF_3)_2$, Et_3N, THF, −78 °C followed by 1 N NaOH, MeOH, $NaBH_4$ (5 equiv), −78 °C. (b) *n*-Bu_4NF, THF.

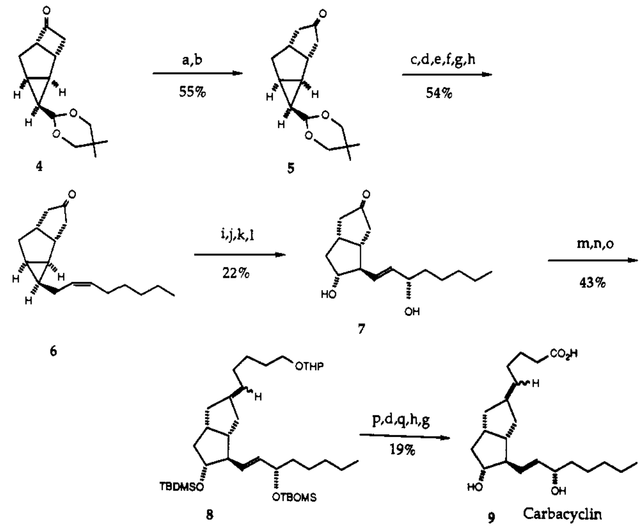
The acetylenic alcohol 3 was prepared in four steps from (*R*)-4-(*tert*-butyldimethylsiloxy)-2-cyclopentenone using the group's trademark tandem organocopper conjugate addition/aldol reaction[98] as a key step. This new procedure relied heavily on the stereospecificity of the reductive demercuration of vinylmercurys. In this manner, the stereospecific construction of the (*Z*)-2-alkylidenetetrahydrofuran was achieved through the auspices of the intramolecular oxymercuration of acetylenic alcohol 3 in a 5-exo-dig manner followed by reductive demercuration with sodium borohydride. The overall yield for Scheme 2 was >80% for the two steps.

2. Carbacyclin

As the inherent chemical lability and route of administration of epoprostenol severely restrict the therapeutic utility of the drug, a major effort within the pharmaceutical industry has been dedicated toward finding a stable analog of 2. In addition, it has been considered desirable by clinicians that such an analog should also be able to exert antithrombotic effects without displaying untoward hypotensive effects.

Without doubt, the major efforts in this area have been focused on carbacyclic analogs of 2 of which carbacyclin 9 itself is the progenitor. Carbacyclin has been shown to exhibit a pharmacodynamic profile similar to 2. It is, for example, a potent inhibitor of platelet aggregation,[99] a vasodilator[100] and an inhibitor of gastric acid secretion.[101] Human studies have shown that 9 is effective, when administered orally, at inhibiting platelet aggregation; however, side effects were observed at doses at which a clinical effect was observed. These included headache, facial flush, tachycardia, and

Scheme 3[a]

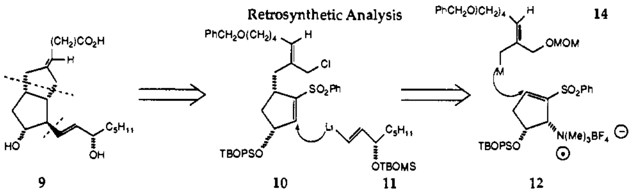


[a] (a) $(CH_3)_2S(O)CH_2Na$, Me_2SO, THF. (b) LiI, DMF. (c) $NaBH_4$, EtOH. (d) Ac_2O, 4-DMAP. (e) HCO_2H, 0 °C. (f) $Ph_3P{=}CH(CH_2)_4CH_3$, $PhCH_3$. (g) KOH, CH_3OH/H_2O. (h) H_2CrO_4, acetone, −20 °C. (i) OsO_4, NMNO, acetone, *t*-BuOH. (j) $CH_3CH_2C(OEt)_3$, pyridine HCl, $PhCH_3$. (k) HCO_2H. (l) K_2CO_3, CH_3OH/H_2O. (m) TBDMS chloride, imidazole, DMF. (n) $THPOCH_2(CH_2)_3CH_2S(O)(NMe)Ph$ MeMgBr, THF, −20 °C. (O) Al(Hg), THF, HOAc, H_2O. (p) *n*-Bu_4NF, THF. (q) HOAc, H_2O, THF, Δ.

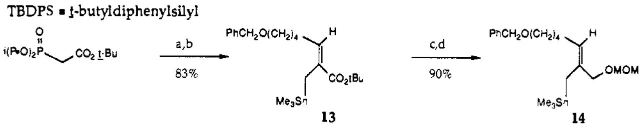
changes in blood pressure[102] and have as such precluded the use of carbacyclin as a clinically useful agent for the treatment of thrombotic disorders.

The synthesis of carbacyclin was first reported in 1978 independently by four groups[103–106] and the first asymmetric synthesis in 1979 by a group from Upjohn.[107] This synthesis is outlined in Scheme 3. Key features included (a) ring expansion of the optically pure cyclobutanone 4 to the cyclopentanone 5 via its oxirane derivative and its subsequent conversion to the critical bicyclo[3.3.0]octane 7 and (b) elaboration of the upper side chain using sulfoximine addition/elimination chemistry to afford the olefin mixture 8. This synthesis also illustrates the two major problems associated with any synthetic undertaking in the carbacyclin arena, namely, the construction of the relevant bicyclo[3.3.0]octanone nucleus and the control of the 5(*E*)-olefin geometry present in 9 and its congeners.[108] Several ingenious approaches toward the solution of these problems have been documented and some recent efforts are included here. One of the most notable of these syntheses has been communicated by Fuchs et al.[109,110] and is illustrated in Scheme 4. This chemodirected, triply convergent synthesis of *d*-(+)-carbacyclin addresses both major problems cited previously. Treatment of *tert*-butyl bromoacetate with triisopropyl phosphite under Arbusov conditions afforded a 95% yield of the phosphonate ester which was subsequently deprotonated with sodium hydride in THF followed by reaction with trimethyliodomethylstannane to provide the requisite stannane. This material was deprotonated upon exposure to sodium hydride in THF and then treated with 5-(benzyloxy)pentanal to afford the vinyl ester 13 in a highly selective manner (96:4). Reduction of 13 followed by protection of the pendant alcohol as its MOM ether produced the key allyl stannane 14. Conversion of 14 to its corresponding "trimethylenemethane" reagent was accomplished by treatment with *n*-butyllithium. Subsequent treatment with copper(I)

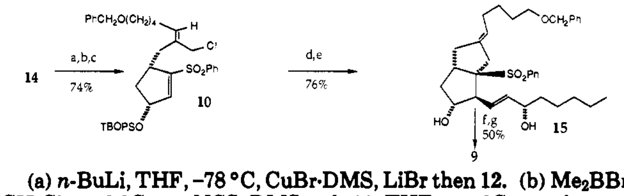
Scheme 4. Retrosynthetic Analysis



TBDPS = t-butyldiphenylsilyl



(a) NaH, THF, Me_3SnCH_2I. (b) NaH, THF, cat. H_2O, $PhCH_2O(CH_2)_4CHO$. (c) DIBAL-H, CH_2Cl_2, 25 °C. (d) $MeOCH_2Cl$, i-Pr_2NH, 0 → 25 °C.



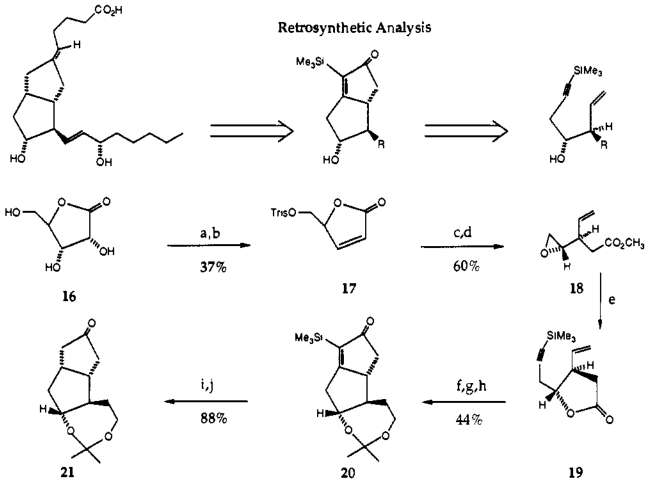
(a) n-BuLi, THF, −78 °C, CuBr·DMS, LiBr then 12. (b) Me_2BBr, CH_2Cl_2, −78 °C. (c) NCS, DMS. (d) 11, THF, −78 °C, 15 mins, −50 °C, 10 mins. (e) n-Bu_4NF, THF. (f) 20 equivs of Li/NH_3. (g) Pt/O_2, acetone/water, $NaHCO_3$, 57 °C.

bromide complex provided the corresponding cuprate reagent which upon addition of optically pure 12[110] afforded the desired coupled product which was converted to allyl chloride 10 by subsequent sequential treatment with dimethylboron bromide in dichloromethane, and N-chlorosuccinimide/dimethyl sulfide (Corey–Kim procedure). Coupling of 10 with the well-known chiral vinyl lithium reagent 11 proceeded smoothly, affording, after treatment with tetra-n-butylammonium fluoride in THF, the diol sulfone 15. Treatment of 15 with lithium in ammonia effected concomitant debenzylation and desulfonylation to afford the expected triol which was oxidized to carbacyclin using the procedure of Fried.[111]

An interesting approach to the bicyclo[3.3.0]octanone nucleus in homochiral form has been reported by the Magnus group[112] and is outlined in Scheme 5. The approach relies significantly upon a crucial intramolecular Pauson–Khand cobalt octacarbonyl mediated cyclization reaction of intermediate 19. Briefly, D-(+)-ribonolactone (16) was converted into the butenolide 17 by pyrolysis of the derived ortho ester and subsequent trisylation. 17 was transformed into oxirane 18 upon exposure, firstly to lithium divinylcyanocuprate, and then methanolic potassium carbonate. Conversion to lactone 19 was accomplished by reaction of 18 with lithium (trimethylsilyl)acetylide in the presence of boron trifluoride etherate. The lactone was reduced with lithium aluminum hydride to afford the anticipated diol which was protected as its acetonide derivative under standard conditions. When this material was subjected to Pauson–Khand cyclization conditions, bicyclo[3.3.0]octenone 20 was formed in a highly stereoselective process. Conversion of 20 into carbacyclin precursor 21 was achieved by sequential reduction and desilylation.

Other recent approaches to the synthesis of the ubiquitous bicyclo[3.3.0]octane building block for carbacyclin synthesis have highlighted the use of enzymes or microorganisms to access key intermediates.[113,114]

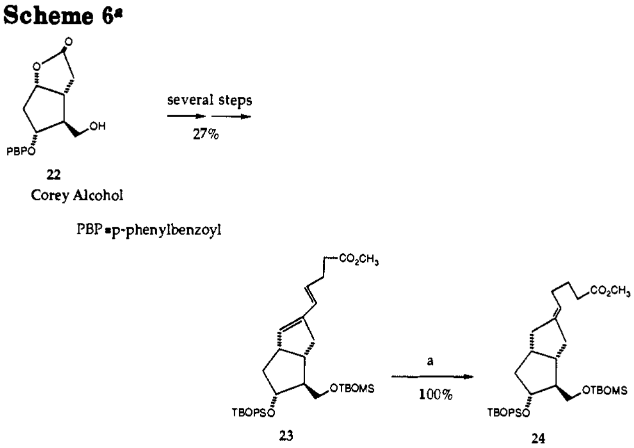
Scheme 5.[a] Retrosynthetic Analysis



[a] (a) $HC(OEt)_3$, then Δ, 200 °C, 40 mmHg. (b) Trisyl bromide, pyridine, 0 °C. (c) $Li_2(CH_2{=}CH)_2CuCN$, Et_2O, −78 °C. (d) K_2CO_3, MeOH. (e) Li—≡—$SiMe_3$, $BF_3·OEt_2$, THF, −78 °C. (f) $LiAlH_4$, Et_2O. (g) Acetone, PhH, p-TsOH, 4A sieves. (h) $Co_2(CO)_8$, heptane, then n-Bu_3PO, heptane, 85 °C, 3 days. (i) H_2, 5% Pd/C, EtOAc. (j) n-Bu_4NF, THF/H_2O.

Efforts to control the 5(E)-olefinic stereochemistry present in 9 have been reported.[115,116] An efficient synthesis of 9 was described in which the stereospecific 1,4-hydrogenation of a 1,3-diene to an internal monoene plays a key role. Diene–carbacyclin derivative 23 (Scheme 6), obtained from the Corey alcohol 22, in 27%

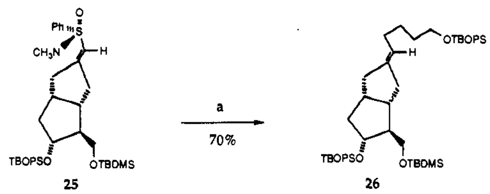
Scheme 6[a]



[a] (a) MBZ–$Cr(CO)_3$ (MBZ = methyl benzoate), H_2 (70 kg/cm^2), acetone, 120 °C, 15 h.

overall yield (multistep procedure) was hydrogenated in the presence of methyl benzoate and chromium tricarbonyl (20 molar %). The desired (E)-disubstituted olefin 24 was formed in essentially quantitative yield and converted to carbacyclin itself, using standard protocol. Gais and co-workers have described a stereoselective route to the carbacyclin framework based on the nickel-catalyzed cross-coupling of alkenyl sulfoximines with organometallics. The process is illustrated in Scheme 7. Alkenyl sulfoximine 25 was treated with the appropriate four-carbon-containing dialkylzinc in the presence of 2 equiv of magnesium bromide and 1,3-bis(diphenylphosphino)propane nickel(II) chloride at 0 °C for 5 days to give a 70% yield of the carbacyclin precursor 26 containing only 1% of the Z-isomer.

Scheme 7[a]



[a] (a) $Zn((CH_2)_4OTBDPS)_2$, $MgBr_2$, $NiCl_2(dppp)$, 0 °C, Et_2O, 5 days.

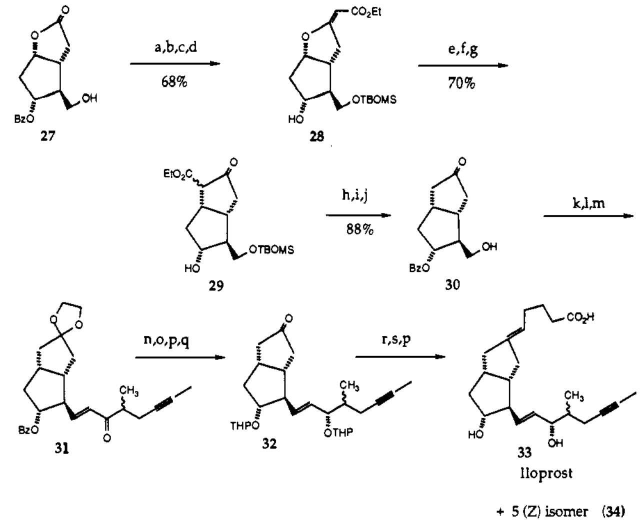
3. Iloprost

Iloprost (**33**) is a stable epoprostenol analog from the carbacyclin genus that is being developed by Schering AG for ischemic heart disease and peripheral vascular disease. An injectable form is registered in New Zealand. It is licensed to Italfarmo for Italy (to be launched as Endoprost) and Esai for Japan. A topical form for skin ulcers is scheduled for launch in 1994.

Preclinical experiments have revealed that iloprost has similar potency to epoprostenol as an antiplatelet and hypotensive agent. In phase I clinical trials, **33** was effective in terms of inhibition of *ex vivo* platelet aggregation after intravenous (iv) or oral administration in healthy volunteers. Clinical studies have demonstrated its therapeutic efficacy in peripheral arterial occlusive disease and patients with Raynaud's phenomenon.[117] The pharmacokinetics of the compound were characterized primarily by strictly dose-dependent plasma levels after iv infusion and half lives of disposition from plasma of 3–5 (α-phase) and 20–30 min (β-phase). The total clearance of iloprost was approximately 15–20 mL min^{-1} kg^{-1}. Metabolic degradation was subject to the general principle of fatty acid metabolism, i.e., β-oxidation.[118] The structure of iloprost is characterized by its unique 16-methyl, alkynyl ω-chain. The methyl substituent at C-16 retards metabolism by the 15-PGDH pathway.

Schering have reported several distinct syntheses of iloprost.[119] One of the more recent of these is shown in Scheme 8.[120] Lactone **27**, after protection as its corresponding *tert*-butyldimethylsilyl (TBDMS) ether, was condensed with lithiated ethyl acetate and the product treated sequentially with *p*-toluenesulfonic acid and potassium carbonate in methanol to provide α,β-unsaturated ester **28**. **28** was treated with chromium trioxide in pyridine to provide the expected ketone. Next, in the key step, exposure to DBN in THF, followed by treatment with sodium borohydride and methanol afforded the bicyclo[3.3.0]octane derivative **29** in a regio- and stereocontrolled manner. Decarbethoxylation of the β-keto ester, benzoylation, and cleavage of the silyl ether yielded the ketone **30**. Starting from lactone **27** the overall yield of the ketone **30** was about 40–50%. The α- and ω-chains were incorporated as follows. The keto group of **30** was protected as its 1,3-dioxolane derivative and conversion of the primary hydroxy group to the aldehyde accomplished by treatment with Collins reagent. Homologation to the α,β-unsaturated ketone occurred smoothly upon exposure to the sodium salt of phosphonate **35** in dimethoxyethane at 0 °C. Sodium borohydride reduction, separation of the epimeric alcohol mixture, removal of the benzoate of the less polar α-carbinol by transesterification with potassium carbonate and methanol, cleavage

Scheme 8[a]



[a] (a) TBDMSCl, DMF, imidazole. (b) $LiCH_2CO_2Et$, −70 °C. (c) *p*-TsOH. (d) K_2CO_3, CH_3OH. (e) CrO_3–py. (f) DBN, THF, 0 °C. (g) $NaBH_4$, CH_3OH, −20 °C. (h) DABCO, $PhCH_3$, Δ. (i) PhCOCl, 0 °C. (j) AcOH, H_2O, THF. (k) $HOCH_2CH_2OH$, *p*-TsOH. (l) CrO_3–py. (m) $(CH_3O)_2P(O)CH_2C(O)CH(CH_3)CH_2C{\equiv}CCH_3$ (**35**), NaH, DME, 0 °C. (n) $NaBH_4$, CH_3OH, −40 °C. (o) K_2CO_3, CH_3OH. (p) H_3O^+. (q) DHP, *p*-TsOH. (r) Wittig. (s) *E*/*Z* separation.

of the ketal unit, followed by treatment with dihydropyran in the presence of acid furnished the ketone **32**. Wittig homologation of the former afforded, after chromatographic separation, the 5(*E*)-isomer and the less polar 5(*Z*)-isomer which were converted, upon exposure to aqueous acid, to iloprost (**33**) and ZK 36375 (**34**). The configuration of the trisubstituted Δ^5-double bond was established by comparison of the biological activities of **33** and **34**. **34**, not surprisingly, was considerably less active than **33** in its ability to inhibit platelet aggregation.

Iloprost (**33**) is essentially a 1:1 mixture of 16α- and 16β-methyl diastereomers. Single isomers were obtained by resolving racemic 2-methylhexynoic acid via its optically active (−)-cinchonidin and (+)-3-(aminomethyl)pinane salts. The absolute configurations of the resulting optically active acids were determined by hydrogenation to 2(*R*)- and 2(*S*)-methylhexanoic acids, the absolute configurations of which are known. The homochiral acids were subsequently transformed into the 16(*S*)- and 16(*R*)-isomers of iloprost. The 16(*S*)-isomer was approximately 5 times as potent as the 16-(*R*)-isomer as an inhibitor of ADP-induced platelet aggregation.

4. Cicaprost

Cicaprost (**40**) is a metabolically stable, orally active carbacyclin analog developed by Schering AG as a second-generation congener of iloprost. It is in phase II clinical trials in Europe for cardiovascular indications including the treatment of Raynaud's phenomenon.

40 is a potent inhibitor of platelet aggregation in human platelet rich plasma and is essentially equipotent to iloprost in its affinity for the PGI_2 receptor and has been claimed to show a better separation of antiplatelet versus hypotensive effects in animals. **40** was designed as a metabolically stable analog of iloprost and was engineered to contain the 3-oxa group in order to negate

Table 2

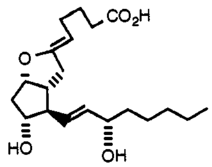
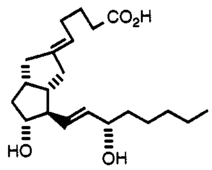
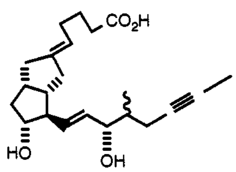
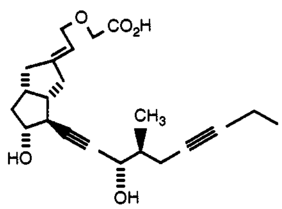
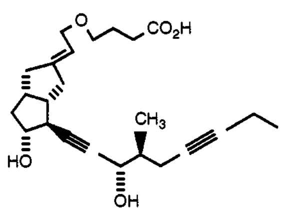
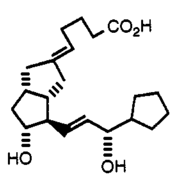
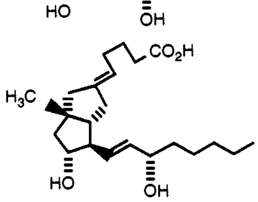
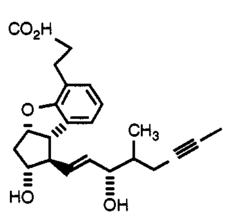
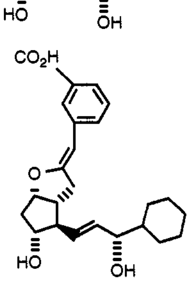
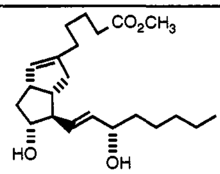
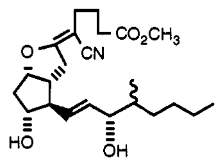
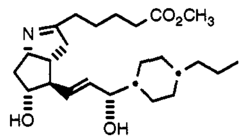
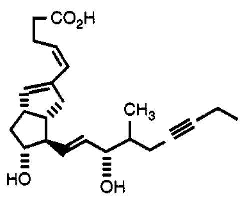
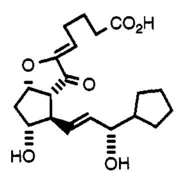
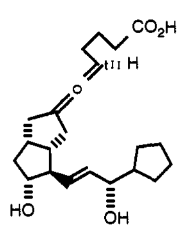
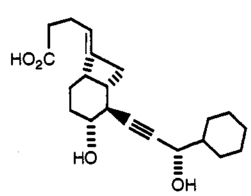
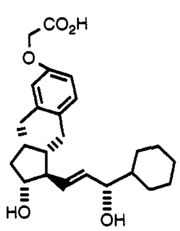
compound	structure	company	code no.	therapeutic indication	clinical/market status
Epoprostenol		Upjohn/Wellcome	ZK-36374	antithrombotic	marketed: Flolan
carbacyclin		Upjohn/Wellcome	ZK-96480	antithrombotic	dropped
iloprost		Schering AG/Eisai	ZK-97951	peripheral vascular disease	registered
cicaprost		Schering AG	OP-41483	antithrombotic	phase II
eptaloprost		Schering AG	U-61431	antithrombotic antimetastatic	phase I
ataprost		Ono/Dainippon	TRK-1000	antithrombotic	phase III
ciprostene		Upjohn/Wellcome	CG-4203	antithrombotic	phase II/dropped
beraprost		Toray/Kaken		antithrombotic	registered
taprostene		Gruenenthal	ZK-34,798	antithrombotic, sudden hearing loss	phase II

Table 2 (Continued)

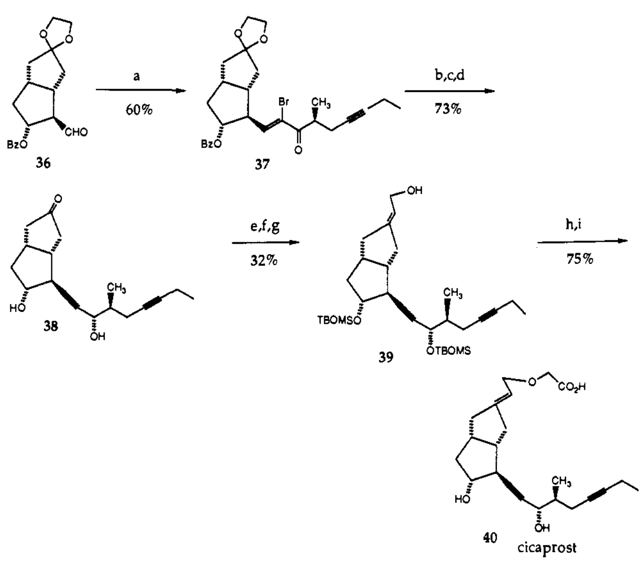
compound	structure	company	code no.	therapeutic indication	clinical/market status
lipo-isocarbacyclin		Teijin/Taisho	TTC-909	antithrombotic	phase II
nileprost		Schering AG		antiulcer	dropped
		Ono	OP-2507	antihypoxic	dropped
		Mitsubishi/Kasei	KP-10614	antithrombotic	preclinical
		Chinoin	CH-5084	antithrombotic	preclinical
		Searle	SC-43350	antithrombotic	preclinical
		Syntex	RS-93427	antithrombotic	preclinical
		Upjohn	U-68,215	antiulcer	preclinical

β-oxidation. The relatively short duration of action of iloprost after oral administration is due to rapid metabolism primarily by β-oxidation ($t_{1/2}$ = 20–30 min). In phase I study, the tolerability, pharmacodynamics, and pharmacokinetics of cicaprost have been investigated. The compound was characterized by complete oral bioavailability, a terminal half-life in plasma of 1–2 h, a total clearance of 4–5 mL min^{-1} kg^{-1}, and metabolic stability in plasma and urine.[121]

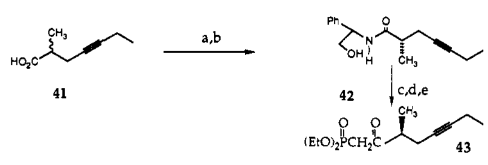
Another potential avenue for therapeutic exploitation of **2** is in the area of tumor metastasis since an involvement of platelet aggregation has been found in the metastatic process. **40**, in this context, has been shown to be a potent inhibitor of tumor metastases in different tumor models in rodents.

The synthesis of cicaprost has been described by the Schering group[122] and is outlined in Scheme 9. Initially, the ω-side chain was prepared by resolving racemic

Scheme 9



(a) **43**, NaH, DME, NBS, −20 °C. (b) $NaBH_4$, MeOH, −40 °C, then separation of epimers. (c) 50% aqueous NaOH, $PhCH_3$, n-Bu_4HSO_4, 25 °C. (d) HOAc, H_2O. (e) TBDMS chloride, imidazole, DMF. (f) $(EtO)_2P(O)CH_2CO_2Et$, KO-t-Bu, THF, 0 °C. (g) DIBAL-H, $PhCH_3$, 0 °C, separation of (E)-isomers. (h) $BrCH_2CO_2$-t-Bu, 50% aqueous NaOH, $PhCH_3$, cat. n-Bu_4NHSO_4. (i) n-Bu_4NF, THF, 25 °C.

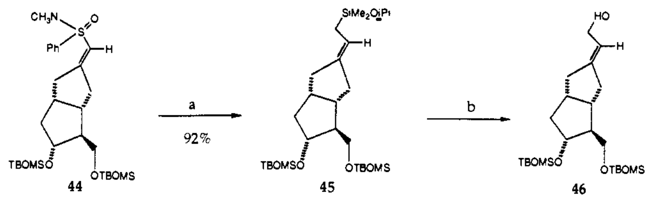


(a) PCl_3. (b) D-(−)-α-Phenylglycinol. (c) 3 N H_2SO_4, dioxane. (d) CH_2N_2, Et_2O. (e) $LiCH_2P(O)(OEt)_2$.

2-methyl-4-heptynoic acid (**41**). By using the method of Helmchen and co-workers,[123] **41** was converted via its acid chloride to a pair of diastereomeric D-(−)-α-phenylglycinol derived amides which could be separated on silica gel. The more polar amide **42** was hydrolyzed (3 N H_2SO_4 in dioxane) to afford the 2(S)-acid. Esterification with ethereal diazomethane followed by reaction of the methyl ester with the lithium salt of ethyl methylphosphonate afforded the optically pure phosphonate **43**. Condensation of the sodium salt of **43** with the known aldehyde **36**[120] in the presence of N-bromosuccinimide furnished the α,β-unsaturated bromo ketone **37** in 60% yield. Reduction with sodium borohydride, chromatographic separation of the 1:1 mixture of allylic alcohols, dehydrobromination and concomitant saponification of the benzoate group followed by ketal hydrolysis afforded ketone **38**. **38** was protected as its bis-TBDMS ether and then subjected to Horner–Wittig homologation using triethylphosphonoacetate. Reduction of the 1:1 mixture of isomeric α,β-unsaturated esters with DIBAL-H provided allylic alcohol **39** after separation from its unwanted (Z)-isomer. Etherification of **39** with *tert*-butyl bromoacetate under phase transfer conditions was accompanied by simultaneous cleavage of the *tert*-butyl ester followed by deprotection of both carbinols with tetra-n-butylammonium fluoride to afford cicaprost (**40**).

It is evident that the major problem associated with this synthesis (as in the carbacyclin synthesis itself) is the lack of stereoselectivity in the attachment of the upper side chain to the bicyclo[3.3.0]octane ring. Attempts to solve this dilemma through Horner–Wadsworth–Emmons (HWE) reactions of the key bicyclic ketone with chiral lithio phosphonoacetates have not been entirely satisfactory with regard to selectivity.[124,125] A potential solution to this problem has recently been disclosed by Gais and co-workers[126] and is shown in Scheme 10. The key steps involve Gais's trademark nickel/magnesium catalyzed cross-coupling reaction of the alkenyl sulfoximine **44** with diorganozinc reagent **47** followed by transformation of the resultant allylsilane to an alcohol through the auspices of the excellent Tamao–Kumada hydroxyalkylation protocol.[127] An impressive E/Z ratio was obtained from the sulfoximine coupling reaction with only 1% of the (Z)-isomer being formed. Whether this process will prove amenable to the industrial-scale preparation of cicaprost remains, at present, a matter of conjecture.

Scheme 10[a]



[a] (a) $Zn(CH_2SiMe_2O$-i-$Pr)_2$ (**47**), $NiCl_2$(dppp) (20 molar %), $MgBr_2$ (3 equiv), Et_2O, 25 °C. (b) 30% H_2O_2, THF/MeOH, $KHCO_3$, 70 °C.

5. Eptaloprost

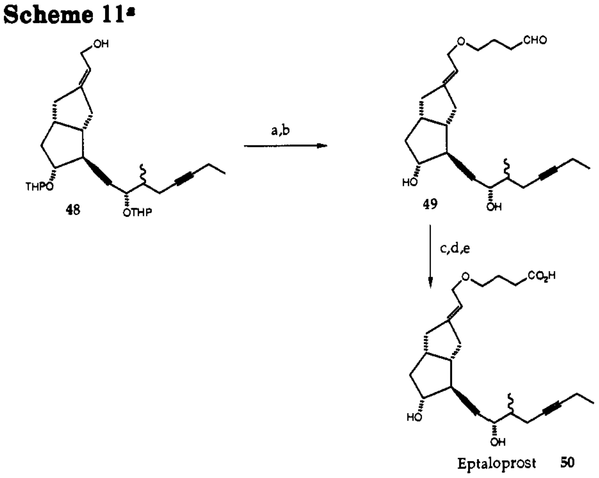
Eptaloprost (**50**) is a metabolically stable, orally active carbacyclin analog also out of the Schering stable. It appears to be their third generation iloprost congener and is currently in phase I clinical trials in Europe for cardiovascular indications. Interestingly enough, the majority of the preclinical pharmacology published on this compound has been from studies in *in vivo* tumor models.[128] Eptaloprost is a prodrug of cicaprost which is converted to the pharmacologically active agent by a single-step of β-oxidation.[129] **50** is a much weaker inhibitor of ADP induced platelet aggregation than cicaprost *in vitro* (IC_{50} = 703 nm versus 0.64 nm cicaprost); however, in *in vivo* experiments in rats, both compounds showed comparable activity in inhibiting platelet aggregation (induced by ADP) when given by iv infusion.

Although no definitive publication has appeared on the design and synthesis of eptaloprost, a synthesis of the compound is available through the German patent literature[130] and is outlined in Scheme 11. Intermediate **48**, obtained in a similar manner to intermediate **39** used for the cicaprost synthesis, was alkylated with 1,1-diethoxy-4-bromobutane in THF at reflux and then the protecting groups were removed by acid-catalyzed hydrolysis to provide diol–aldehyde **49**. Acetylation followed by Jones oxidation and saponification afforded eptaloprost (**50**).

6. Ataprost

Ataprost (**57**) is a carbacyclin derivative currently under joint development by Ono and Dainippon in Japan. It inhibits human platelet aggregation induced by ADP, collagen, and arachidonic acid, although it is

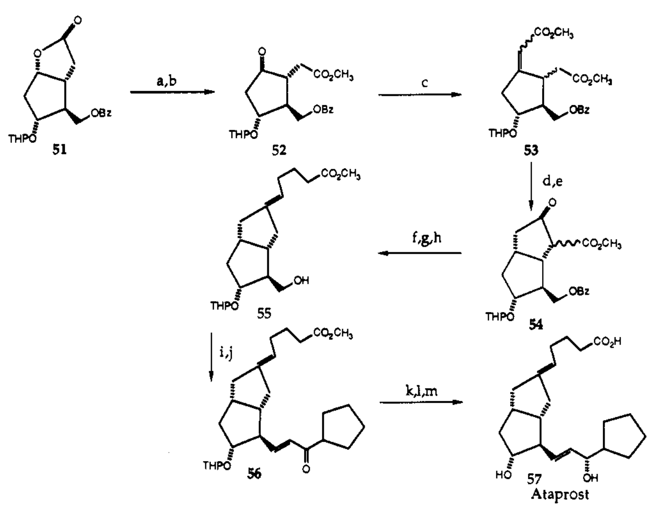
Scheme 11[a]



[a] (a) NaH, THF, 24 °C, 30 min then $Br(CH_2)_3C(OEt)_2$, THF, Δ. (b) AcOH, THF, H_2O, 6/5:3/5:1. (c) Ac_2O, pyridine. (d) Jones' oxidation. (e) K_2CO_3/MeOH.

only about 1/10th as potent as prostacyclin in this regard. However, the compound, at equiactive anti-aggregatory doses, has less hypotensive activity than PGI_2.[131] 57 is currently in phase III clinical trials for peripheral vascular disease.[132-134] The maximum tolerated dose was 2.5 ng kg^{-1} min^{-1} when administered iv or 200 mg given orally. Higher doses caused flushing, headache, and phlebitis but no changes in blood pressure or heart rate. Ataprost is characterized, in a structural sense, by its 15-cyclopentyl group. Introduction of this group has been shown, in analogy with the introduction of the 16-methyl group into the carbacyclin framework, to retard oxidation of the 15-hydroxyl group to the corresponding ketone via the 15-PGDH pathway. Several routes to the synthesis of **57** have been described; however, all these reports have, with one exception, emanated from the patent literature.[135] The one exception was a report from the Shibasaki group[115] once again demonstrating the utility of their procedure for the stereocontrolled synthesis of exocyclic olefins using arenetricarbonylchromium complex catalyzed hydrogenation and its application to carbacyclin synthesis. The synthesis shown in Scheme 12 is taken from the United States patent literature.[136] Corey lactone congener **51** was ring opened with sodium hydroxide and the resultant hydroxy acid esterified using ethereal diazomethane. Subsequent treatment with Etards reagent in carbon tetrachloride afforded keto ester **52**. Peterson olefination using the lithium enolate derived from methyl (trimethylsilyl)acetate provided the olefinic mixture **53** which was transformed to the cyclic β-keto ester by sequential treatment with hydrogen gas in the presence of 5% palladium on carbon and potassium *tert*-butoxide in refluxing benzene. Keto ester **54** was smoothly decarboxmethylated in aqueous hexamethylphosphoric triamide at 175 °C and the benzyloxy protecting group removed by catalytic hydrogenolysis under acidic conditions. Olefination to provide ester–carbinol **55** was achieved upon exposure to the Wittig type ylide derived from (4-carboxybutyl)-triphenylphosphonium bromide. Chromatographic separation of the unwanted olefinic regioisomer provided pure **55**. Collins oxidation followed by HWE homologation to introduce the ω-chain proceeded uneventfully using standard protocols to generate enone **56**. Removal of the tetrahydropyranyl protecting group

Scheme 12[a]



[a] (a) CH_3OH, NaOH, then CH_2N_2. (b) CrO_2Cl_2, CCl_4. (c) $(CH_3)_3SiCH_2CO_2CH_3$, LDA, THF, −78 °C. (d) H_2, 5% Pd/C. (e) KO-*t*-Bu, PhH, Δ. (f) HMPA/H_2O, 175 °C. (g) H_2, 5% Pd/C, H^+. (h) $NaCH_2S(O)CH_3$, DMSO $Ph_3PCH_2(CH_2)_3CO_2H$, Br. (i) CrO_3–pyridine. (j) $(MeO)_2P(O)CH_2CO$-c-C_5H_9, NaH, THF. (k) HOAc/THF/H_2O, 3:1:1. (l) $NaBH_4$, CH_3OH, −20 °C. (m) NaOH, MeOH, H_2O.

followed by reduction with sodium borohydride and subsequent saponification afforded ataprost (**57**).

7. Ciprostene

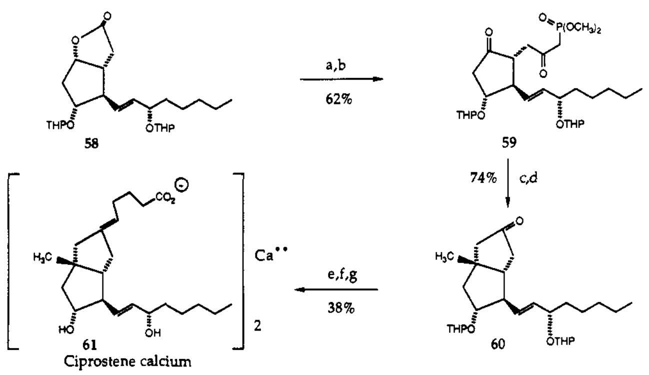
Ciprostene calcium (**61**), a 9β-methyl derivative of carbacyclin has been jointly evaluated by Upjohn and Wellcome as an antithrombotic agent and data from phase II clinical trials have been published.[137-139] This agreement has, however, been terminated and further evaluation of the compound seems to have been suspended.

The pharmacodynamics of **61** in healthy volunteers have, however, been reported.[140] The data demonstrated that this compound has similar pharmacological activity to prostacyclin including the effects on platelet function and heart rate although the compound is approximately 100 times less potent. A randomized, double-blind study investigated the effect of **61** in patients with peripheral vascular disease characterized by ischemic ulcers. A total of 106 patients received iv infusions of ciprostene calcium (120 mg kg^{-1} min^{-1} in 8-h daily infusions for 7 days). Good tolerance and safety of **61** were documented in this patient population; however, disappointingly, the therapeutic benefit was limited to partial reduction of ulcer size.[141]

Ciprostene is distinguished structurally by its 9β-methyl group which is, in fact, its only variation from the standard carbacyclin framework. **61** was selected from a series of 9-substituted carbacyclin analogs synthesized by Aristoff and co-workers.[142] Ciprostene was chosen for development primarily because of its stability and because its pharmacological profile closely resembled that of prostacyclin. For the purposes of obtaining easily characterizable material, ciprostene was converted to its solid calcium salt and developed as such.[143] The original innovative synthesis of **61** is shown in Scheme 13.

The known lactone **58**[144] was treated with the lithio carbanion derived from dimethyl methylphosphonate and the product lactol oxidized under Jones conditions to provide keto phosphonate **59**. **59** was elegantly

Scheme 13[a]



[a] (a) *n*-BuLi, $CH_3P(O)(OMe)_2$, THF. (b) H_2CrO_4, acetone. (c) K_2CO_3, 18-crown-6, $PhCH_3$. (d) Me_2CuLi, Et_2O. (e) $Ph_3P{=}CH(CH_2)_3CO_2Na$, DMSO. (f) HOAc/THF/H_2O, 3:1:1. (g) CaO, THF, H_2O.

cyclized via an intramolecular HWE reaction to the desired bicyclic[3.3.0]enone which underwent smooth conjugate addition of dimethylcopper lithium to provide the 9-β-methylbicyclo[3.3.0]octanone **60**. **60** was converted to ciprostene calcium in a three-step procedure involving condensation with (4-carboxybutyl)triphenylphosphorane in dimethyl sulfoxide, acid-catalyzed removal of the alcohol protecting groups, and treatment with calcium oxide in THF.

8. Beraprost

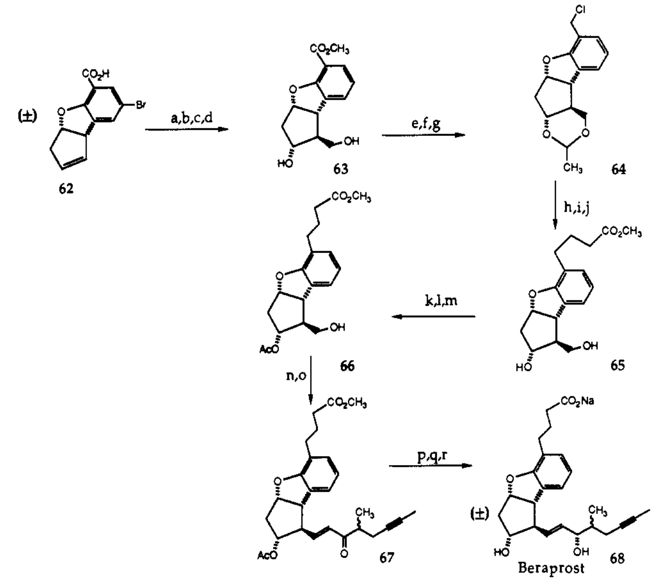
Beraprost (**68**) is an orally active antithrombotic prostacyclin derivative being developed by Toray Industries. It was launched in Japan in 1992 for use in peripheral vascular disease as "Dorner" by Toray and as "Procyclin" by Kaken Pharmaceutical. It is licensed to Marion Merrell Dow for marketing in Canada and the United States and to Roussel-Uclaf in France and Southern Europe.

Preliminary results from clinical studies have been reported. Forty-four healthy male volunteers were given single (25, 50, 100, and 200 mg) or repeated (25 and 50 mg × 3 for 10 days) oral doses of beraprost sodium salt. Following single doses, platelet aggregation induced by ADP and collagen was inhibited with a maximum effect at 1 h. After repeated administration, platelet adhesion was dose dependently reduced. The drug was generally well tolerated although facial flushing and headache was reported after single doses >50 mg and repeated doses >75 mg.[145] Beraprost was absorbed rapidly and reached peak plasma levels at 30–60 mins.[146] The drug was metabolized primarily by β-oxidation. Results from a pilot study in patients with carotid atheromatous lesions demonstrated that **68** at a dose of 40 mg 3 times daily for 4 weeks reduced platelet accumulation in carotid atheroma. The antithrombotic effect was systemic as well as local, as indicated by a decrease in ADP-induced platelet aggregation.[147]

From a structural perspective, beraprost is a hybrid carbacyclin analog combining the discoveries of the Upjohn group related to benzopyran analogs of prostacyclin[148] and the Schering group's patented ω-chain analogs exemplified by iloprost. It was selected for development due to excellent chemical stability in aqueous solution imparted by its cyclopenta[*b*]benzofuranyl skeleton.

The synthesis of **68** is elaborated in Scheme 14.[149] Prins reaction of racemic bromo acid **62** with trioxane

Scheme 14[a]



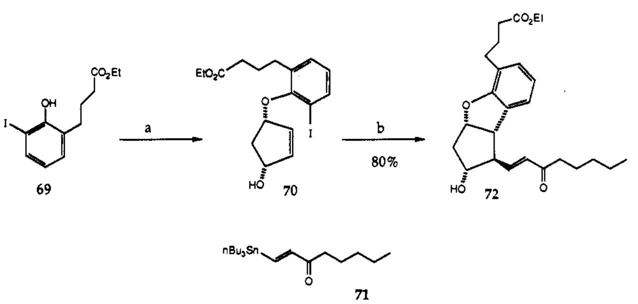
[a] (a) Trioxane, H_2SO_4. (b) 1 N NaOH. (c) CH_2N_2, Et_2O. (d) H_2, Pd/C. (e) $CH_3CH(OEt)_2$, *p*-TsOH, THF. (f) $LiAlH_4$, THF. (g) $SOCl_2$. (h) Mg, β-propiolactone. (i) CH_2N_2, Et_2O. (j) IN HCl. (k) TBDMSCl, DMF, imidazole. (l) Ac_2O, pyridine. (m) CH_3CO_2H. (n) DMSO, DCC. (o) $(MeO)_2P(O)CH_2C(O)CH(CH_3)CH_2C{\equiv}CCH_3$, NaH, DMF. (p) $NaBH_4$, $CeCl_3$, MeOH. (q) $NaOCH_3$, CH_3OH. (r) NaOH.

and sulfuric acid followed by saponification, methylation with diazomethane, and debromination with H_2 over Pd/C gave the diol **63**. The compound was protected as its ketal with 1,1-diethoxyethane in the presence of *p*-toluenesulfonic acid, and the ester was reduced with lithium aluminum hydride in THF to provide the corresponding carbinol which was converted to chloride **64** upon exposure to thionyl chloride and DMF. Sequential treatment of **64** with magnesium (to generate a Grignard reagent) and β-propiolactone produced, after esterification with diazomethane and acid hydrolysis, ester **65**. Selective acetylation of **65** by reaction with *tert*-butyldimethylsilyl chloride, then acetic anhydride and desilylation with acetic acid furnished acetate **66**. This alcohol was oxidized under modified Pfitzner–Moffatt conditions to the corresponding aldehyde which was condensed with the sodium enolate derived from dimethyl (3-methyl-2-oxohept-5-yn-1-yl)phosphonate to access α,β-unsaturated enone **67**. This material was reduced using the excellent Luche protocol to the requisite carbinol which was deacetylated and saponified under standard conditions, thereby generating racemic beraprost sodium in 18 steps from **62**.

The Toray group has recently published a modification of their original patent process.[150] One innovation which involved the resolution of bromo acid **62** with (+)-*cis*-*N*-benzyl-2-(hydroxymethyl)cyclohexylamine provided access to optically pure **68**.

The above syntheses of beraprost could be construed as being somewhat lengthy and rather pedestrian in nature. Larock and co-workers have recently reported an efficient new route to benzo prostacyclins.[151] The aryl ether **69** (Scheme 15) prepared in six steps from *o*-iodophenol was coupled with cyclopentadiene monoepoxide under Pd(O) catalysis. The requisite regio- and stereochemistry was established in this step. **70** was treated with AIBN to generate the aryl radical

Scheme 15[a]



[a] (a) Cyclopentadiene monoepoxide, 2% $Pd(Ph_3P)_4$, THF. (b) 71, AIBN, $PhCH_3$, 90 °C, 12 h.

which was trapped *in situ* by the β-stannyl enone 71 to provide the beraprost analog precursor 72 in a highly effective manner. It seems reasonable that this result may well presage the application of this methodology to the synthesis of beraprost itself.

9. Taprostene

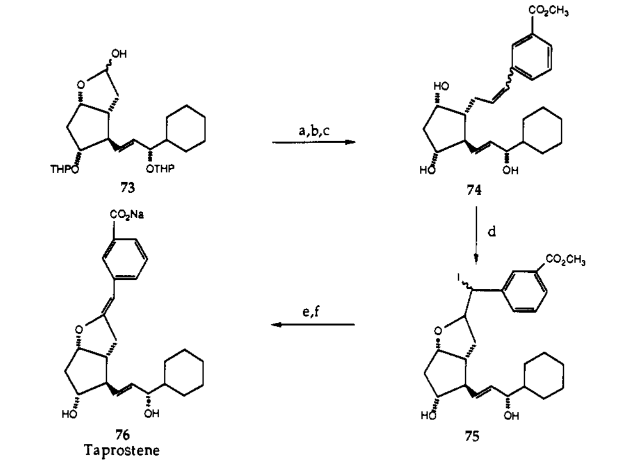
Taprostene (76) is an epoprostenol analog currently being developed by Grünenthal GmbH for cardiovascular indications including peripheral vascular disease (PVD), and as a replacement for heparin in hemodialysis patients.

76 has shown a promising *in vitro*[152] and *in vivo*[153] profile as an antiplatelet agent in man (in phase I and II studies). In a randomized double-blind study taprostene (iv, 25 ng kg^{-1} min^{-1}) was administered to patients with PVD for 6 h on 5 consecutive days resulting in prolongation of platelet half-life and improvement in absolute and relative walking distance as determined by exercise testing on a treadmill.[154] The drug was, reportedly, well tolerated. 76 exhibits dose-dependent inhibition of ADP-induced platelet aggregation, which is approximately 20% of the inhibitory effect of PGI_2.[155] The antiaggregatory activity was further demonstrated *ex vivo* up to 90 minutes after iv infusion into volunteers.[156] Results from a phase II trial in patients with sudden hearing loss have recently been reported.[157]

From a structural standpoint the taprostene architecture is denoted by its 2,3,4-trinor-1,5-inter-*m*-phenylene containing α-chain and the characteristic 16-substituent incorporated into the ω-chain in order to block 15-PGDH and ω-20 hydroxylase activity. In taprostene, the cyclohexyl group was chosen for this task and the rationale and medicinal chemistry pertaining to the identification of this compound have been described by the Grünenthal group.[158]

One of the original syntheses of 76 is shown in Scheme 16.[159] The Wittig condensation of 73 with [(m-carboxyphenyl)methyl]triphenylphosphonium bromide by means of *n*-butyllithium in dimethyl sulfoxide gave 74 after methylation with ethereal diazomethane and removal of alcohol protecting groups with acetic acid/THF/water. Reaction of 74 with iodine and sodium bicarbonate in ether/water yielded the cyclized iodide 75 as a mixture of isomers. This material was treated with DBN in toluene at room temperature for 16 h to provide the product olefin as a mixture of geometric isomers ($Z/E = 3/2$). The isomers were separated by preparative reversed-phase chromatography. Conversion to taprostene sodium was accomplished in the usual manner (NaOH, CH_3OH/H_2O).

Scheme 16[a]



[a] (a) *n*-BuLi, DMSO, $[Ph_3PCH_2\text{-}C_6H_4\text{-}m\text{-}CO_2H]^+Br^-$, benzoic acid, room temperature, 16 h. (b) CH_2N_2, Et_2O. (c) $AcOH/THF/H_2O$, 3:1:1. (d) I_2, Et_2O, aqueous $NaHCO_3$. (e) DBN, $PhCH_3$, room temperature, 16 h. (f) NaOH, MeOH, H_2O, then chromatography.

10. Lipo-isocarbacyclin

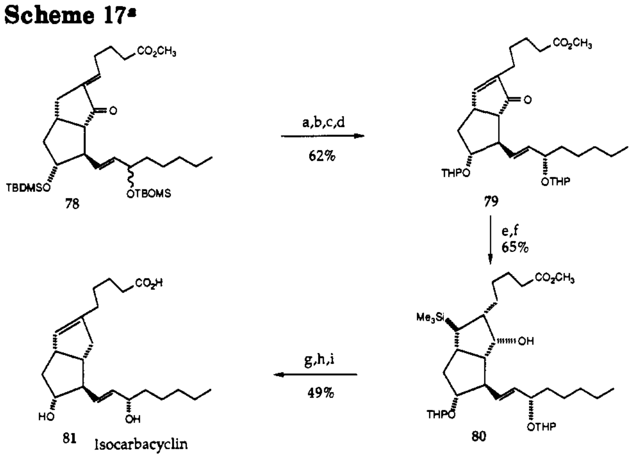
Lipo-isocarbacyclin (77) is a lipid encapsulated carbacyclin analog (isocarbacyclin methyl ester) being jointly developed by Taisho and Teijin in Japan. Taisho is providing the lipid encapsulation technology. Isocarbacyclin methyl ester (TEI-9090) has 500 times greater activity when administered iv as the liposome formulation (TTC-909).[160] 77 is currently in phase II clinical trials for application in myocardial infarction, cerebrovascular disorders, and chronic arterial obstruction.

The area of lipid microsphere-encapsulated prostaglandins has recently been reviewed with a focus on formulation, vascular delivery, pharmacology, clinical efficacy, and safety.[161] Lipo-PGE_1 and lipo-TEI-9090 are included in this review. The results from a preliminary crossover trial of lipo-isocarbacyclin in cerebral infarction have been published.[162] Seventeen patients with chronic cerebral infarction received 2 μg of 77 and placebo daily for 1 week each in a crossover double-blind study. A significant improvement was noted for 77 compared to placebo in the overall improvement in neurological and mental symptoms ($p < 0.01$). No adverse reactions were observed.

Due to its high chemical stability and its impressive antiaggregatory profile relative to carbacyclin, isocarbacyclin (6,9-carba-$\Delta^6(9\alpha)$-prostacyclin, 81) has been a particularly seductive target for practicioners of both synthetic and medicinal chemistry.

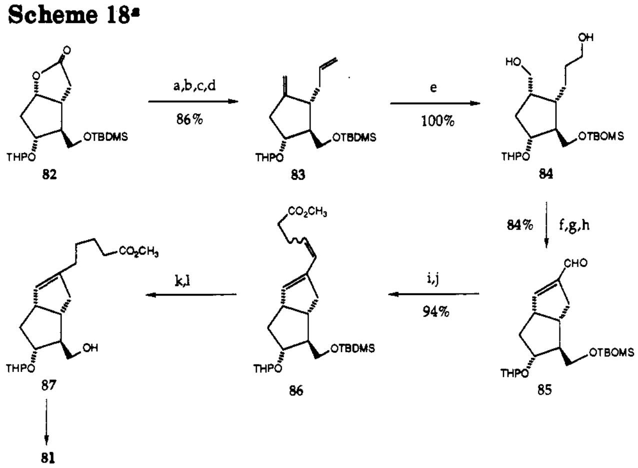
A vast number of syntheses of 81 have been reported.[163] One of Ikegami and Shibasaki's original syntheses[163b] and a route that allows for the synthesis of kilogram quantities of 81[163n] are illustrated in Schemes 17 and 18. In the former, the known ketone 78 was transformed to the *endo*-enone 79 via a four-step procedure using rhodium trichloride catalyzed double-bond migration as a key step. This enone was converted to isocarbacyclin (81) via an aesthetically pleasing sequence of reactions of which the addition of trimethylsilyl anion to 79 was pivotal. In this manner, the β-trimethylsilyl ketone was reduced with sodium

Scheme 17[a]



[a] (a) $RhCl_3 \cdot 3H_2O$, K_2CO_3, EtOH, 70 °C, 24 h. (b) n-Bu_4NF, THF. (c) Chromatography to separate C-15 epimers. (d) DHP, p-TsOH. (e) $Me_3SiSiMe_3$ (1.5 equiv), n-Bu_4NF (0.3 molar equiv), HMPA, room temperature, 30 min. (f) $NaBH_4$, MeOH, $CeCl_3$, −25 °C. (g) Trifluoromethanesulfonic anhydride, pyridine, 4-DMAP, CH_2Cl_2, 0 °C, 2 h. (h) $HOAc/H_2O$. (i) NaOH, CH_3OH.

Scheme 18[a]



[a] (a) DIBAL-H, $PhCH_3$. (b) $Ph_3P^+CH_3Br^-$, KO-t-Bu, THF. (c) PCC, NaOAc, CH_2Cl_2. (d) Zn, CH_2Br_2, $TiCl_4$, CH_2Cl_2. (e) diisoamylborane, THF, 0 °C. (f) DMSO, oxalyl chloride, CH_2Cl_2, −60 °C, then Et_3N. (g) $(PhCH_2)_2N^+H$, $CF_3CO_2^-$. (h) Δ, 70 °C, 6 h. (i) (3-Carboxypropyl)triphenylphosphonium bromide, KO-t-Bu, THF. (j) CH_2N_2. (k) 10% Pd/C, MeOH, H_2, 1 atm, 23 °C. (l) n-Bu_4NF, THF.

borohydride in methanol containing cerium trichloride to provide the intermediate carbinol **80**, which on treatment with trifluoromethanesulfonic anhydride in pyridine gave, after protecting group removal and hydrolysis, **81**. The authors speculated that the olefin was formed directly by protodesilylation of the intermediate allylsilane by pyridinium trifluoroacetate. In the latter process, the known lactone **82** was converted to the diene **83** in four steps (i. DIBAL-H, ii. methyltriphenylphosphonium bromide, KO-t-Bu in THF, iii. PCC, NaOAc, CH_2Cl_2, iv. Zn, CH_2Br_2, $TiCl_4$.) in 86% overall yield. **83** was hydroborated with diisoamylborane in THF at 0 °C to provide diol **84** which underwent intramoleculer aldol condensation in a one-pot procedure involving initial Swern oxidation, followed by *in situ* treatment of the dialdehyde with dibenzylammonium trifluoroacetate and heating at 70 °C for 6 h after changing the solvent to benzene. This practical process to obtain α,β-unsaturated aldehyde **85** proceeded in 85% yield. Wittig reaction of **85** with the ylide derived from (3-carboxypropyl)triphenylphosphonium bromide and potassium *tert*-butoxide in THF gave, after workup and treatment with ethereal diazomethane, diene **86** (cis:trans = 2.2:1). Regioselective hydrogenation of **86** occurred in the presence of 10% Pd/C at 23 °C. Chromatographic purification to remove overreduction and 1,4-reduction products was followed by treatment with tetra-n-butylammonium fluoride in THF to provide the isocarbacyclin precursor **87**.

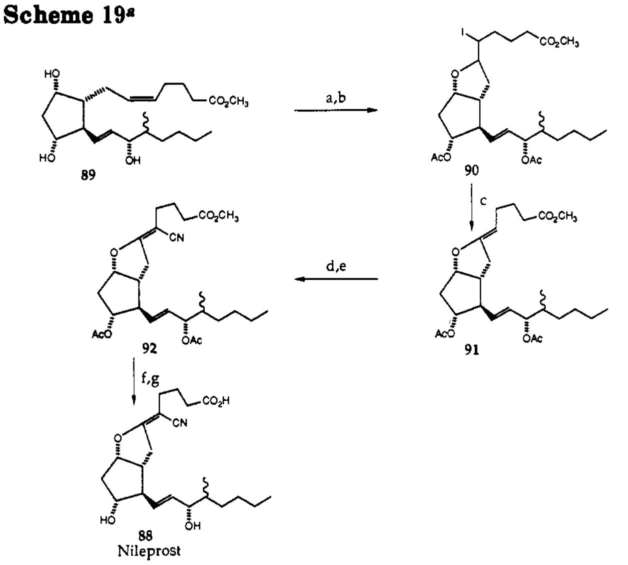
This route, which is characterized by a high overall yield of product, is also applicable to the synthesis of other ω-chain-modified analogs.

11. Nileprost

Nileprost (**88**) is another prostacyclin analog from Schering AG whose clinical development as an antiulcer agent has recently been discontinued. It had been in phase II trials where at oral doses of 250 μg, it reduced gastric acidity by 50%. In animal studies, **88** prevented the development of indomethacin-induced gastric lesions in rats with an ED_{50} of 60.7 μg/kg, much lower than the dose required to inhibit gastric acid secretion.[164]

From a structural perspective **88** is characterized by its 5-cyano and 16-methyl groups. The former imparts acid stability to the molecule relative to PGI_2 while the latter provides protection against the otherwise profligate 15-PGDH. The synthesis of **88** has been described and is outlined in Scheme 19.[165] 16-Methyl-$PGF_{2\alpha}$ (**89**)

Scheme 19[a]



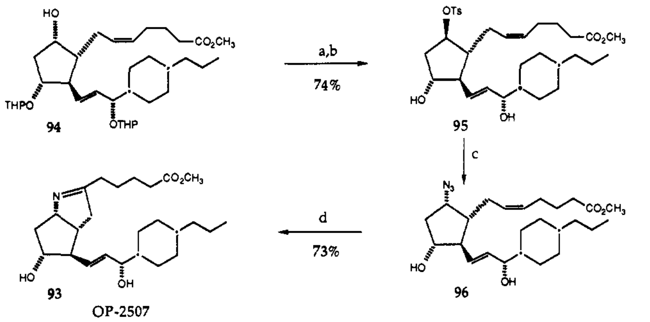
[a] (a) I_2, $NaHCO_3$. (b) Ac_2O, pyridine. (c) DBN. (d) $ClSO_2NCO$. (e) NEt_3, CH_3CN. (f) KOH, H_2O, MeOH. (g) H_3O^+.

was cyclized under standard conditions using iodine/sodium bicarbonate to form the expected iodo ether which was bis-acetylated with acetic anhydride in pyridine providing **90**. This material underwent smooth dehydrohalogenation to **91** upon exposure to DBN. This protected prostacyclin analog was then treated with chlorosulfonyl isocyanate to provide an intermediate chlorosulfimide which, upon treatment with triethylamine in acetonitrile, afforded the 5-cyano-PGI_2 derivative **92**. Potassium hydroxide treatment of **92** provided concomitant acetate and ester cleavage and, upon acid workup, nileprost (**88**) was produced in optically pure form as a colorless viscous oil.

12. OP-2507

Development of OP-2507 (**93**, Scheme 20) has been discontinued by Dainippon and Ono. **93** was targeted

Scheme 20[a]



[a] (a) Ph_3P, $(TsO)_2Zn$, $EtO_2CN{=}NCO_2Et$. (b) 65% aqueous AcOH. (c) NaN_3, DMSO, 40 °C. (d) Δ, $PhCH_3$, 70 °C, 16 h.

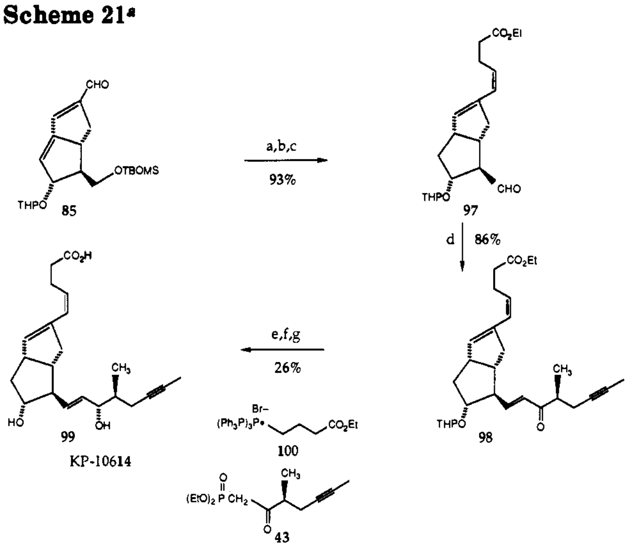
for the treatment of cerebral ischaemia following surgery, subarachnoid hemorrhage, and cerebral infarction and was in phase II clinical trial. In rats and mice, OP-2507 dose dependently increased survival times in models of cerebral anoxia including KCN-induced anoxia, hypobaric, and normobaric hypoxia.[166] **93** was effective in reducing cerebral edema induced by occlusion of the middle cerebral artery (4 h) in cats at infusion rates of 10 and 50 ng kg^{-1} min^{-1} started at 30 min before occlusion and continued for 4–5 h thereafter.[167]

Structurally, OP-2507 contains a key imino group replacement for the enol ether of PGI_2 and a *cis*-4-*n*-propylcyclohexane ring incorporated into the ω-chain. The imino unit is claimed to be less chemically labile than the enol ether of PGI_2. The synthesis of **93** is shown in Scheme 20.[168] A key step in this synthesis was the construction of the *cis*-4-*n*-propylcyclohexane ring. This was achieved through hydrogenation of 4-*n*-propylbenzoate in the presence of a catalytic amount of the commercially available dimer of chloro(1,5-cyclooctadiene)rhodium at 50 atm, in hexane at pH 7.6. A cis/trans ratio of 5.3/1.0 was obtained, and the isomers separated by chromatography. This unit was incorporated into the ω-chain using standard methodology. The rest of the synthesis proceeded as follows. Tosylation of the bis-protected $PGF_{2\alpha}$ analog **94** using the Still–Galynker protocol furnished the requisite C-9β-tosylate **95** in 74% yield after the removal of the THP groups with aqueous acid. The tosylate was displaced with sodium azide in dimethyl sulfoxide to access azide **96**. **96** underwent smooth intramolecular cycloaddition on heating in toluene at 70 °C to provide OP-2507.

13. KP-10614

KP-10614 (**99**) is an isocarbacyclin analog currently being evaluated as an antithrombotic agent by the Mitsubishi Kasei Corporation in Japan. **99** is claimed to display higher intrinsic activity than either isocarbacyclin or iloprost in *in vitro* assay systems. It exhibited an IC_{50} of 1 nm for inhibition of ADP-induced human platelet aggregation. At oral doses of 25, 50, and 100 μg/kg, **99** caused a dose-dependent inhibition of *ex vivo* platelet aggregation in rats, whereas iloprost and isocarbacyclin were only effective at a dose of 500 μg/kg.[169] The synthesis of KP-10614 is shown in Scheme 21. Wittig reaction of the known aldehyde **85** with the ylide derived from **100** afforded the expected (*Z*)-olefin with high stereoselectivity (*Z*/*E* > 98:2). This material

Scheme 21[a]



[a] (a) **91**, KO-*t*-Bu, THF, −78 °C. (b) TBAF, THF. (c) SO_3·py, Et_3N, DMSO. (d) **43**, NaH, THF. (e) $NaBH_4$, MeOH, −40 °C. (f) 65% aqueous acetic acid, then chromatography. (g) NaOH, MeOH, H_2O.

was desilylated under standard conditions and then oxidized using the Parikh protocol to provide aldehyde **97**. **97** was treated directly with the sodium enolate derived from the optically pure β-keto phosphonate **43** (the same phosphonate as used for the cicaprost synthesis) to access enone **98** in 86% isolated yield. Reduction of **98** with sodium borohydride in methanol at −40 °C afforded the C-15 epimeric alcohols which were exposed to aqueous acetic acid and the resultant diols separated chromatographically. Hydrolysis with sodium hydroxide in aqueous methanol provided **99**.[170]

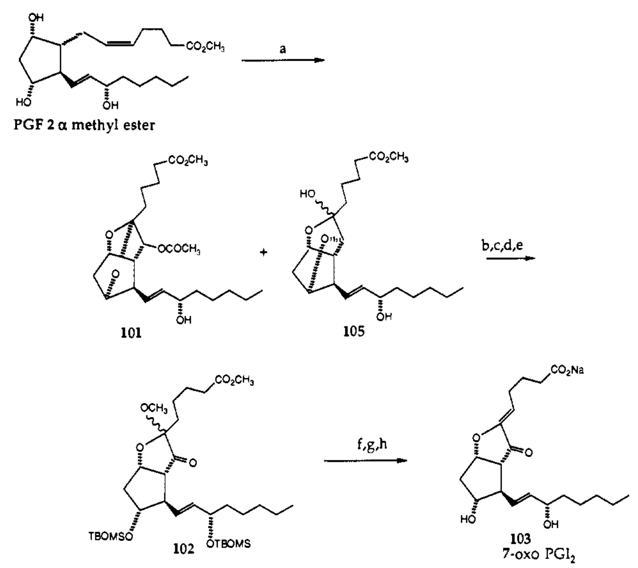
In light of the purported potency of KP-10614 and its greater separation of antiaggregatory versus hypotensive activity relative to iloprost, further news on the clinical development of this compound is awaited.

14. CH-5084

CH-5084 (**104**, Table 2) is a prostacyclin analog currently being examined for cardiovascular indications by Chinoin in Hungary. This compound, which is characterized structurally by its 7-oxo and 15-cyclopentyl groups is their second-generation analog of 7-oxo-PGI_2 **103**. 7-oxo-PGI_2, itself, had been shown previously to be chemically more stable than PGI_2[171] with a $t_{1/2}$ at pH 2 of 96 h. 7-Oxo-PGI_2 was approximately 1/10 as active as PGI_2 as an antiaggregatory agent (ADP-induced human platelet aggregation). Recent studies have compared the relative potencies of CH-5084, 7-oxo-PGI_2, and prostacyclin on arterial smooth muscle tone, blood pressure,[172] and platelet aggregation.[173]

Scheme 22 shows the original synthesis of 7-oxo-PGI_2. $PGF_{2\alpha}$ methyl ester is treated with thallium triacetate in acetic acid to generate the tricyclic internal ketal **101** and diol **105**. Transacetalization of **101** in methanol under Lewis acid catalysis produced an isomeric mixture of diol–methyl acetals which were exposed sequentially to *tert*-butyldimethylsilyl chloride in DMF, potassium carbonate in methanol, and pyridinium chlorochromate in methylene chloride (buffered with sodium acetate) to afford ketone **102**. At this point, **102** was desilylated under standard conditions and the resulting diol heated in HMPA at 160 °C to induce thermal elimination of

Scheme 22[a]



[a] (a) $Tl(OCOCH_3)_3$, CH_3CO_2H. (b) $BF_3{\cdot}Et_2O$, MeOH. (c) TBDMS chloride, imidazole, DMF, 40 °C, 5 h. (d) K_2CO_3, MeOH. (e) PCC, NaOAc, CH_2Cl_2. (f) TBAF, THF. (g) HMPA, 160 °C, 2 h. (h) NaOH, MeOH, H_2O.

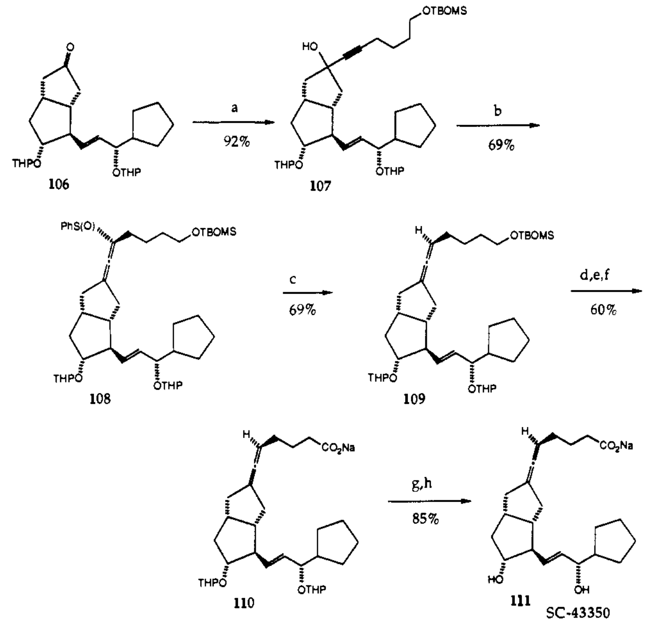
methanol. The enone, thus obtained, was saponified with aqueous sodium hydroxide to provide crystalline **103** sodium salt.

15. SC-43350

SC-43350 (**111**) is a chemically stable carbacyclin analog that has undergone evaluation as an antithrombotic agent by Searle. Although this compound was much less potent as an inhibitor of platelet aggregation than PGI_2 in *in vitro* assay systems, (IC_{50} 0.1 μM versus 2 nM for PGI_2), it exhibited an encouraging profile in *in vivo* assays; for example, in a rat ADP-induced thrombocytopenia paradigm it was only 7.5 times less active than PGI_2 (ED_{50} = 7.2 μg/kg) and also showed much less hypotensive activity at equieffective doses when compared to PGI_2 (ED_{50} in the normotensive rat 88 μg/kg versus PGI_2 0.12 μg/kg). This compound was also effective in maintaining clot-free dialysis in dogs at doses of 15 μg kg^{-1} min^{-1} with no statistically significant hypotensive effects being observed.[174]

The synthesis of SC-43350 is outlined in Scheme 23.[175] Treatment of bicyclic[3.3.0]ketone **106** with the lithio derivative of 5-hexyn-1-ol TBDMS ether at −20 °C provided the acetylenic carbinols **107** as a 9:1 mixture (α:β carbinols). Exposure of this mixture to phenylsulfenyl chloride triggered a [2,3]-sigmatropic rearrangement of the intermediate sulfenate esters to produce the allene sulfoxides **108**. Treatment of **108** with ethereal methyl lithium at −70 °C induced a clean conversion to the required allenes **109**. The remainder of the synthesis proceeded uneventfully; demasking of the primary alcohol, followed by Jones oxidation and workup with ethereal diazomethane afforded the esters **110** in excellent overall yield. Conversion to allene–carbacyclin **111** was accomplished by protecting group removal, separation of the minor allene isomer by chromatography, and saponification with 1 equiv of sodium hydroxide in methanol/water. SC-43350 obtained in this manner is a free-flowing powder with excellent chemical stability in aqueous solution.

Scheme 23[a]



[a] (a) H—≡—$(CH_2)_4$ OTBDMS, n-BuLi, THF, 0 °C. (b) PhSCl, Et_3N, CH_2Cl_2, −70 °C → 25 °C. (c) MeLi, Et_2O, −70 °C. (d) n-Bu_4NF, THF, 25 °C. (e) Jones' reagent, −25 °C. (f) CH_2N_2, Et_2O. (g) HOAc, H_2O, THF (3:1:1), 25 °C. (h) NaOH, MeOH.

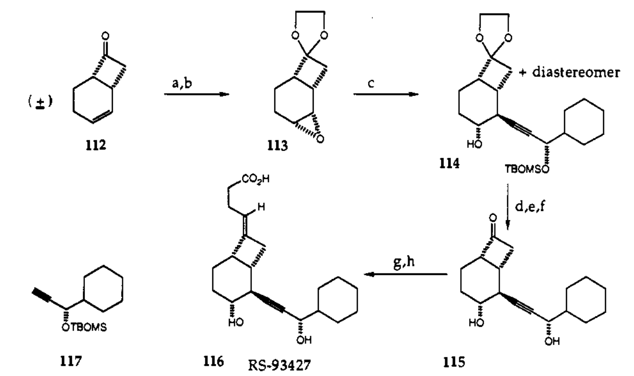
16. RS-93427

RS-93427 (**116**) is an orally active prostacyclin mimetic being developed by Syntex for the treatment of vascular occlusive disease associated with atherosclerosis.

The *in vitro* and *in vivo* pharmacologic profiles of this compound have been thoroughly reviewed by Willis et al.[176] **116** has potent *in vitro* activity in suppression of platelet aggregation induced by a wide variety of agonists and also inhibits clotting in whole blood. The oral bioavailability and duration of action of **116** have been examined in both guinea pigs and rabbits. The compound was rapidly absorbed and was long-lived in the circulation (>3.5 h). In the cavine, animals receiving 750 μg/kg of **116** and bled 2 hours later, homologous aggregation induced by ADP at 1.6 μg/mL was inhibited by ~49%. This compared to a 69% decrease in heterologous aggregation response. The antiatherosclerotic potential of RS-93427 has been examined. It was found to inhibit release of platelet mitogens more potently than its ability to inhibit aggregation. **116** also inhibits mitogen release from macrophages and vascular endothelial cells and is a very potent inhibitor of macrophage accumulation of cholesteryl esters.[177]

The discovery of RS-93427 and, in particular, its unique bicyclo[4.2.0]octane ring system, was based on a working hypothesis for a prostacyclin active shape derived from molecular modeling and SAR studies on a related series of compounds. The synthesis of RS-93427 by Kluge and co-workers was originally reported in 1987[178] and is outlined in Scheme 24. Briefly, **116** was prepared in a sequence based on the regioselective opening of epoxide **113** with the lithium acetylide derived from homochiral acetylenic ether **117** in the presence of boron trifluoride etherate. The regioselectivity was consistent with a mechanism involving coordination in the transition state of the epoxide and *endo*-acetal oxygen with the Lewis acid boron. The

Scheme 24[a]



[a] (a) $HOCH_2CH_2OH$, p-TsOH, C_6H_6, Δ. (b) N-Bromoacetamide, H_2O, Me_2CO. (c) 117, n-BuLi, −78 °C then $BF_3{\cdot}Et_2O$, −78 °C. (d) $Co_2(CO)_8$, Et_2O then flash chromatography. (e) $Ce(NH_4)_2(NO_3)_4$. (f) H_3O^+. (g) $CH_3SOCH_2^-Na^+$, $Br^-Ph_3P^+CH_2CH_2CH_2CO_2H$, CH_3SOCH_3. (h) H_3O^+.

diastereoisomeric mixture **114** was separated through formation of their respective dicobalt hexacarbonyl complexes followed by chromatography and decomplexation with ceric ammonium nitrate. Acid treatment of the requisite individual isomeric acetal afforded ketone **115** which was homologated under standard Wittig olefination procedures to provide, after separation of the unwanted (E)-olefin, RS-93427.

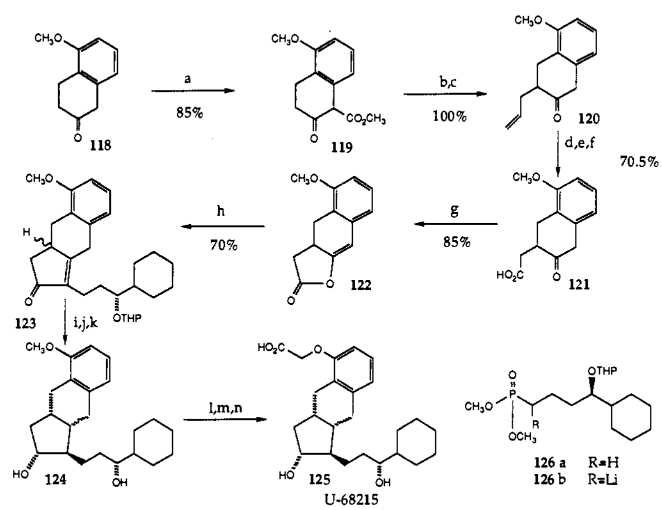
The application of Bakers' yeast mediated reduction of bicyclo[4.2.0]oct-2-en-7-ones to the enantioselective synthesis of **116** has been recently reported.[179]

17. U-68,215

U-68,215 (**125**) is a benzindene prostacyclin analog that has been investigated by Upjohn as a potential antiulcer agent. Their original lead in this area U-60,959 had previously been shown to exhibit good gastric cytoprotective activity and modest inhibition of gastric acid secretion in rats.[180] Reduction of the 13,14-double bond of this compound and incorporation of the 16-cyclohexyl moiety provided **125** which, when administered orally, was an extremely potent antisecretory and cytoprotective agent. In fact, **125** was shown to be an effective antiulcer agent in rats at microgram per kilogram levels. **125** is a stable, high-melting crystalline solid, which has been purported to be completely devoid of the typical side effects associated with PGEs; ie., even at doses 100 times the antiulcer dose, it does not cause diarrhea, has no antifertility activity, and does not induce cellular proliferation of the gastrointestinal mucosa.[181]

In a randomized study, intragastric U-68215 suppressed gastric acid secretion (ED_{50} = 45.3 μg/kg) and gastric emptying in unanesthetized rhesus monkeys when administered 30 min after subcutaneous treatment with the histalog dimaprit. No diarrhea was observed at any dose tested. **125** reduced diastolic blood pressure (DBP) but only reduced systolic blood pressure at the highest dose (100 μg/kg). The reduction in DBP was positively correlated with acid secretion inhibition. Transient side effects (lethargy, paleness, passiveness) were observed at the two highest dose levels (50 and 100 mg/kg).[182] Although the authors suggested that prostacyclin analogs may be a useful alternative to PGE analogs for the treatment of peptic ulcer disease, the notable paucity of further reports on U-68,215 suggests that this compound is not undergoing further development.

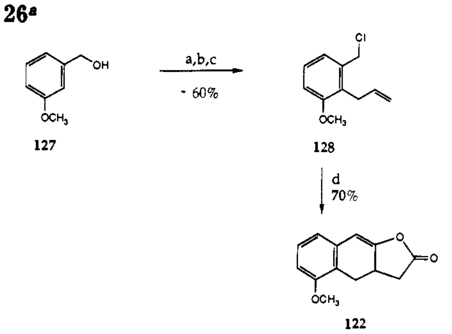
Scheme 25[a]



[a] (a) NaOMe, $(MeO)_2CO$, Δ. (b) 2 LDA, THF, ?. (c) LiCl, H_2O, Me_2SO, Δ. (d) $HO(CH_2)_2OH$, p-TsOH. (e) $NaIO_4$, $KMnO_4$. (f) H_3O^+. (g) Ac_2O, H^+. (h) **126b**, (2 equiv), THF, −78 °C → −10 °C, then AcOH, 60 °C. (i) 10% Pd/C, EtOH, 3 atm. (j) $NaBH_4$, NaOH, MeOH, −10 °C. (k) HOAc, THF, H_2O. (l) $LiPPh_2$, THF, 75 °C. (m) K_2CO_3, $ClCH_2CN$, CH_3COCH_3, 60 °C. (n) KOH, H_2O, CH_3OH, 90 °C.

The original, elegant synthesis of **125** by Aristoff and co-workers[183] is summarized in Scheme 25. U-68,215 was prepared via a cyclopentane annulation sequence in optically pure form in 14 steps and 12% overall yield from 5-methoxy-2-tetralone. Briefly, carbomethoxylation of 5-methoxy-2-tetralone (**118**), afforded the β-keto ester **119** in high yield. Alkylation of the dianion derived from **119** with allyl bromide followed by decarbomethoxylation of the crude β-keto ester under modified Krapcho conditions provided the crude ketone **120**. This material was sequentially ketalized, the olefin oxidatively cleaved and the ketal hydrolyzed to access **121** in 70% yield for the three steps. The crystalline keto acid **121** was dehydrated upon exposure to acetic anhydride/perchloric acid providing the key enol lactone **122** in 85% yield. This material was condensed with the optically active phosphonate **126a**, which had been synthesized in seven steps from cyclohexanecarboxaldehyde using a Sharpless kinetic resolution procedure as a key step. In the pivotal step, treatment of enol lactone **122** with 2 equiv of the anion derived from **126a** at −70 °C in THF followed by warming to −10 °C, addition of 1 equiv of acetic acid, and then heating at 60 °C afforded a 70% yield of the desired enone **123**. Hydrogenation of the enone in the presence of 10% palladium on carbon effected the anticipated reduction to provide the desired 1:1 mixture of cis-ring-fused ketones in excellent yield. Treatment of this mixture directly with sodium borohydride and sodium hydroxide in methanol at −10 °C led exclusively to a 1:1 mixture of ring fused alcohols which were deprotected upon exposure to acetic acid/THF/water. At this juncture, the methyl ether diol mixture was separated by chromatography on silica gel. The synthesis was completed by sequential methyl ether cleavage using an excess of lithium diphenylphosphide in refluxing THF, alkylation of the phenol with chloroacetonitrile in the presence of potassium carbonate in acetone, and nitrile hydrolysis

Scheme 26[a]



[a] (a) TBDMSCl, imidazole, DMF. (b) n-BuLi then allyl bromide. (c) NCS, Me_2S. (d) CO (600 psi), NEt_3 (2 equiv), 5% $Cl_2Pd(PPh_3)_2$, MeCN, 100 °C, 36 h.

(ethanolic potassium hydroxide). A recent report by the Negishi group[184] has highlighted an alternative approach toward the synthesis of enol lactone 122. This route is outlined in Scheme 26. The key step in this synthesis was the conversion of 2-allyl-3-(chloromethyl)-anisole to 122 via an intramolecular palladium-catalyzed carbonylative cyclization reaction.

Acknowledgment

We wish to thank Drs. Huff, Malecha, Penning, and Gasiecki of Searle's Chemistry Department for their review and comments on the manuscript, Lot Soliman-Paramo and Candace Martin for secretarial assistance, and Todd Minske and Judy Balazs for artwork.

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