Prostaglandins, Thromboxanes, Leukotrienes, and Related Arachidonic Acid Metabolites

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Reviewing the literature published during 1982

(Continuing the coverage of literature in *Aliphatic and Related Natural Product Chemistry*, Vol. 3, p. 107)

1 Introduction

This review is a continuation of previous Reports on Prostaglandins and Leukotrienes,[1] and its purpose as such is to present a comprehensive report of the synthesis of arachidonic acid metabolites and their related analogues published during 1982. Owing to the limitation of space, we have precluded the patent literature and confined ourselves largely to the primary chemical and biochemical journals. Abbreviations are used for prostaglandin (PG), thromboxane (TX), and leukotriene (LT).

Much of the new synthetic effort in this area is now focused on modified arachidonic acid metabolites, with only a few syntheses directed towards natural prostaglandins and leukotrienes.

Several major reviews and books on various aspects of arachidonic acid, prostaglandins, prostacyclin, thromboxane, and leukotrienes have been published; these are included in the bibliography, and most of them are mentioned in the text at appropriate points.

Highlights of 1982 are the discovery of a new series of dihomo-prostaglandins, produced by cells within the renal medulla,[2] and the 4,12-dihydroxylated prostaglandins that have been isolated from the soft coral *Clavularia viridis*.[3,4] The synthetic improvement of the 'conjugate-addition enolate-trapping' method in prostaglandin synthesis by Noyori's group is also notable.[5] In the leukotriene field, three additional leukotrienes have been reported: these are (7*E*,9*E*,11*Z*,14*Z*)-(5*S*,6*R*)-6-(γ-glutamylcystein-*S*-yl)-5-hydroxyicosa-7,9,11,14-tetraenoic acid (LTF_4),[6] (5*Z*,8*Z*,10*E*,12*E*)-(14*R*,15*S*)-14-(glutathion-*S*-yl)-15-hydroxyicosa-5,8,10,12-tetraenoic acid,[7] and (6*Z*,8*E*,10*E*,14*Z*)-(5*S*,12*R*)-5,12-dihydroxyicosa-6,8,10,14-tetraene-1,20-dioic acid.[8] Further progress in the understanding of the catabolism of leukotrienes has been made by the discovery of the novel sulphide oxidative degradation of leukotriene C_4 in Man.[9]

2 Prostaglandins and their Analogues

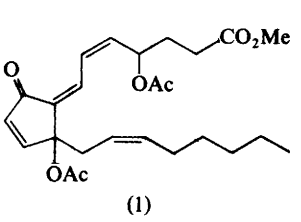
2.1 General

Reviews on the chemical synthesis,[10,11] biosynthesis,[12] and general biological[12–14] and pharmacological[14,15] aspects of prostaglandins have been published. Prostaglandins in relation to cancer,[16–18] fertility,[19] fever,[20] inflammation,[21] and schizophrenia[22] have been reviewed. The drugs that modulate the biological activity of prostaglandins have also been the subject of a review.[23]

Two Japanese research groups[3,4] have independently isolated a novel class of prostaglandins from the soft coral *Clavularia viridis*. The prostaglandins have been named claviridenone-a (1), claviridenone-b (2), claviridenone-c (3), and claviridenone-d (4). These compounds are unusual in that they are hydroxylated at C-4 and C-12 and possess an exocyclic double-bond at C-7. Claviridenones-b, -c, and -d [(2), (3), and (4)] display anti-inflammatory properties.[3]

The C_{22} tetraenoic acid adrenic acid (5) has been shown to be metabolized in rabbit renal medullary tissue to a novel class of dihomo-prostaglandins and -thromboxanes which may play a physiological role in kidney function (Scheme 1).[2]

The complex oligomeric mixture, termed PGB_x, that is derived from the treatment of 15-dehydro-PGB_1 methyl ester (12) with ethanolic potassium hydroxide displays interesting physiological properties,[24] and insights into the mechanism for



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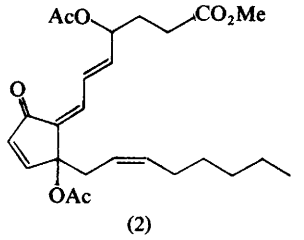

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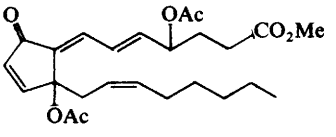

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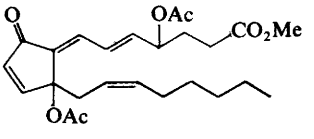

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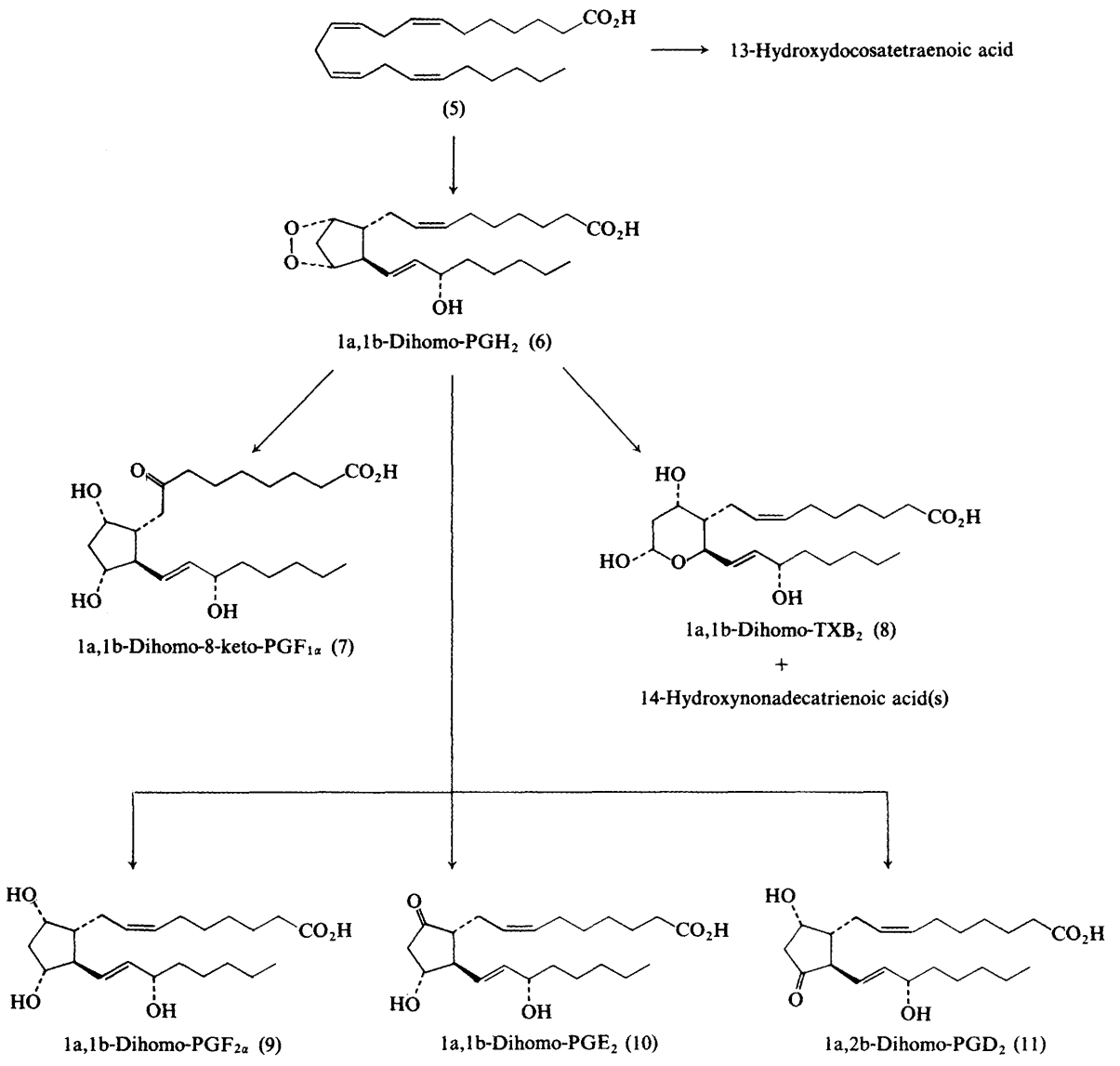
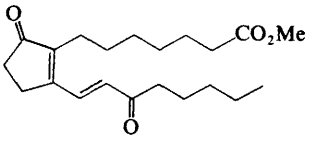


Scheme 1 The metabolism of adrenic acid by rabbit renal medullary tissue

the oligomerization of (12) and the structures of the constituents of PGB_x have been reported.[25,26]

Calculations of conformational energies,[27,28] carbon-13 n.m.r. studies,[29] and proton n.m.r. n.O.e. experiments[30] on some prostaglandins have been reported.



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2.2 The Synthesis of Natural Prostaglandins

2.2.1 The Prostaglandin A Series

An improved method for the conversion of 11-deoxy-PGE_2 (13) into PGA_2 (15) has been reported (Scheme 2).[31] The dehydrogenation step was achieved *via* the oxidation [by palladium(II) acetate] of the trimethylsilyl enol ether (14), derived from (13). The overall yield (65%) is an improvement over that from the selenoxide elimination technique (46%).[32]

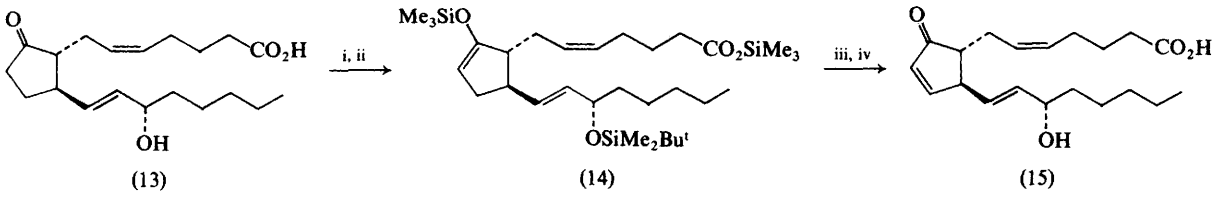
2.2.2 The Prostaglandin D Series

Hewson *et al.*[33] have reported a total synthesis of PGD_1 methyl ester (20) which utilizes a thiomethyl-substituted vinylphosphonium salt in the construction of the cyclopentanone ring (Scheme 3). Two steric effects of the dithiane group were observed: the conjugate addition of the lithium cuprate to (16) led to the formation of a 2.2:1 mixture of the *trans*- and the *cis*-adduct, (17) and (18) respectively, and the reduction of (17) resulted in exclusive formation of the 9β-hydroxy-compound (19). An inversion of the β-hydroxy-group at C-9 of (19) was necessary for the final conversion into PGD_1 methyl ester (20).

2.2.3 The Prostaglandin E Series

A particularly interesting biomimetic approach to the synthesis of PGE_1 (23) has been reported by Matsumoto *et al.* (Scheme 4).[34] The remarkable cationic pentannulation of the trienoic ester (21) generates, in a single step, the *trans*-13–14 double-bond and fixes the relative stereochemistry at the contiguous centres C-9, C-8, C-12, and C-11 of the cyclopentane derivative (22). Unfortunately, the relative stereochemistry at C-11 was incorrect, and an inversion at C-11 was required for the conversion of (22) into PGE_1.

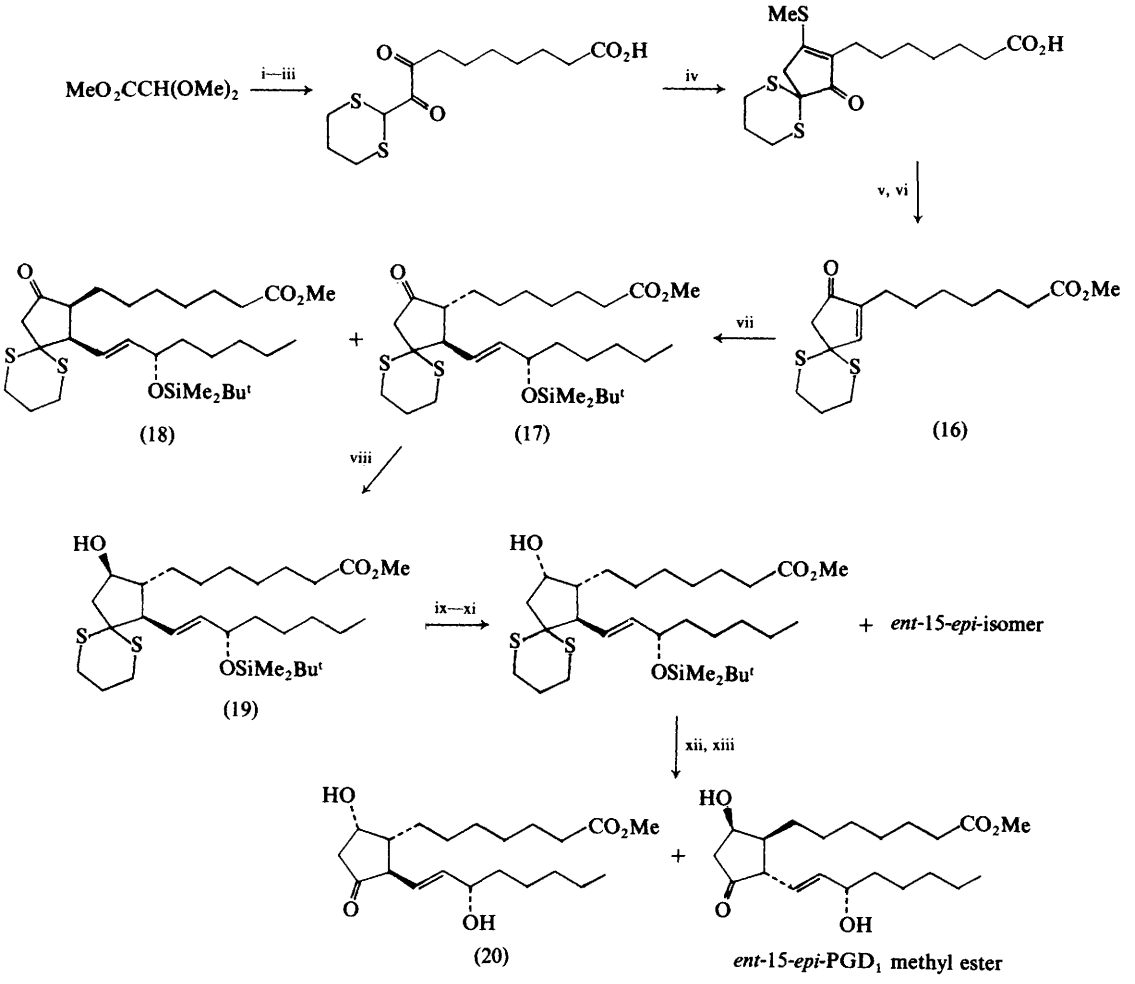
Noyori *et al.* have reported a much improved synthesis of (−)-PGE_1, *via* a three-component coupling process (Scheme 5).[5] The success of this '1,4-addition enolate-trapping' strategy rests on the use of stoicheiometric quantities of lithium cuprate and the aldehyde trap. Under the conditions specified, incorporation of the ω-side-chain occurred in a regiospecific manner (94–97% asymmetric induction) *via* the kinetically defined enolate (24). The one-pot reaction afforded (25) in 83%



(13) (14) (15)

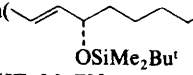
Reagents: i, Bu^tMe_2SiCl, imidazole; ii, $LiNPr^i_2$, Me_3SiCl, Et_3N; iii, $Pd(OAc)_2$, MeCN; iv, AcOH

Scheme 2



(18) (17) (16) (19) (20)

ent-15-*epi*-PGD_1 methyl ester

Reagents: i, $I[CH_2]_6CO_2H$, Bu^nLi; ii, dithiane, $LiNPr^i_2$; iii, CF_3CO_2H; iv, $H_2C{=}C(SMe)\overset{+}{P}Ph_3\ Cl^-$, NaH; v, $LiBH_4$, MeOH, THF; vi, HCl, MeOH; vii, LiCu()$_2$; viii, $NaBH_4$, MeOH; ix, $MeSO_2Cl$, pyridine; x, $Bu^n_4N^+\ OAc^-$; xi, NaOMe, MeOH; xii, HgO, $BF_3{\cdot}OEt_2$; xiii, HF, MeCN

Scheme 3

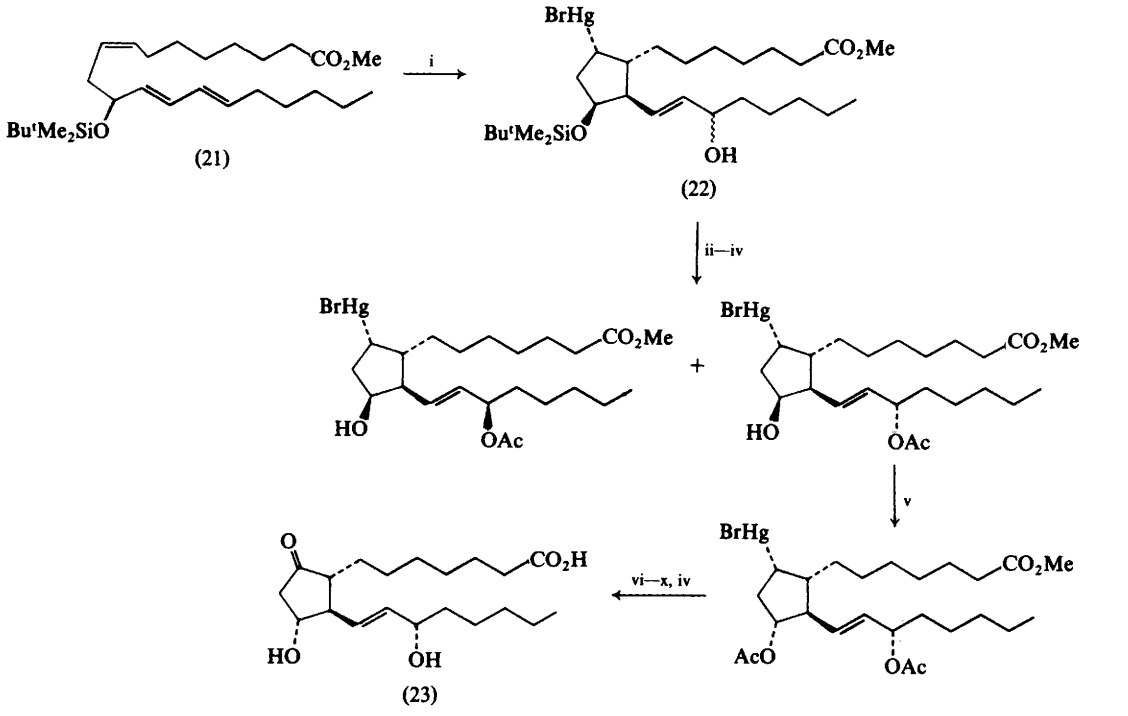
yield, and no C-10 aldol products, formed by enolate equilibration, were detected. The tetrahydropyranyl-deprotected analogue of (25) displayed a potent inhibitory effect on the aggregation of blood platelets.

The above methodology has been extended by Noyori and co-workers to include the synthesis of chiral 5,6-dehydro-PGE_2 (28).[35] The key intermediate in the synthesis of (28) is the protected 7-hydroxy-5,6-dehydro-PGE_2 methyl ester (26). Mild deoxygenation of the hydroxy-group at C-7 by Barton's free-radical reduction method[36] afforded (27), which could by converted into PGE_2 and PGE_1 by controlled hydrogenation followed by removal of the protective groups. The conversion of (27) into $PGF_{2\alpha}$ by asymmetric reduction of the oxo-group at C-9 followed by selective hydrogenation of the acetylenic group and deprotection was readily achieved, using established methods.

The conjugate addition of the allylic carbanion derived from 1-phenylthio-oct-2-ene (29) to the cyclopentanone (30) in hexamethylphosphoramide has been reported to give the adduct (31).[37] Oxidation of (31) to the sulphoxide derivative (32), followed by sulphoxide–sulphenate rearrangement and deprotection, furnished PGE_1 methyl ester. It is worth noting, however, that similar conjugate addition of the carbanion that is derived from the sulphoxide (33) and the 11-deoxy-analogue of (30) gave the 1,4-γ-adduct (34) as the major product.

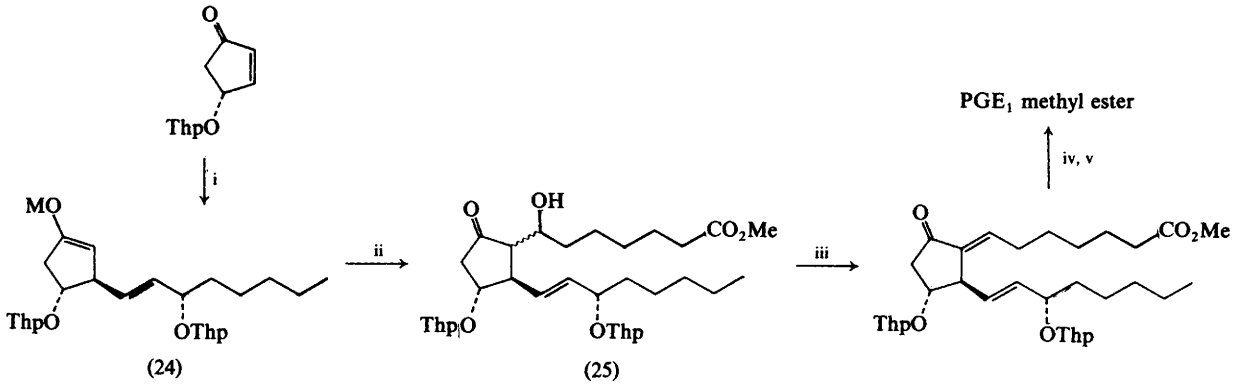
2.2.4 The Prostaglandin F Series

A synthesis of 15-keto-$PGF_{1\alpha}$ methyl ester (36) *via* the conjugate addition of the carbanion derived from the sulphone (35) to the protected cyclopentenone (30) has been described.[38]

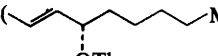


Reagents: i, $Hg(OCOCF_3)_2$, $MeNO_2$, at −20 °C, followed by KBr, catalytic LiOH, MeOH; ii, chromatography, separation of 15α- and 15β-isomers; iii, Ac_2O, pyridine; iv, 40% HF, MeCN; v, $EtO_2CN{=}NCO_2Et$, PPh_3, AcOH, THF; vi, K_2CO_3, MeOH; vii, Bu^tMe_2SiCl, imidazole; viii, O_2, $NaBH_4$; ix, NaOH, MeOH; x, Jones oxidation

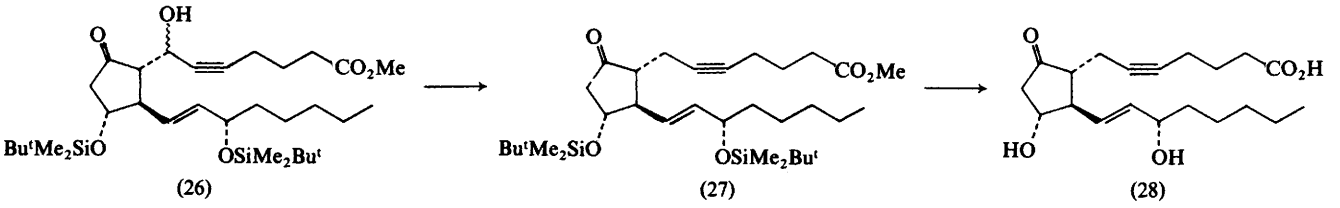
Scheme 4



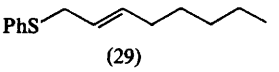
(Thp = tetrahydropyran-2-yl)

Reagents: i, LiCu( Me)$_2$, Bu_3P, Et_2O, at −78 °C; ii, $OHC[CH_2]_5CO_2Me$; iii, $MeSO_2Cl$, 4-dimethylaminopyridine; iv, Zn, AcOH, Pr^iOH; v, AcOH

Scheme 5



Details of the total synthesis of (+)-$PGF_{2\alpha}$ (40) from chiral substrates have been described by Johnson *et al.* (Scheme 6).[39] (−)-(*S*)-Malic acid was converted, in three steps, into the γ-acetoxycyclopentenone (37), which bears the desired chirality. Stereoselective hydrogenation of (37) gave (38), which was readily transformed into the protected Corey lactone (39). The latter was elaborated to $PGF_{2\alpha}$ by established methodology. The chiral phosphonium salt (41) for the ω-side-chain was prepared from D-mannitol by a modification of Corey's method.[40]



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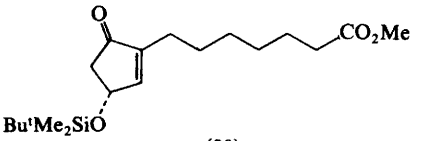

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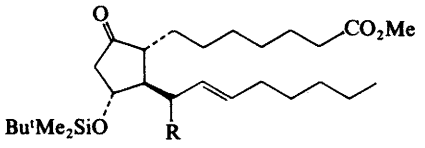
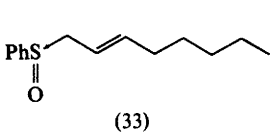


(31) R = SPh
(32) R = S(O)Ph



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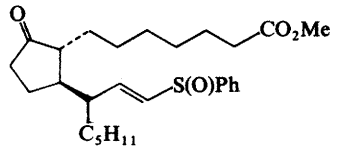

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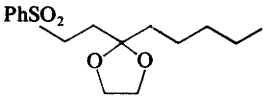

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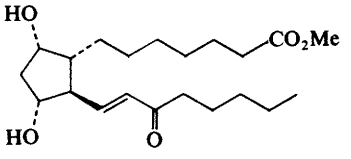

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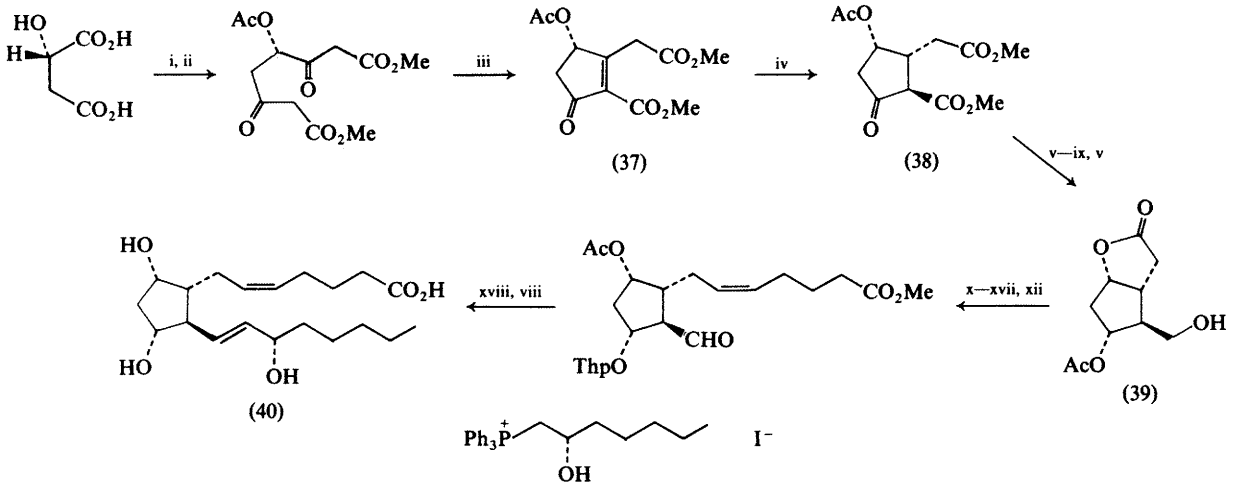
2.3 The Synthesis of Prostaglandin Analogues

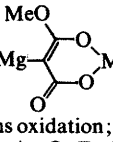
2.3.1 Side-chain-modified Variants

A successful attempt to block the metabolic action of 15-dehydrogenase and develop a long-acting hypotensive PGE_2 analogue has been described by the research group at American Cyanamid (Scheme 7).[41] The modified ω-side-chain (44) was prepared in four steps from hept-1-en-3-ol (43). The conversion of (44) into a lithium cuprate derivative, followed by conjugate addition to the protected cyclopentanone (42), furnished (±)-(16*RS*)-15-deoxy-16-hydroxy-16-vinyl-PGE_2 (45). Unlike (−)-PGE_2, which has only a transient effect, (45) displayed a relatively prolonged hypotensive effect when administered by an intravenous or a transdermal route.

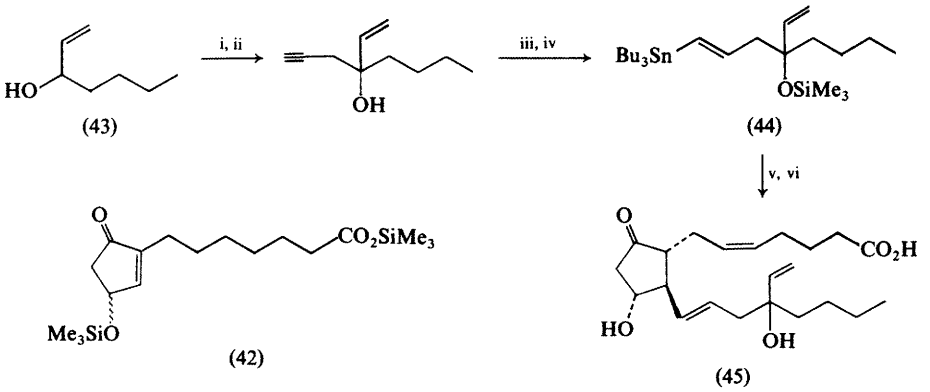
A series of 13-thiaprostanoids of the PGE type has been reported by Szántay *et al.*[42] In a specific example, the (2*S*)-mercaptan (46), prepared in six steps from racemic heptane-1,2-diol, was allowed to react with the protected cyclopentenone (47) in the presence of di-isopropylamine, to give the Michael adduct (49) after deprotection. Initial studies showed that when the unprotected cyclopentenone (48) was used as a Michael acceptor, base-catalysed dehydration of (49) occurred, followed by enolization and rearrangement of the mercaptan side-chain to give a mixture of (50) and (51).



(37) (38) (39) (40) (41)

Reagents: i, AcCl, then $MeOCHCl_2$, $ZnCl_2$; ii, BrMg–  –MgBr; iii, $MgCO_3$, Et_2O; iv, H_2, 5% $Pd/BaSO_4$; v, $NaBH_4$; vi, K_2CO_3; vii, citric acid; viii, KOH; ix, $MeOCHCl_2$, $ZnCl_2$; x, Collins oxidation; xi, MeOH, HCl; xii, TsOH, dihydropyran, PhH; xiii, $NaAlH_2(OCH_2CH_2OMe)_2$; xiv, $Ph_3P{=}CH[CH_2]_3CO_2Na$; xv, CH_2N_2; xvi, Ac_2O, Et_2O; xvii, Ac_2O, H_2O; xviii, (41), Bu^nLi

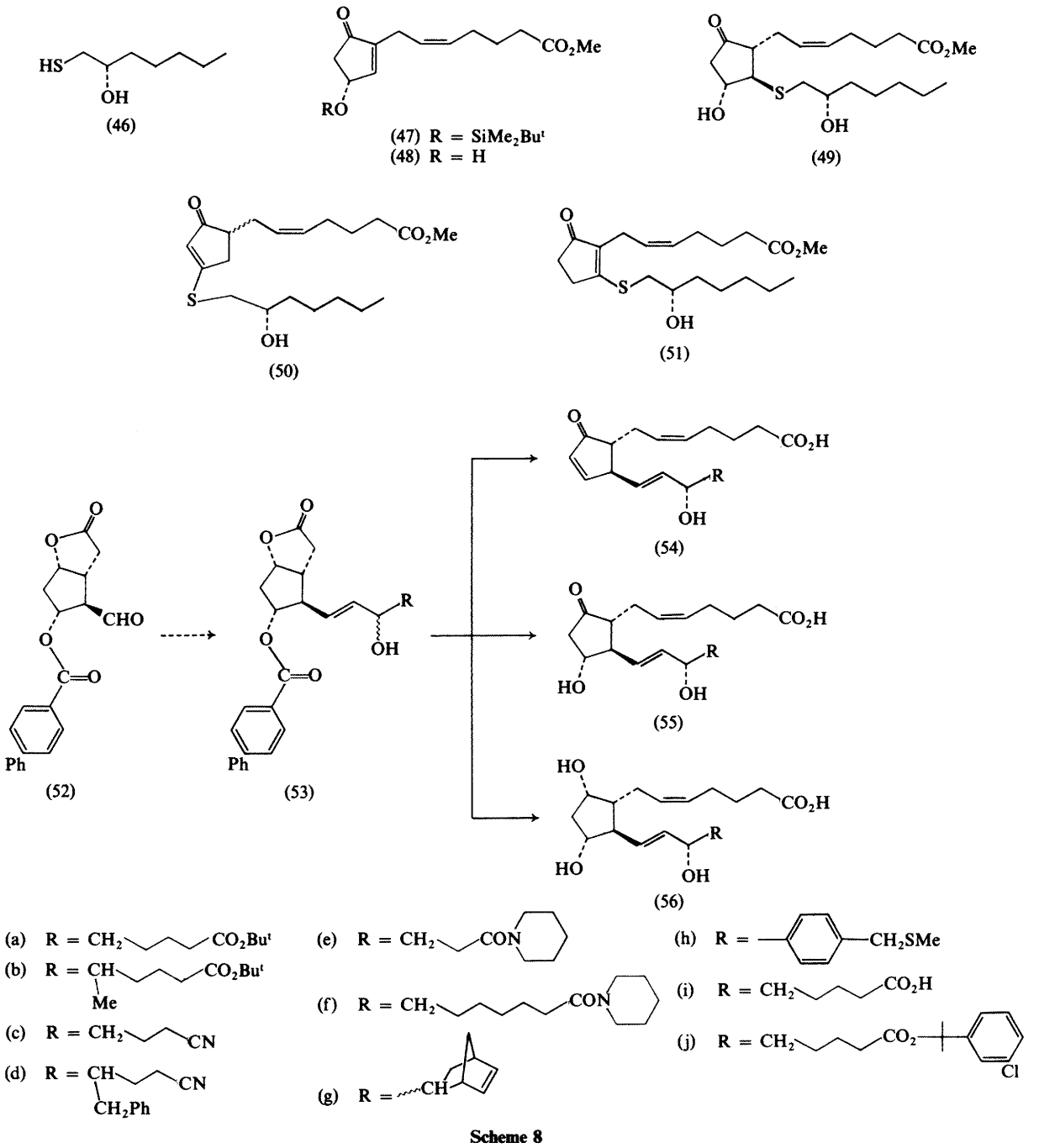
Scheme 6



(42) (43) (44) (45)

Reagents: i, pyridinium chlorochromate; ii, $HC{\equiv}CCH_2MgBr$; iii, Me_3SiCl, imidazole; iv, Bu^n_3SnH, azobisisobutyronitrile; v, Bu^nLi, $C_3H_7C{\equiv}CCu$, Bu_3P, THF, then (42); vi, deprotection and chromatography

Scheme 7



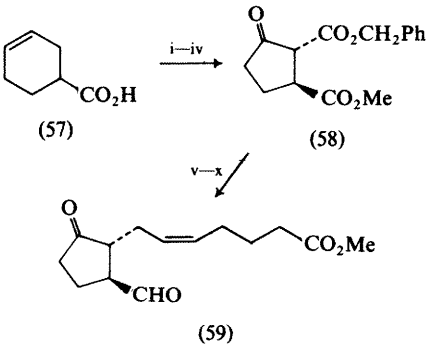
Scheme 8

The Bayer research group has described a series of ω-side-chain variants of the PGA_2 (54), PGE_2 (55), and PGF_2 (56) types (Scheme 8).[43] These were prepared by Corey's procedure[44] from the lactone (52) *via* (53). Detailed experimental procedures and spectroscopic data were presented for all of the compounds, although no biological data were given.

2.3.2 *Ring-modified Variants*

The 11-deoxy-PGE-type analogues have attracted much attention, because they are inherently more stable than the natural prostaglandins E. In addition, some of these analogues are known to have potent bronchodilating[45] and anti-gastric secretion[46] activities.

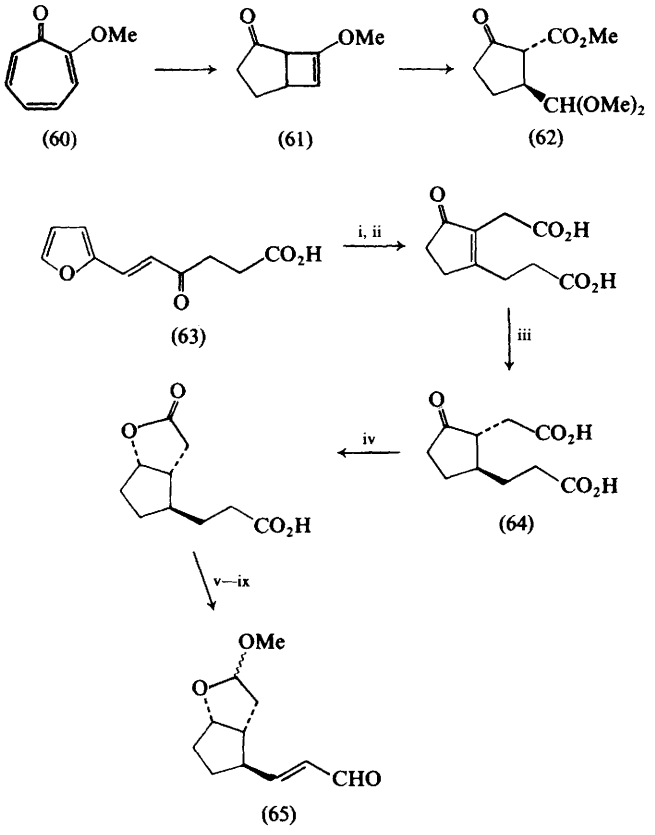
A short route to 11-deoxy-PGE-type analogues has been described by Johnson *et al.* (Scheme 9).[47] Commercially available cyclohex-3-enecarboxylic acid (57) was transformed into the key cyclopentanone intermediate (58). Introduction of the α-side-chain *via* an ω-cyanopropargyl mesylate then gave (59), which was further elaborated to variants of 11-deoxy-PGE by following standard procedures.



Reagents: i, Cu, HNO_3, NH_4VO_3; ii, H_2SO_4, MeOH, $ClCH_2CH_2Cl$; iii, NaH, MeOH, *p*-xylene; iv, $PhCH_2OH$, at 180 °C; v, $MeSO_3CH_2C{\equiv}C[CH_2]_3CN$, NaH, DMF; vi, H_2, 5% $Pd/BaSO_4$, pyridine, then heat, Na_2CO_3, H_2O, MeOH; vii, $SOCl_2$, then $NaBH_4$; viii, KOH, MeOH; ix, CH_2N_2; x, Collins oxidation

Scheme 9

The route that has been devised by Crabbé *et al.* and which utilizes the established tropolone (60) → (61) → (62) methodology has been described.[31] The key cyclopentanone (62) can be further elaborated to 11-deoxy-PGE-type analogues.



Reagents: i, HCl, EtOH; ii, 2% NaOH; iii, H_2, 10% Pd/C; iv, L-Selectride, THF, then H_3O^+; v, disiamylborane, THF; vi, H^+, MeOH; vii, $LiNPr^i_2$, THF, then PhSeBr, then 3% H_2O_2; viii, Bu^i_2AlH, Et_2O; ix, Ag_2CO_3 on Celite

Scheme 10

An alternative approach to the synthesis of 11-deoxyprostaglandins has been described by Rens *et al.* (Scheme 10).[48] The 5-furfurylidenelevulinic acid (63) was converted, in nine steps, into the key intermediate (65). The introduction of the pendant side-chains was accomplished by established procedures. It is noteworthy that from a list of eight reducing agents, L-Selectride was the most effective reagent for delivery of a hydride ion to the β-face of the cyclopentanone derivative (64). The synthon (65) may be used for the preparation of 11-deoxy-PGE-, 11-deoxy-PGF-, and 11-deoxy-PGI-type analogues.

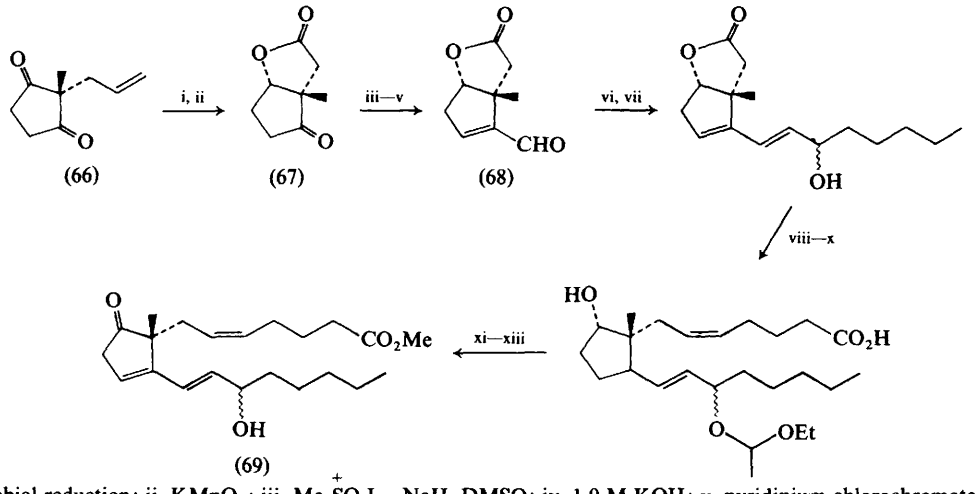
Other syntheses of 11-deoxy-PGE_1 and related analogues, using more conventional methods, have also been described.[49,50]

A synthesis of the interesting 8-methyl-PGC_2 methyl ester (69) has been reported by Schwarz *et al.* (Scheme 11).[51] The chiral keto-lactone (67) was obtained either by microbial reduction and chemical modification of (66) or from a seco-steroid. Homologation of (67), followed by hydrolysis (using a base) and oxidation, furnished the key intermediate lactone (68), which was elaborated (by conventional means) to the unstable ester (69). Attempts to separate the (15*R*)- and (15*S*)-epimers of the ester (69), or of the acid (70) that could be derived from it, proved unsuccessful, owing to extensive decomposition. Ultraviolet absorption spectral data suggested that rearrangement of (70) to (71) and subsequent dehydration to the 9-oxo-10,12,14-triene (72) had occurred.

The synthesis of 11-deoxy-11α-methyl-PGE_2 has been described by Crabbé *et al.*[31] The electrocyclization–conjugate addition–ozonolysis sequence (60) → (74) effectively furnished the key methylcyclopentanone (74), for further elaboration to 11-deoxy-11-methyl-prostaglandins. This strategy has also been extended to accommodate the synthesis of 11-butyl-11-deoxy-11-methyl-prostaglandins *via* the reaction sequence (73) → (75).

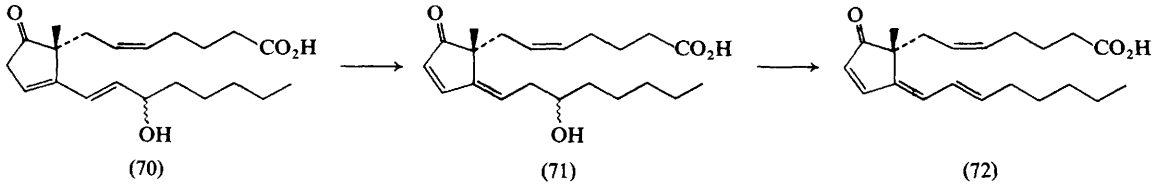
A simple synthetic route to the (5*Z*,13*E*)-(15*S*)-15-hydroxy-10-oxoprosta-5,13-dienoate (77) from the norborn-5-en-2-ols (76) has been described by the Miles research group.[52] The reaction sequence (76) → (77) illustrates the strategy.

A short synthesis of the aza-prostanoid (79) from (78) has been described by Wang.[53] Compound (79) and its methyl ester displayed activity in both cytoprotection and anti-bronchoconstriction assays.

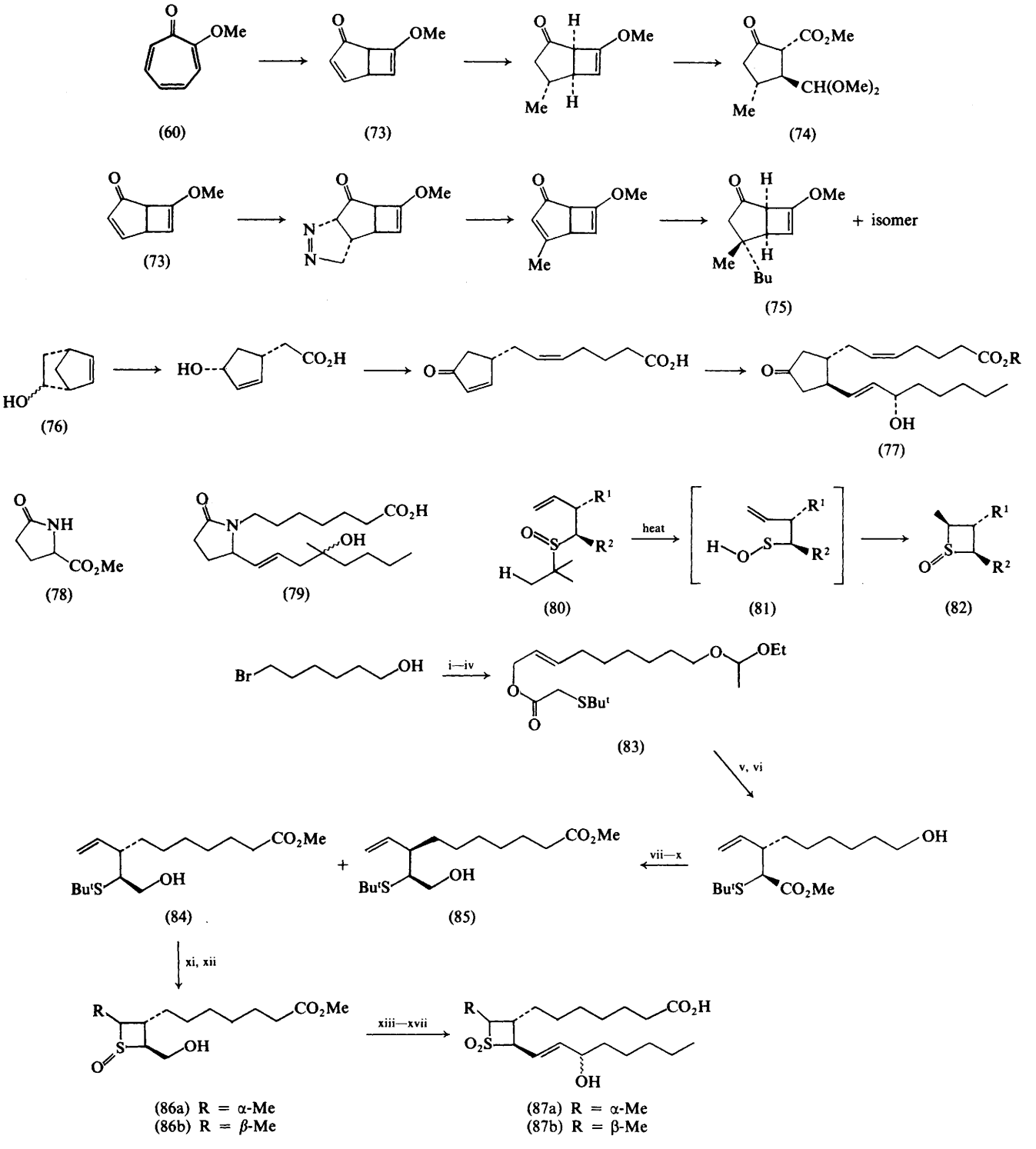


Reagents: i, microbial reduction; ii, $KMnO_4$; iii, $Me_3\overset{+}{S}O\ I^-$, NaH, DMSO; iv, 1.0 M-KOH; v, pyridinium chlorochromate; vi, $(MeO)_2P(O)=CHCOC_5H_{11}$; vii, $NaBH_4$; viii, $H_2C=CHOEt$, pyridinium tosylate; ix, Bu^i_2AlH, hexane; x, $Ph_3P=CH[CH_2]_3CO_2Na$; xi, CH_2N_2; xii, Collins oxidation; xiii, pyridinium tosylate

Scheme 11



The approximate isosteric relationship between thietan and cyclopentane rings has prompted Jones and co-workers to synthesize a novel series of thietanoprostanoids (Scheme 12).[54] The key reaction in the synthesis is the formation of the 2,3,4-trisubstituted thietan ring (82), *via* an intramolecular addition of the sulphenic acid (81), which can be generated *in situ* by thermolysis of the t-butyl sulphoxide (80). According to Scheme 12, the Claisen rearrangement of (83) afforded a separable mixture of the *threo*- and *erythro*- isomers, (84) and (85) respectively. The *threo*-isomer (84) was converted into a mixture of (86a) and (86b), the components of which were separated by chromatography; (86a) and (86b) were elaborated to (87a) and (87b) respectively. In the case of (87b), the 15α- and 15β-isomers were separated, and both analogues displayed thromboxane-like activity on smooth muscle preparation. In addition, the 15α-isomer of (87b) was a moderate PGE_2 agonist. Although the C-15 isomers of (87a) could not be separated, the mixture showed activity similar in nature to that



Reagents: i, $H_2C{=}CHOEt$, TsOH; ii, $LiC{\equiv}CCH_2OLi$, NH_3(liq.); iii, $LiAlH_4$; iv, Bu^tSCH_2COCl, pyridine; v, lithium cyclohexylisopropylamide, Me_3SiCl, then heat at 60 °C, then HCl; vi, H_2SO_4, MeOH; vii, TsCl, KOH, then KCN, DMSO; viii, $LiBH_4$; ix, KOH; x, CH_2N_2; xi, peroxydodecanoic acid; xii, xylene, heat; xiii, Moffatt oxidation; xiv, $Bu_3P{=}CHCOC_5H_{11}$; xv, $NaBH_4$; xvi, chromatography, separation of (15*R*)- and (15*S*)-isomers; xvii, NaOH

Scheme 12

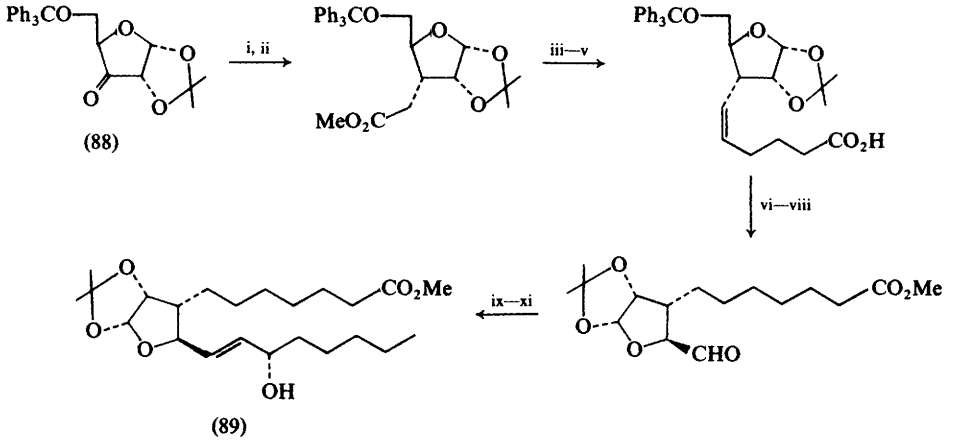
of the 15α-isomer of (87b), but with only one-tenth of the potency. Interestingly, the mixture had weak thromboxane antagonist activity. None of the thienoprostanoids affected the aggregation of blood platelets.

A variety of 11-oxa-11-deoxy-PGF analogues has been reported by Koekemoer *et al.*[55] For example, the prostanoid (89) was prepared from the sugar-derived furanose (88) (Scheme 13). Two other related analogues (91) and (93) were synthesized from the furanoses (90) and (92) respectively. Some of these analogues were inhibitors of the secretion of gastric acid in the rat.

A number of ring-modified prostaglandins have been derived from PGA_2 through photochemical transformation of the double-bond between C-10 and C-11 (Scheme 14).[56] The photochemical [2 + 2] addition of vinyl acetate to the protected PGA_2 methyl ester (94) afforded 87% of the adduct (95), which was oxidized and separated into the lactones (96a) and (96b).

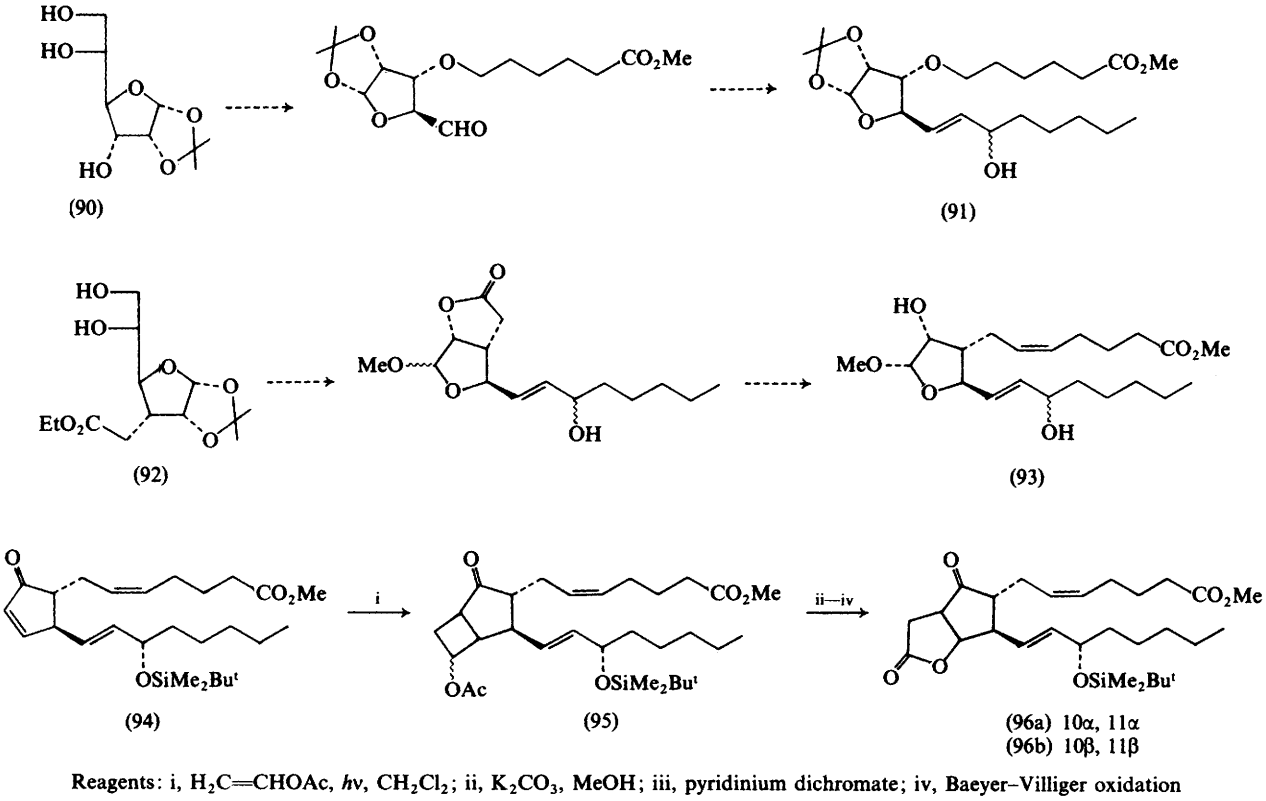
The Upjohn research group has reported the synthesis of the $PGF_{1\alpha}$ analogue (99) *via* the intramolecular oxymercuration of the protected $PGF_{2\alpha}$ (97) (Scheme 15).[57] The isomers (98a) and (98b) were separated by chromatography and independently converted into the enol ethers (99a) and (99b) respectively. The sodium salts of (99a) and (99b) were inactive against the ADP-induced aggregation of human blood platelets, but the sodium salt of (99b) displayed 0.1—0.3% of the depressor activity of PGE_1 in the rat blood-pressure test whereas (99a) was inactive.

The synthesis of the novel secoprostaglandins (100), (101), and (102) has been reported by Tanaka *et al.*[58] These compounds were shown to induce aggregation of blood platelets.



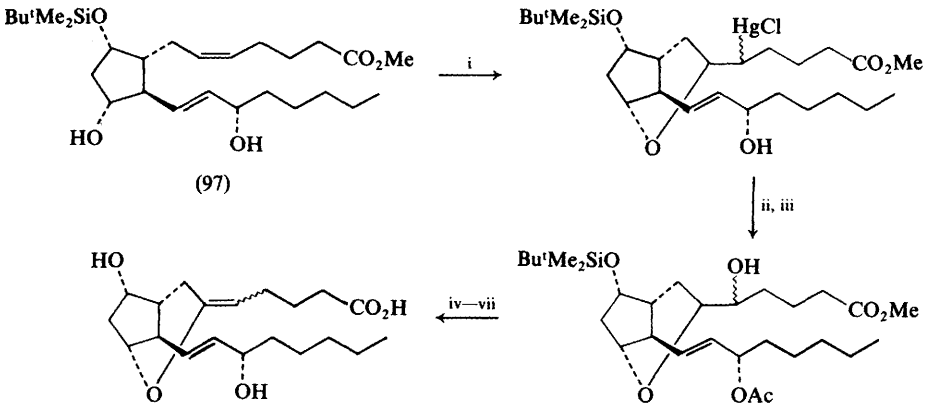
Reagents: i, $(MeO)_2P(O)CH_2CO_2Me$, KH, DMF; ii, H_2, Raney nickel; iii, $LiAlH_4$; iv, Collins oxidation; v, $Ph_3P{=}CH[CH_2]_3CO_2Na$, DMSO; vi, H_2, PtO_2, AcOH; vii, CH_2N_2; viii, Pfitzner–Moffatt oxidation; ix, $(MeO)_2P(O)CH_2COC_5H_{11}$, NaH, DME; x, $Zn(BH_4)_2$; xi, chromatography, separation of (15*R*)- and (15*S*)-isomers

Scheme 13



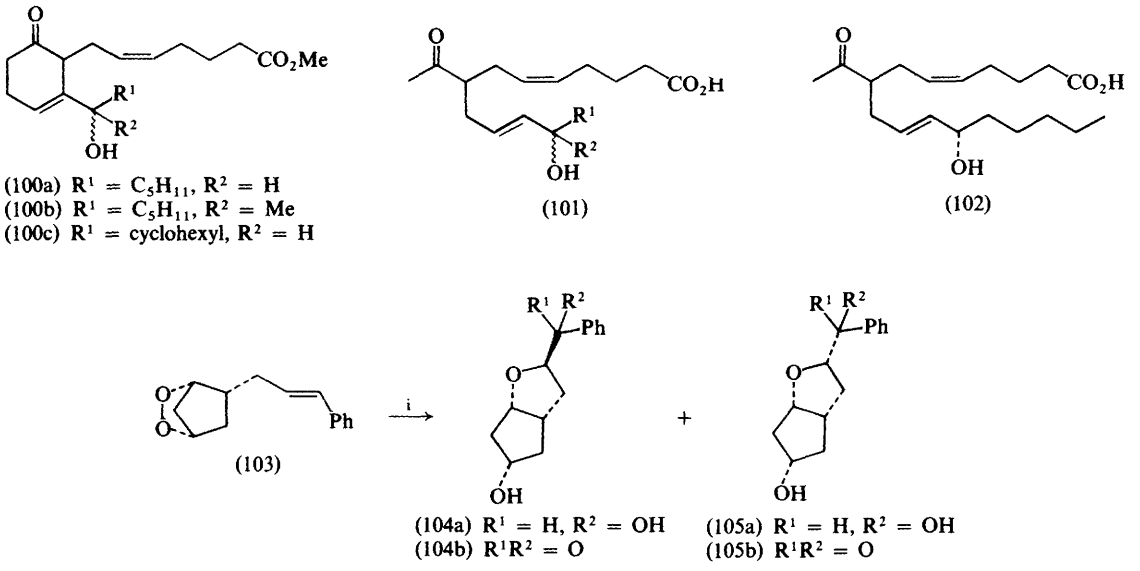
Reagents: i, $H_2C{=}CHOAc$, *hν*, CH_2Cl_2; ii, K_2CO_3, MeOH; iii, pyridinium dichromate; iv, Baeyer–Villiger oxidation

Scheme 14



Reagents: i, $Hg(OAc)_2$, THF; ii, Ac_2O, pyridine; iii, O_2, $NaBH_4$, DMF; iv, $MeSO_2Cl$, Et_3N; v, $Bu^n_4N^+F^-$; vi, LiOH, MeOH; vii, Bu^{t}OK, DMSO

Scheme 15



Reagents: i, $FeSO_4$, MeCN, H_2O, at 0 °C

Scheme 16

3 Prostaglandin Endoperoxides and Thromboxanes

3.1. General

A review of the biosynthesis of thromboxane A_2 (TXA_2), its properties, and its effects on platelets has been published by Samuelsson's group.[59]

The enzyme complex prostaglandin synthetase, which catalyses the dioxygenation of arachidonic acid to PGG_2 (prostaglandin cyclo-oxygenase) and the subsequent reduction of PGG_2 to PGH_2 (prostaglandin hydroperoxidase), has been isolated and successfully reconstituted into phospholipid vesicles without significant loss of enzymatic activity.[60,61] Other studies that relate to prostaglandin hydroperoxidase activity[62,63] and the cofactor requirement[64,65] of the prostaglandin synthetase enzyme complex have been reported.

The enzyme which catalyses the rearrangement of PGH_2 to TXA_2 (thromboxane synthetase) has been reviewed by Hammarstrom.[12] Ullrich and co-workers have reported the isolation of thromboxane synthetase and its characterization as a cytochrome *P*-450 enzyme.[66,67]

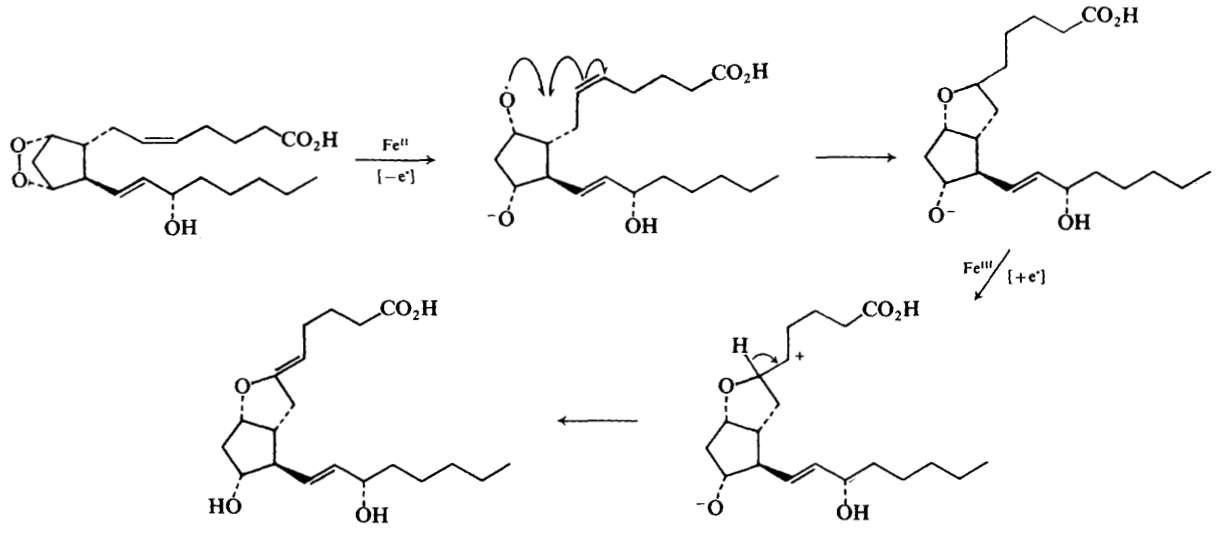
The enzyme prostacyclin synthetase, which is responsible for the conversion of PGH_2 into PGI_2, has also been purified and identified as a cytochrome *P*-450 enzyme.[68]

Porter and Mebane have achieved a biomimetic conversion of the endoperoxide (103) into the prostacyclin analogues (104) and (105), using iron(II) catalysis (Scheme 16).[69] This paper provides further evidence in support of Turner and Herz's earlier proposal for the biosynthesis of PGI_2 *via* a one-electron-transfer reaction from Fe^{II} to PGH_2 (Scheme 17).[70]

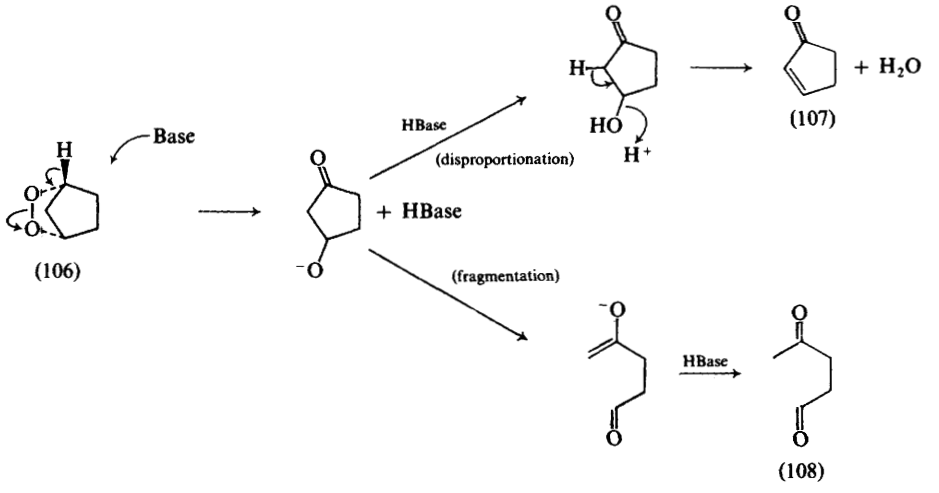
A model for the biosynthesis of 'prostaglandins E' (107) and 'prostaglandins D' (108) from prostaglandin endoperoxides has been proposed, based on studies of the fragmentation of 2,3-dioxabicyclo[2.2.1]heptane (106) (Scheme 18).[71] It was shown that decomposition could be directed towards disproportionation by using an excess of acetic acid in the acetate-catalysed decomposition, the rate-determining step of which is the abstraction of a bridgehead hydrogen atom in (106).

The ruthenium(II)-catalysed radical-induced fragmentation of PGH_2 methyl ester (109) to give malondialdehyde and the corresponding 12-hydroxyheptadecatrienoate (110) has been investigated by Noyori *et al.* (Scheme 19),[72] and the chemistry of saturated bicyclic peroxides has been reviewed.[73]

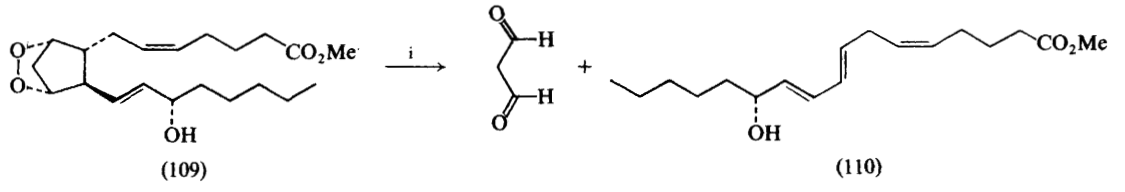
Needleman and co-workers have shown that rabbit renal medullary tissue is capable of metabolizing the endogenous arachidonic acid congener adrenic acid (5) to dihomo-prostaglandins and -thromboxanes *via* the dihomo-prostaglandin endoperoxide (6) (Scheme 1).[2]



Scheme 17 A proposed biosynthesis of PGI_2 from PGH_2



Scheme 18 The acetate-catalysed decomposition of 2,3-dioxabicyclo[2.2.1]heptane



Reagents: i, $RuCl_2(PPh_3)_2$, CH_2Cl_2

Scheme 19

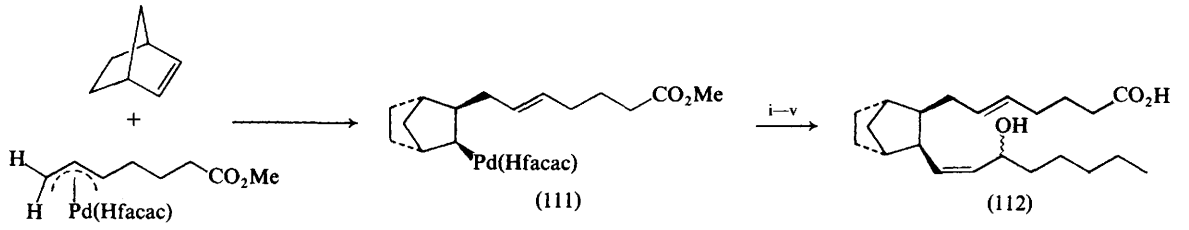
Although there are as yet no reports on the chemical synthesis of TXA_2, its structure has been inferred from that of its precursor PGH_2 and its stable metabolite TXB_2. The potent platelet-aggregatory and vasoconstrictive properties of TXA_2 and PGH_2 have prompted the synthesis of analogues, with the aim of finding physiologically stable antagonists of these agents or inhibitors of their biosynthesis.

3.2 The Synthesis of Analogues

Larock *et al.*[74] have utilized additions of (π-allyl)palladium hexafluoroacetylacetonate to bicyclic olefins to give exclusively the *cis*, *exo*-adducts, *e.g.* (111), having a *trans*-double-bond in the ester side-chain; these were subsequently elaborated to give the 13-*cis* [using the prostaglandin numbering] carbocyclic PGH_2 analogue (112) (Scheme 20). The corresponding 13-*trans*-allylic alcohols were prepared by using the vinyl-lithium cuprate reagents directly on the organopalladium intermediates. The acetylenic precursor to (112) is reported to be a potent inhibitor of aggregation of blood platelets. A similar approach, using the air-stable adduct (113), gave the thiophene-containing PGH_2 analogue (114).[75]

Bicyclo-octane analogues of PGH_2 have been prepared from the cyclohexadiene–maleinaldehyde pseudo-ester adduct (115) by a series of standard transformations to give the enone (116), which, by reduction followed by chromatography, gave the (*R*)- and (*S*)- allylic alcohols. The biological activities of these and of other PGH_2 and TXA_2 analogues have been discussed.[76]

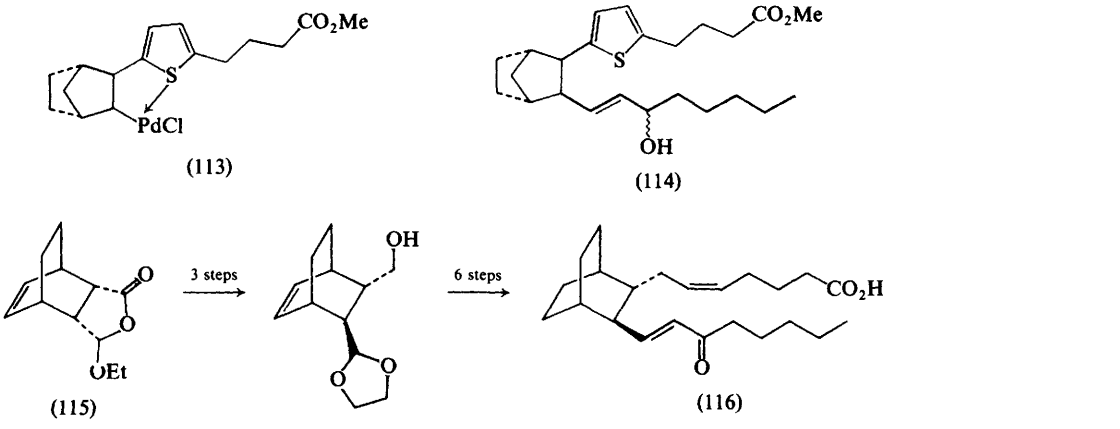
Two research groups have reported the synthesis of the 9,11-ethano-8-aza-PGH_1 analogues (119)[77] and (120)[78] from the cyclopentadiene–imine Diels–Alder adducts (117) and (118), respectively. Whereas the synthesis of (119) involved conver-



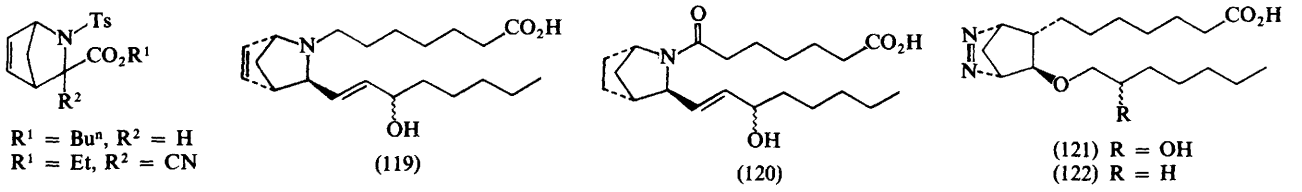
(111) (112)

Reagents: i, PPh_3; ii, $LiC{\equiv}CCH(OThp)C_5H_{11}$; iii, TsOH, MeOH; iv, H_2, 10% Pd/C, quinoline; v, KOH, MeOH

Scheme 20



(113) (114) (115) (116)



(117) R^1 = Bu^n, R^2 = H
(118) R^1 = Et, R^2 = CN
(119) (120)
(121) R = OH
(122) R = H

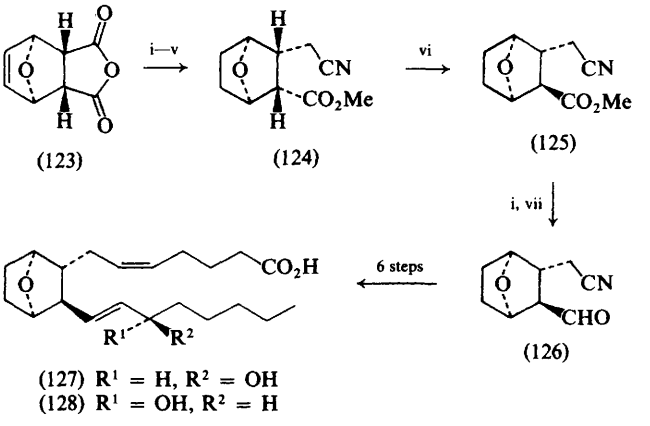
sion of the ester group into the corresponding aldehyde, *via* the alcohol, the strategy that was utilized to prepare (120) involved decarboxylation and reduction of the nitrile with Raney nickel, to introduce the aldehyde functionality directly. In both cases, the β-side-chain was introduced by using a β-ketophosphonate intermediate.

The synthesis of the 15-deoxy-analogue (122) of the combined TXA_2 antagonist/synthetase inhibitor (121)[79] has also been reported.[80]

Kametani *et al.* have reported the synthesis of the 9,11-ethano-10-oxa-PGH_2 analogues (127) and (128) (Scheme 21).[81] The *exo*-adduct (123) of maleic anhydride and furan was smoothly converted into the cyano-ester (124), which was then epimerized to give (125) in 97% yield. The reduction of (125) with sodium borohydride, followed by oxidation, gave the aldehyde (126), which was finally converted into the required analogue and separated into the (15*R*)- (127) and the (15*S*)-epimer (128) by chromatography. Whereas compound (128), with the natural (15*S*) configuration, was a potent TXA_2 agonist, compound (127) was inactive as a proaggregatory agent.

The 9,11-carboxy-PGH_2 analogues (132) and (133) have been prepared from the furan (129) (Scheme 22).[82] The Diels–Alder reaction of (129) with maleic anhydride gave the *exo*-adduct (130) exclusively. Epimerization of (131) with potassium acetate, followed by hydrolysis of the anhydride, esterification, and elaboration of the aldehyde then led to the bis-ester (132) as an epimeric mixture. The corresponding maleimide (133) was prepared in a similar fashion.

The Upjohn research group has reported the synthesis of the seco-PGH_2 analogues (136) and (137), both of which showed PGH_2 agonist activities (Scheme 23).[83] The diol-acetate (135), prepared *via* an epoxidation – periodic acid cleavage sequence from the readily available PGA_2 methyl ester (134), was



(126)
(127) R^1 = H, R^2 = OH
(128) R^1 = OH, R^2 = H

Reagents: i, $NaBH_4$; ii, H_2SO_4; iii, H_2, 5% Pd/C; iv, KCN, DMSO, at 190 °C; v, CH_2N_2; vi, K_2CO_3, MeOH; vii, Me_2S, *N*-chlorosuccinimide, Et_3N

Scheme 21

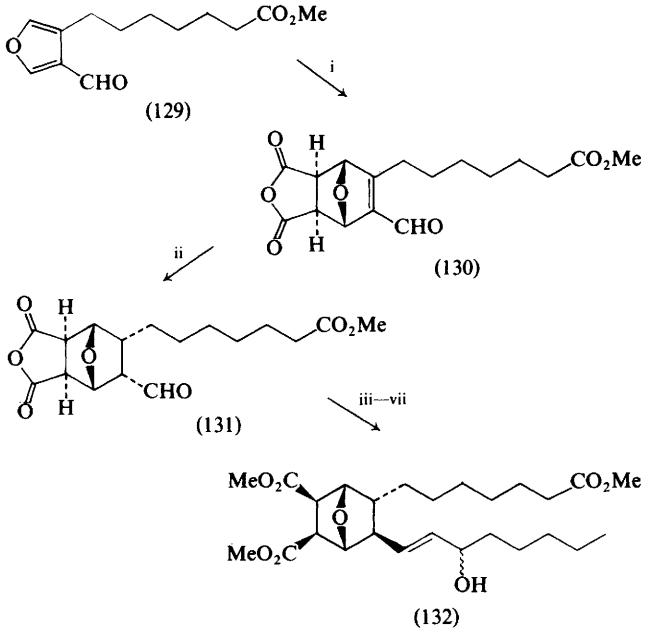
converted into the peroxide (136) by a displacement reaction of the 15-hydroxy-bis-tosylate derivative with potassium superoxide, followed by enzymatic hydrolysis of the ester. The conversion of the diol-acetate (135), *via* its bis-mesylate, into the 9,11-dithioacetate derivative, followed by hydrolysis of the acetate groups, atmospheric oxidation, and hydrolysis of the ester gave the corresponding dithio-endoperoxide analogue (137).

Ansell *et al.*[84] have published a new route to the carbocyclic TXA_2 agonist (140).[85] Intramolecular aldol condensation of the dialdehyde (138) (which is available, in nine steps, from pentaerythritol), using piperidinium acetate in refluxing

benzene, gave (139), which was then converted into (140) *via* conjugate addition followed by two consecutive Wittig reactions.

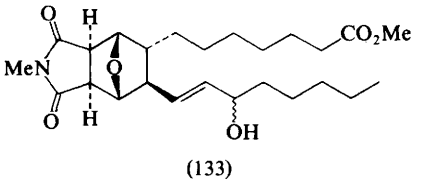
Nicolaou and co-workers have reviewed their work on the synthesis and pharmacology of the carbocyclic and pinane series of thromboxane analogues.[86]

Following their synthesis of dithia-TXA_2,[87] the Ono research group has now prepared the 9α,11α-thia-TXA_2 analogue (142) and also found it to have TXA_2 agonist activity



Reagents: i, maleic anhydride; ii, H_2, Pd/C; iii, KOAc, toluene, at 100 °C; iv, THF–H_2O; v, CH_2N_2; vi, $(MeO)_2P(O)CH_2COC_5H_{11}$; vii, L-Selectride

Scheme 22



(Scheme 24).[88] The key step in this elegant synthesis was the retro-Michael reaction of the mercaptopropanoate ester (141), using sodium hexamethyldisilazide, which proceeded with 51% conversion. Unfortunately, attempts at hydrolysis of the methyl ester in (142) were unsuccessful, owing to ring-opening of the thietane.

The same group has also published a synthesis of the amino-TXA_2 analogue (146) (Scheme 25).[89] The azabicycloheptane skeleton was constructed from (143) by reduction of the azide with chromium(II) chloride followed by treatment with sodium hydride and work-up with trifluoroacetic anhydride. Oxidation of (144) with sodium periodate followed by Pummerer rearrangement afforded the corresponding aldehyde, which was subsequently elaborated to the allylic alcohols (145) and (146). Only the (15*S*)-epimer (146) showed contractile activity on isolated rat aorta; however, neither (145) nor (146) was proaggregatory to human platelets.

Schmidt and Abele have published the preparation of the TXB_2 synthon (151) (Scheme 26).[90] Hetero-Diels–Alder reaction involving the hexadiene (147) first afforded the adduct (148), which was quantitatively epimerized to the α-anomer (149), using boron trifluoride etherate. Hydrolysis of the acetate followed by oxidation and iodolactonization gave the lactone (150), which was converted into the protected lactol (151) *via* reduction with di-isobutylaluminium hydride.

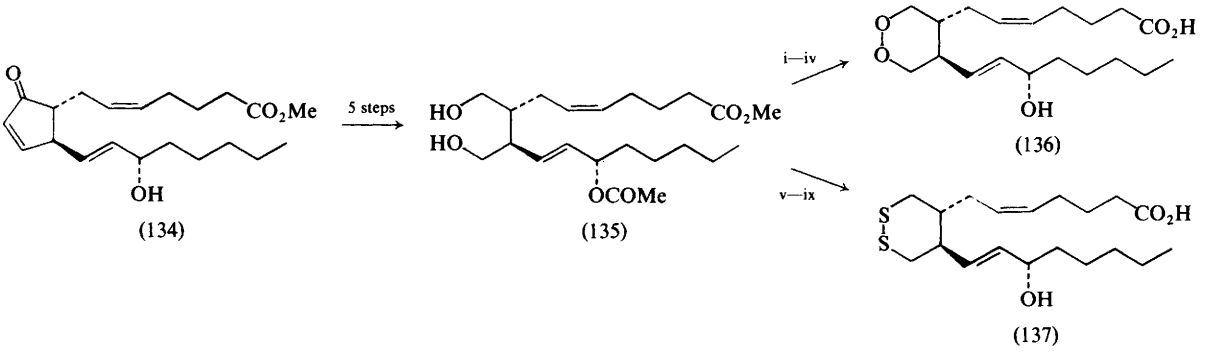
4 Prostacyclin and its Analogues

4.1 General

A review of the biological properties and chemical synthesis of prostacyclin (PGI_2) (152) and its analogues has appeared.[91] Other reviews dealing with various aspects of the biosynthesis of prostacyclin,[92] its metabolism,[93] and its clinical potential[92] have also been published.

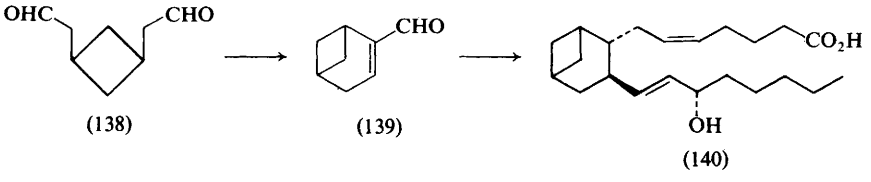
6-Oxo-$PGF_{1\alpha}$ (153), which is a stable metabolite of prostacyclin, can now be detected at 0.5 pg ml^{-1} by a combination of capillary gas–liquid chromatography and negative-ion chemical-ionization mass spectrometry.[94] The concentration of this metabolite in normal human plasma was found to be less than 3 pg ml^{-1}, thus confirming previous findings that PGI_2 is not a circulating hormone in Man under normal physiological conditions.[95]

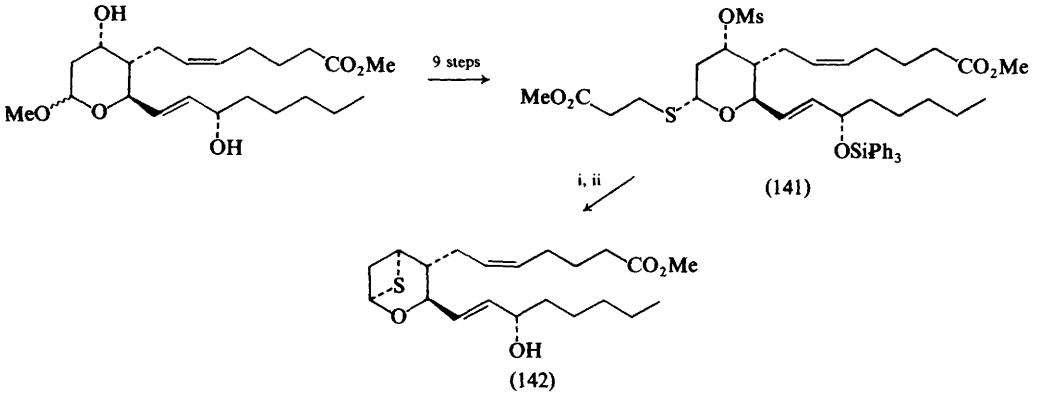
Prostacyclin synthetase has been reported to be a cytochrome *P*-450 enzyme.[68] Porter and Mebane[69] have carried out a model study of the conversion of PGH_2 into PGI_2 (see Section 3.1).



Reagents: i, TsCl, pyridine; ii, NaOMe, MeOH; iii, KO_2, DMF; iv, lipase; v, $MeSO_2Cl$; vi, MeCOSK, DMSO, DMF, at 50 °C; vii, K_2CO_3, MeOH; viii, O_2; ix, KOH, Bu^{t}OH

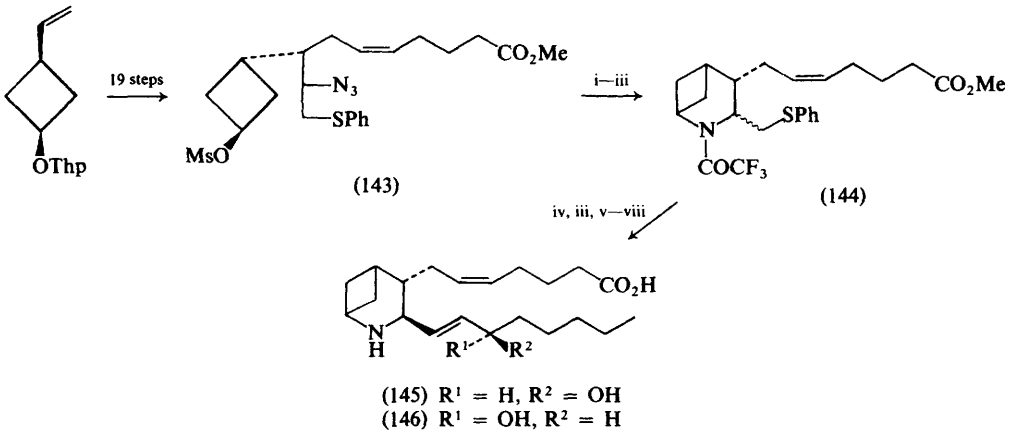
Scheme 23





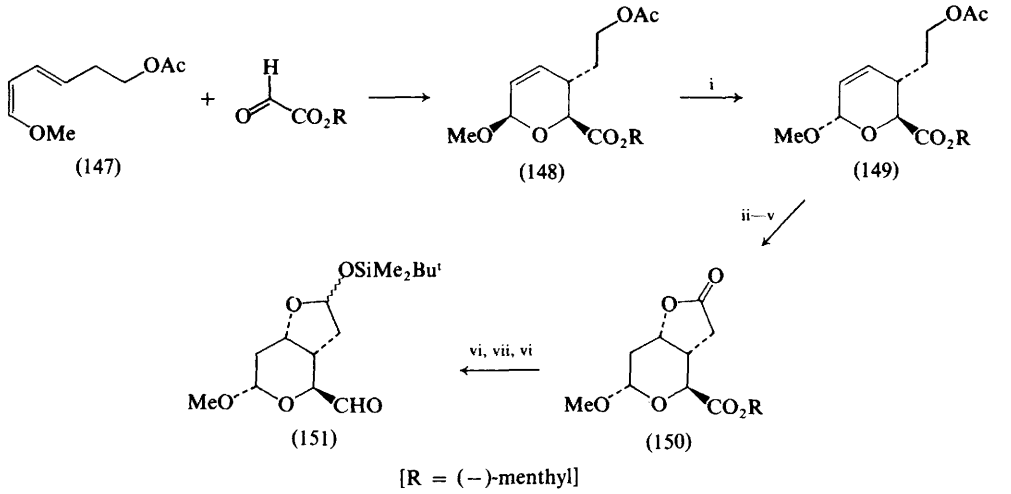
Reagents: i, $NaN(SiMe_3)_2$, at 60 °C, then HMPA at 70 °C; ii, Bu^n_4NF

Scheme 24



Reagents: i, $CrCl_2$; ii, NaH; iii, $(CF_3CO)_2O$; iv, $NaIO_4$; v, $NaHCO_3$; vi, $Bu_3P{=}CHCOC_5H_{11}$; vii, $NaBH_4$; viii, chromatography

Scheme 25



[R = (−)-menthyl]

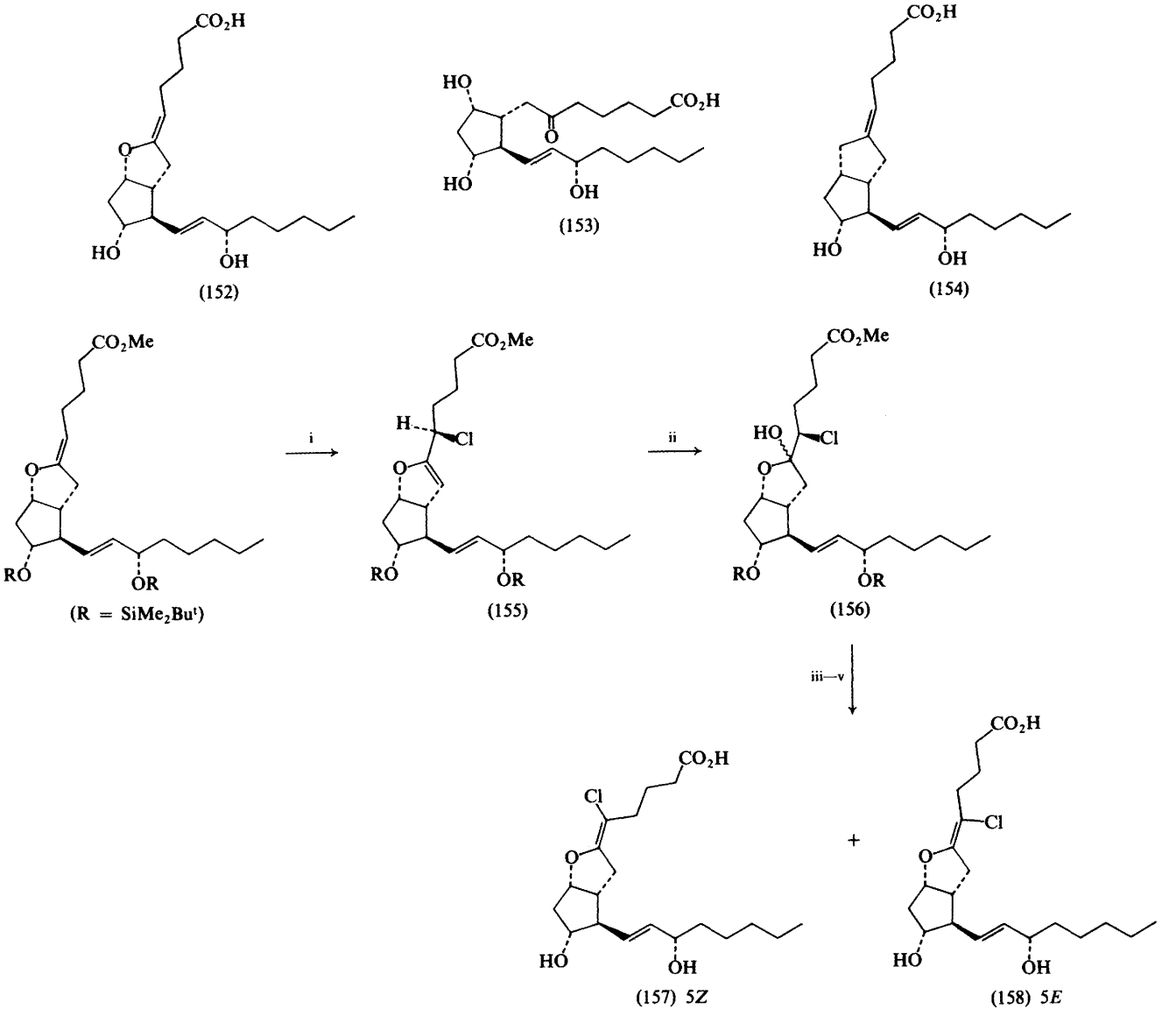
Reagents: i, $BF_3{\cdot}OEt_2$; ii, Na_2CO_3, MeOH; iii, pyridinium dichromate, DMF; iv, KI, I_2, THF; v, Bu^n_3SnH, toluene; vi, Bu^i_2AlH, toluene; vii, Bu^tMe_2SiCl, DMF

Scheme 26

A study of the hydride shift in the solvolysis of 5-substituted derivatives of PGI_1 has been reported,[96] and one-dimensional n.O.e. measurements have been applied to studies of 6a-carbaprostacyclin (154).[97]

4.2 The Synthesis of Prostacyclin Analogues

Much effort has been directed to the design of chemically more stable analogues of PGI_2. This is generally achieved by reducing the electron-density of the labile enol-ether moiety of PGI_2. One such approach has been the introduction of an electron-withdrawing group near the enol-ether moiety, as exemplified by 5-chloro-PGI_2 (158), reported by the Teijin research group (Scheme 27).[98] The *endo–exo* bond isomerization of (155) → (157)/(158) is noteworthy. After much experimentation, it was found that this was best achieved by mild hydration of (155) to the cyclic hemiacetal (156), followed by dehydration, using excess anhydrous magnesium sulphate in refluxing benzene. The (5*E*)-isomer (158) ($t_{\frac{1}{2}}$ = 1.5 h at pH 4.7)



Reagents: i, *N*-chlorosuccinimide, CCl_4; ii, wet benzene, pyridinium tosylate; iii, $MgSO_4$, benzene, heat; iv, Bu^n_4NF, Et_3N, THF; v, NaOH, H_2O

Scheme 27

was shown to be more stable than PGI2 ($t_{\frac{1}{2}}$ = 22 s at pH 5.98) and displayed platelet anti-aggregatory activity (IC_{50} = 0.14 $\mu g\ ml^{-1}$).

A similar approach to stabilized PGI_2 has been reported by the Chinoin group. The synthetic target, 7-oxo-PGI_2 (159), was initially prepared from $PGF_{2\alpha}$ (Scheme 28),[99] but this route has been superseded by an improved synthetic route, *via* (161), starting from the readily available protected PGI_2 isomer (160).[100]

The stable 7-oxo-PGI_2 (159) had a pharmacological profile very similar to that of PGI_2, although its potency was about an order of magnitude lower.

A flexible synthetic approach to the previously reported homo-PGI_2 (168)[101] has been reported by Newton and Wadsworth (Scheme 29).[102] Using the readily available bicyclo[3.2.0]heptan-6-one (162), this versatile synthetic route was adapted to prepare the carbacyclins (163) and (164) and the bicyclo[3.2.0]heptene analogues (165) and (166). Compounds (165) and (166) displayed anti-aggregatory activity in a collagen-induced platelet-aggregation assay.

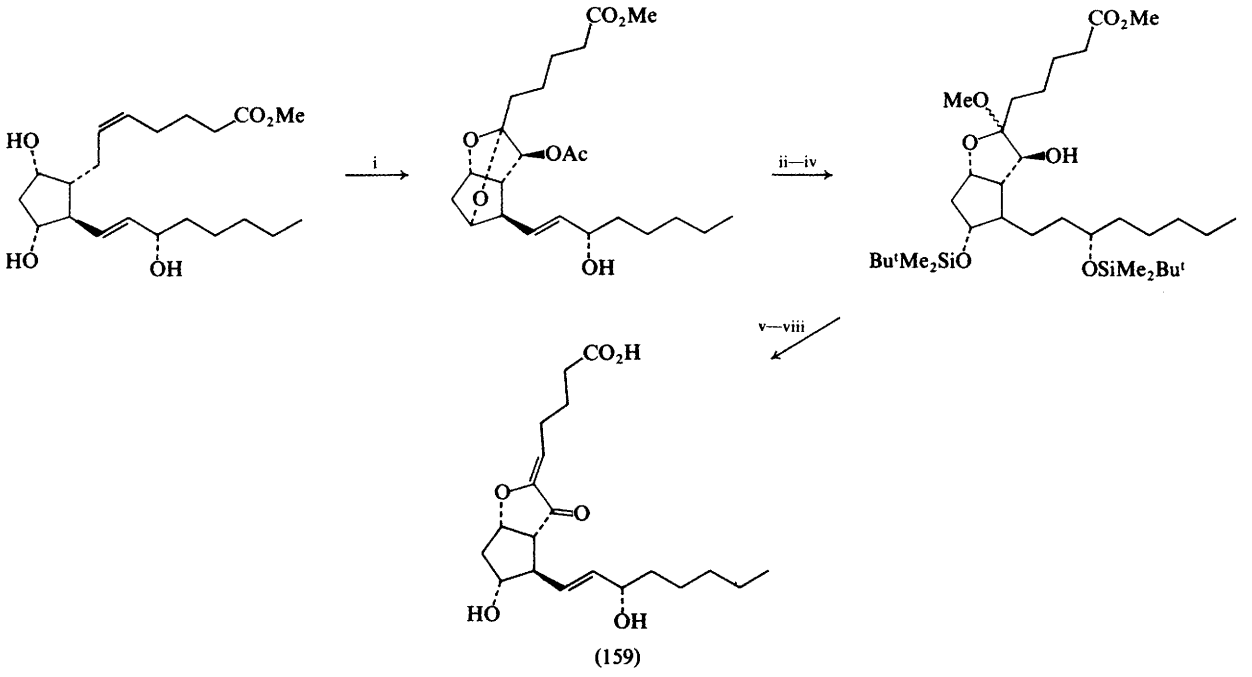
The syntheses of the related 11-deoxy-homo-PGI_2 analogues (167) and (168) have been reported in full.[103] Each of these analogues was only a weak inhibitor of the collagen-induced aggregation of blood platelets (1×10^{-3} times the effectiveness of PGI_2).

The six-membered-ring carbacyclin analogues (170) and (171) have been reported.[104] The synthesis utilized the readily available prostaglandin intermediate (169) (Scheme 30). The (*E*)- and (*Z*)-isomers in each case were separable. The (4*E*)-(170), (5*E*)-(171), and (5*Z*)-(171) were each inactive, *in vitro*, against the ADP-induced aggregation of human blood platelets. The isomer (4*Z*)-(170) showed marginal activity (ED_{50} > 500 < 1500 ng ml^{-1}) relative to PGI_2 (ED_{50} = 1—2 ng ml^{-1}). The (4*E*)- and (4*Z*)-isomers of (170) and (5*Z*)-(171) were comparable to PGE_1 in lowering blood pressure in rats.

Ikegami and co-workers have reported an interesting synthetic approach to the PGI_2 analogue (176) (Scheme 31).[105] The well-known lactone (172) was first converted, by a novel sequence of reactions, into the acetylenic intermediate (174) *via* a vinylstannane (173). The thiazoline ring was subsequently constructed *via* a 5-*endo-dig* ring-closure of the thioacetate (175).

In later work, Ikegami *et al.*[106] also showed that the PGI_2 analogue (176) can be readily prepared from the protected thiaprostacyclin (177) (prepared from PGE_2 by known methods) by isomerization of the exocyclic 5–6 double-bond to the endocyclic 6–7 position under controlled acidic conditions.

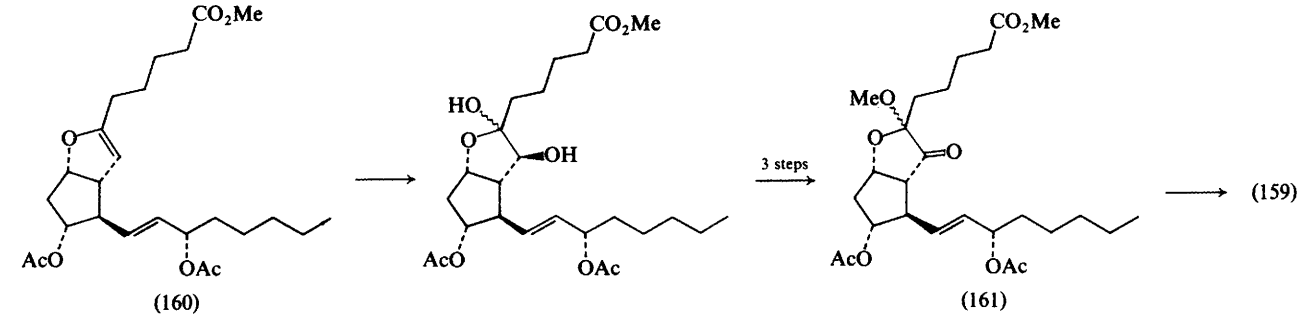
The analogue (176) exhibited the expected improved chemical stability, and had anti-aggregatory activity against rabbit blood platelets (10^{-2} times the potency of PGI_2).



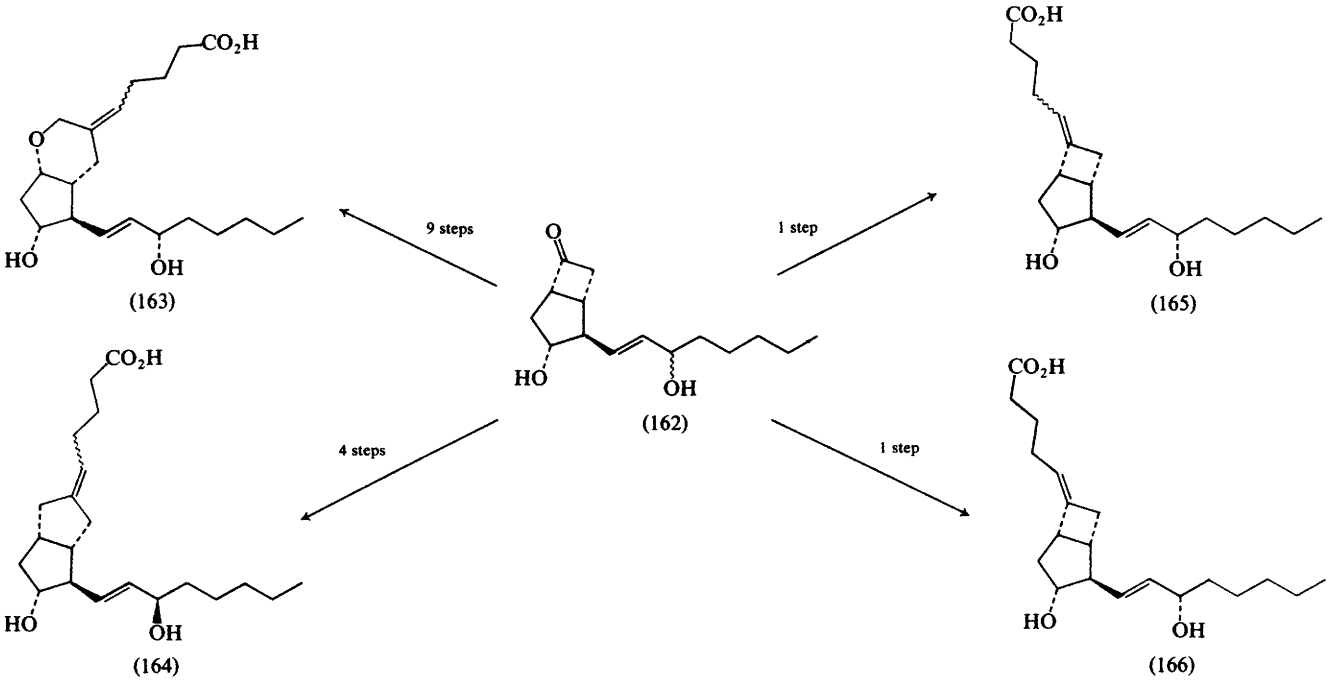
(159)

Reagents: i, $Tl(OAc)_3$, AcOH; ii, $BF_3 \cdot OEt_2$, MeOH; iii, Bu^tMe_2SiCl, imidazole, DMF; iv, KOH, MeOH; v, pyridinium chlorochromate, NaOAc, CH_2Cl_2; vi, $Bu^n_4N^+ F^-$, THF; vii, HMPA, at 150—160 °C; viii, NaOH, MeOH, H_2O

Scheme 28



(160) (161)



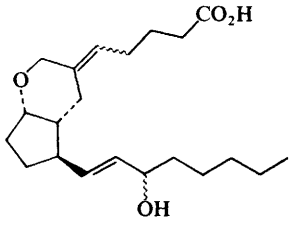
(163) (165) (162) (164) (166)

Scheme 29

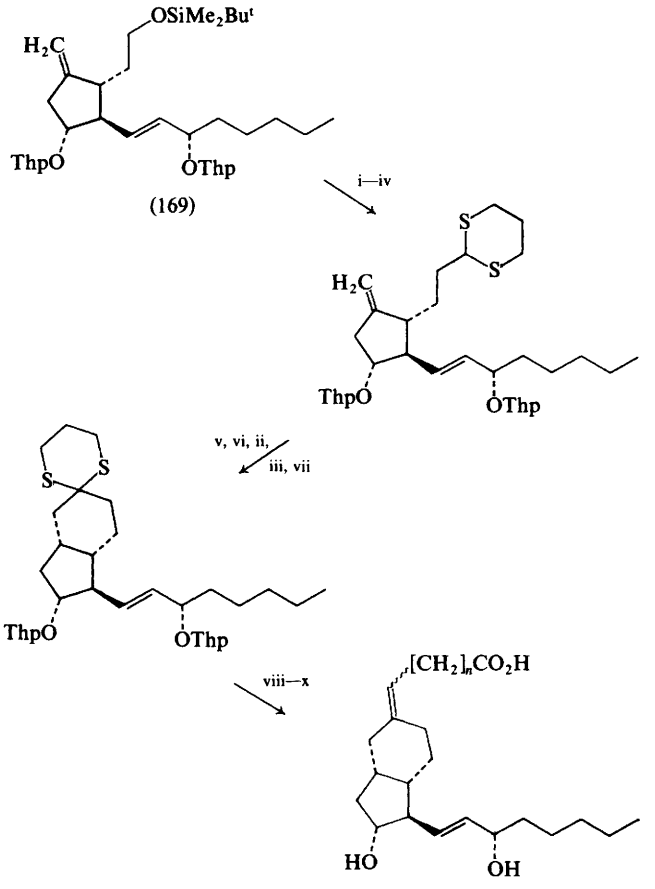
The pyrrole analogues (179) and (180), synthesized in seven steps from prostacyclin methyl ester (178), have been reported by the Upjohn research group.[107] Interestingly, (179) and (180) inhibited the biosynthesis of leukotrienes C_4 and D_4 in rat peritoneal mononuclear cells (IC_{50} = 0.3 and 4.6 μmol dm^{-3}, respectively). These compounds also antagonize leukotriene C_4/D_4 contractions *in vitro* and displayed inhibition of bronchopulmonary changes in animal models *in vivo*.

The Hoechst research group has reported the synthesis of the dihydropyrrole variant (184) from the bicyclo[3.2.0]heptenone (181) (Scheme 32).[108] The key five-membered lactam intermediate (183) was formed, along with its isomer (185), by a modified Beckmann-type rearrangement of the cyclobutanone (182). In the final stages, these isomers and their respective C-15 epimers were separated by chromatography. The deoxypyrrole analogue (187), reported by the same group, was prepared in a similar way from the known lactam (186).[109]

Noyori *et al.*[110] have disclosed a synthetic approach to the novel pyrazole analogue prostacyclin (192) which is based on the recently reported[111] α-alkoxyalkylation of αβ-unsaturated ketones (Scheme 33). The key intermediate enol-ether (191) was prepared by the conjugate addition of phenylselenotrimethylsilane to the chiral cyclopentenone (188), followed by an aldol-type reaction with trimethyl orthoformate. Subsequent oxidation of the intermediate selenide (189) to the selenoxide, followed by β-elimination, afforded (190), which was readily elaborated to the (−)-pyrazole-containing prostacyclin (192) and its isomer (193).



(167) 5*Z*
(168) 5*E*

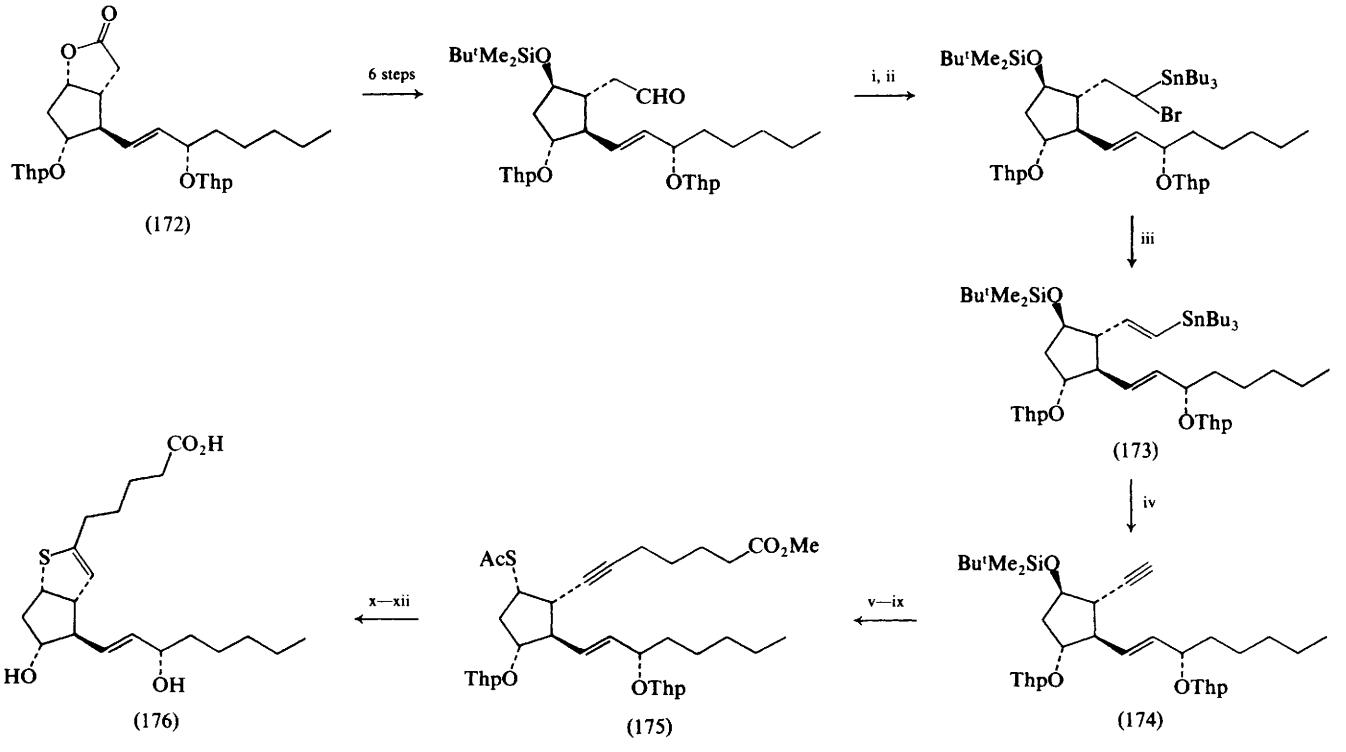


(169)

(170) n = 2 [(4*E*) and (4*Z*)]
(171) n = 3 [(5*E*) and (5*Z*)]

Reagents: i, $Bu^n_4N^+ F^-$; ii, $PhSO_2Cl$, pyridine; iii, LiBr, $NaHCO_3$; iv, dithiane, Bu^nLi; v, 9-borabicyclononane; vi, H_2O_2; vii, $LiNPr^i_2$; viii, MeI, $CaCO_3$; ix, $Ph_3P{=}CH[CH_2]_nCO_2Na$; x, AcOH, H_2O, THF

Scheme 30

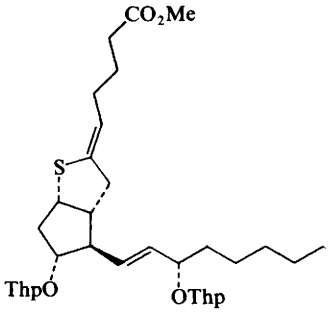


(172) (173) (174) (175) (176)

Reagents: i, Bu^n_3SnLi; ii, CBr_4, PPh_3, iii, DBU; iv, $Pb(OAc)_4$; v, $LiNPr^i_2$, $OHC[CH_2]_3CO_2Me$; vi, CCl_4, HMPA; vii, Bu^n_3SnH, toluene; viii $Bu^n_4N^+ F^-$; ix, PPh_3, $Pr^iO_2CN{=}NCO_2Pr^i$, AcSH; x, H_3O^+; xi, K_2CO_3, MeOH; xii, LiOH, H_2O, THF

Scheme 31

Several thiazole-containing prostacyclin analogues, *e.g.* (197) and (198), have been reported by the Syntex research group.[112] These have been prepared by elaboration of the epoxy-cyclopentene (194), as shown in Scheme 34. It is interesting to note that in this sequence the benzyloxymethyl groups appear to enhance regioselective halohydrination {[(195)]:[(196)] = 5:1} and hinder electrophilic attack on the 13–14 double-bond.



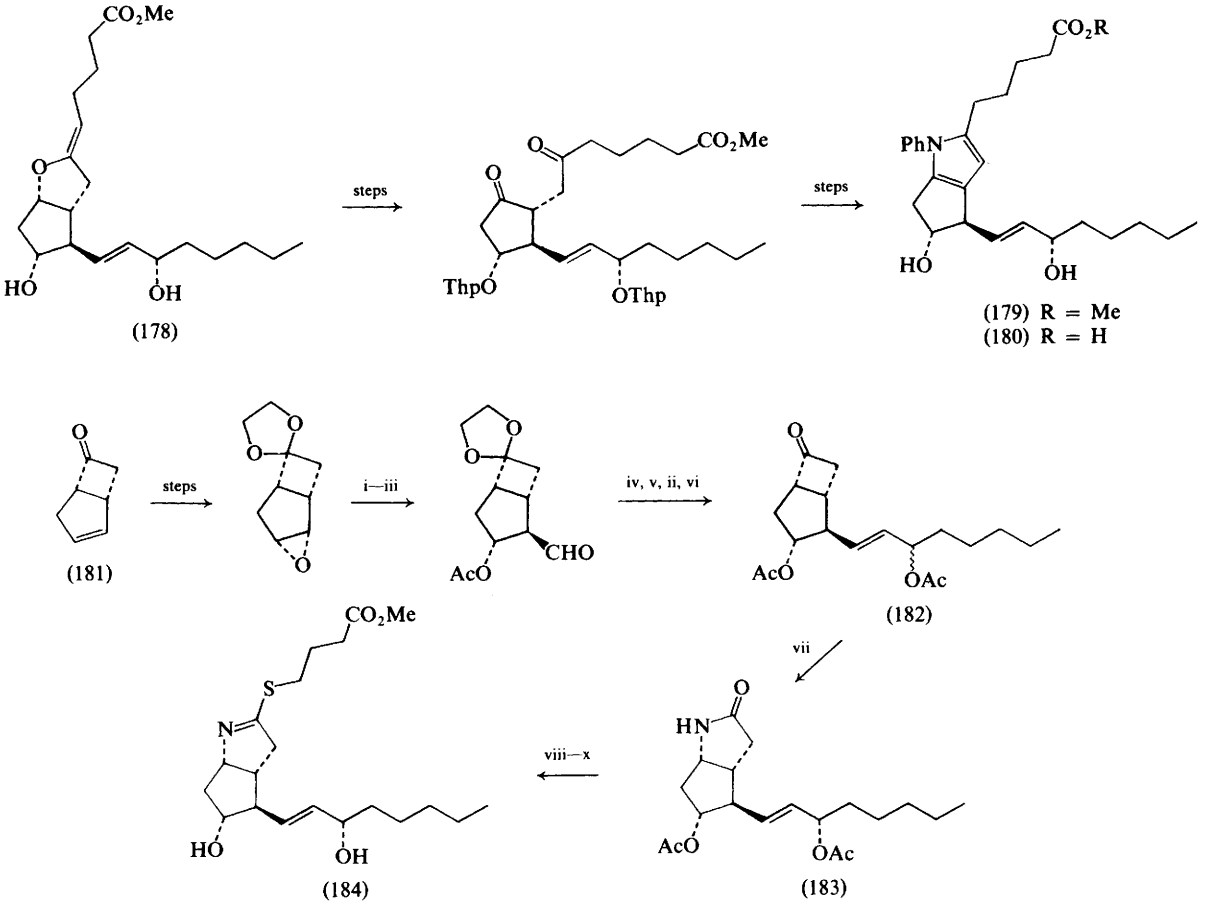
(177)

Most of these analogues showed weak to moderate inhibitory activity in the ADP-induced platelet-aggregation assay. The most potent compound was the methoxy-derivative (199) (0.16 times the activity of PGE_1), which was an intermediate in the synthesis of (198).

The furan-based seco-prostacyclin (200) has been reported by Saunders and co-workers.[113]

The Upjohn research group has described the synthesis of side-chain-modified analogues such as *cis*-4,5-didehydro-PGI_1 [(205), (206)] and 4,4,5,5-tetradehydro-PGI_1 [(203), (204)] (Scheme 35).[114] The early separation of the (6*R*)- and (6*S*)-isomers (201) and (202), respectively, is noteworthy. Subsequent formation of a cyclic ether appeared to proceed *via* tosylation of the less hindered hydroxyl group at C-6 followed by an intramolecular S_N2-type displacement, resulting in the inversion of configuration at C-6.

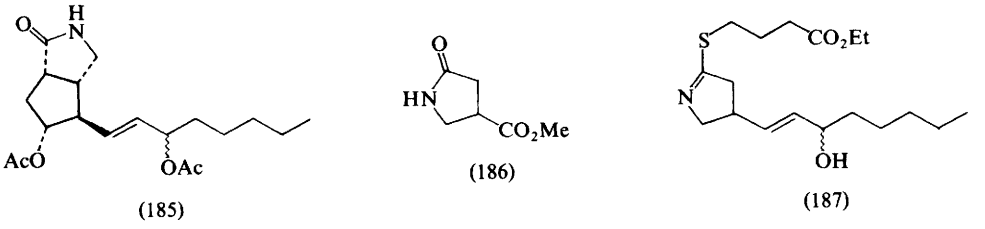
The 4-thiaprostacyclin analogue (209) has been disclosed by the Teijin group (Scheme 36).[115] The starting material, (*R*)-(207), was resolved from racemic material, using (1*R*,5*S*)-4-hydroxy-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (211), *via* the intermediate (212). Conjugate addition of the ω-side-chain to (207) followed by asymmetric reduction afforded



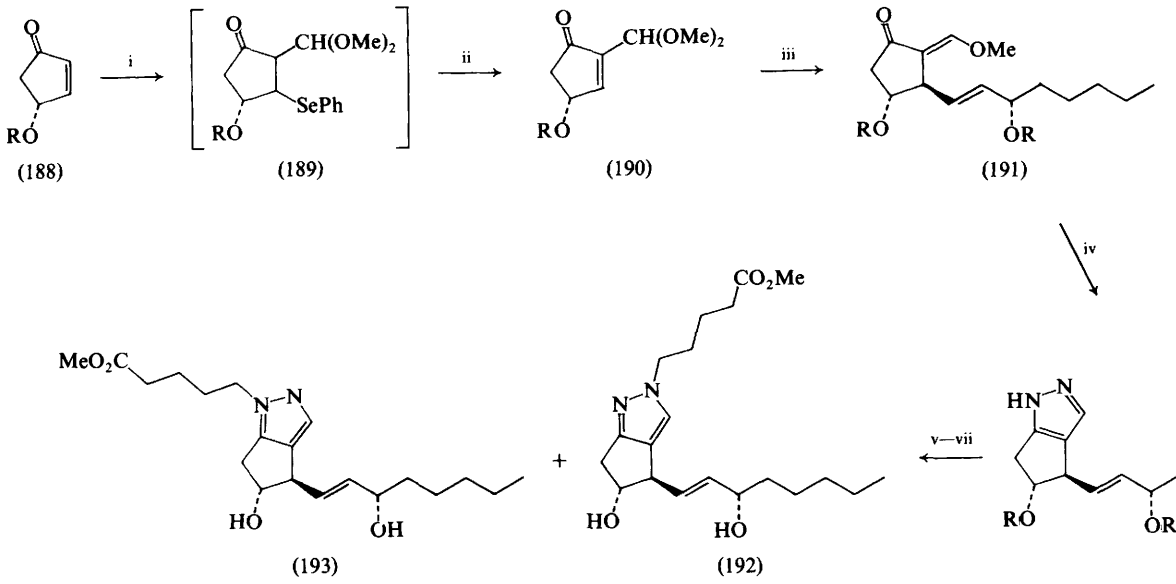
(178) (179) R = Me (180) R = H (181) (182) (183) (184)

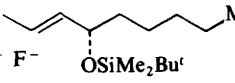
Reagents: i, dithiane, Bu^nLi; ii, Ac_2O, pyridine; iii, HgO, $BF_3{\cdot}OEt_2$; iv, $(MeO)_2P(O)CH_2COC_5H_{11}$, NaH, DME; v, $Zn(BH_4)_2$, diglyme; vi, H_3O^+; vii, 2,4,6-$Me_3C_6H_2SO_2ONH_2$; viii, P_4S_{10}, pyridine; ix, $Br[CH_2]_3CO_2Et$, NaH, DME; x, K_2CO_3, MeOH

Scheme 32

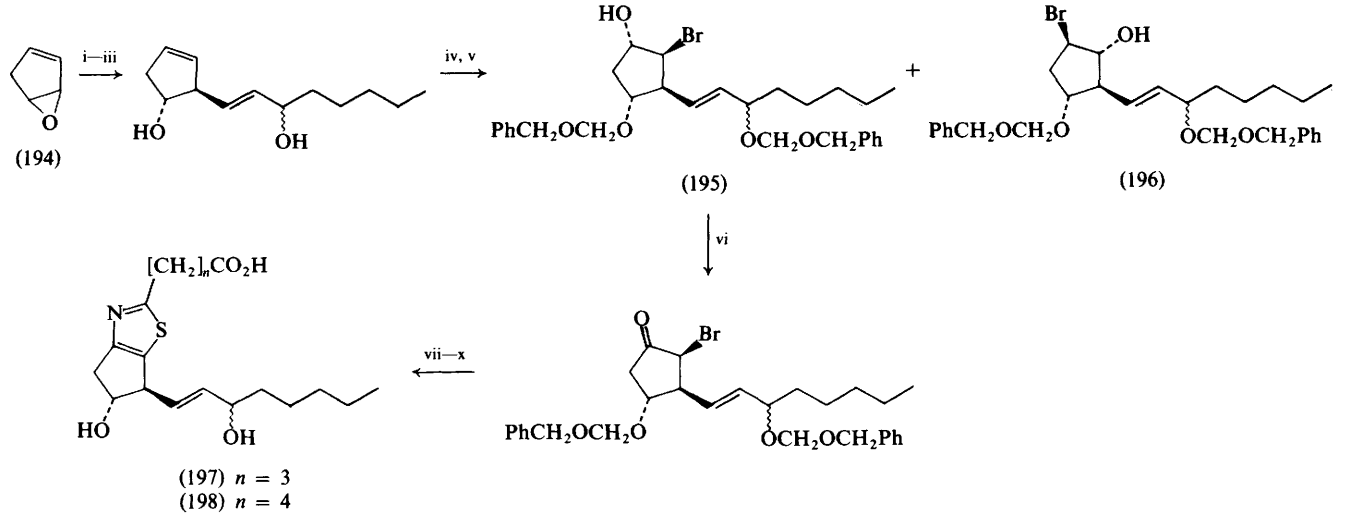


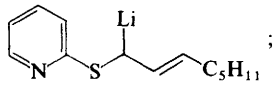
(185) (186) (187)



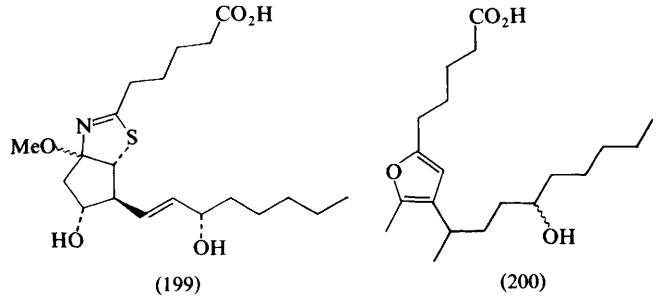
Reagents: i, $PhSeSiMe_3$, $Me_3SiO_2CCF_3$, then $CH(OMe)_3$, then pyridine; ii, H_2O_2; iii, $LiCu(\text{  })_2PBu_3$; iv, NH_2NH_2; v, $I[CH_2]_4CO_2Me$, KH, HMPA; vi, chromatography, separation of isomers; vii, $Bu^n_4N^+\ F^-$

Scheme 33



Reagents: i,  ; ii, *m*-chloroperbenzoic acid; iii, $P(OMe)_3$; iv, $PhCH_2OCH_2Cl$, Pr^i_2NEt; v, *N*-bromosuccinimide, DMSO, H_2O; vi, pyridinium chlorochromate; vii, $MeO_2C[CH_2]_nCSNH_2$; viii, PPh_3, $EtO_2CN{=}NCO_2Et$; ix, TsOH; x, NaOH

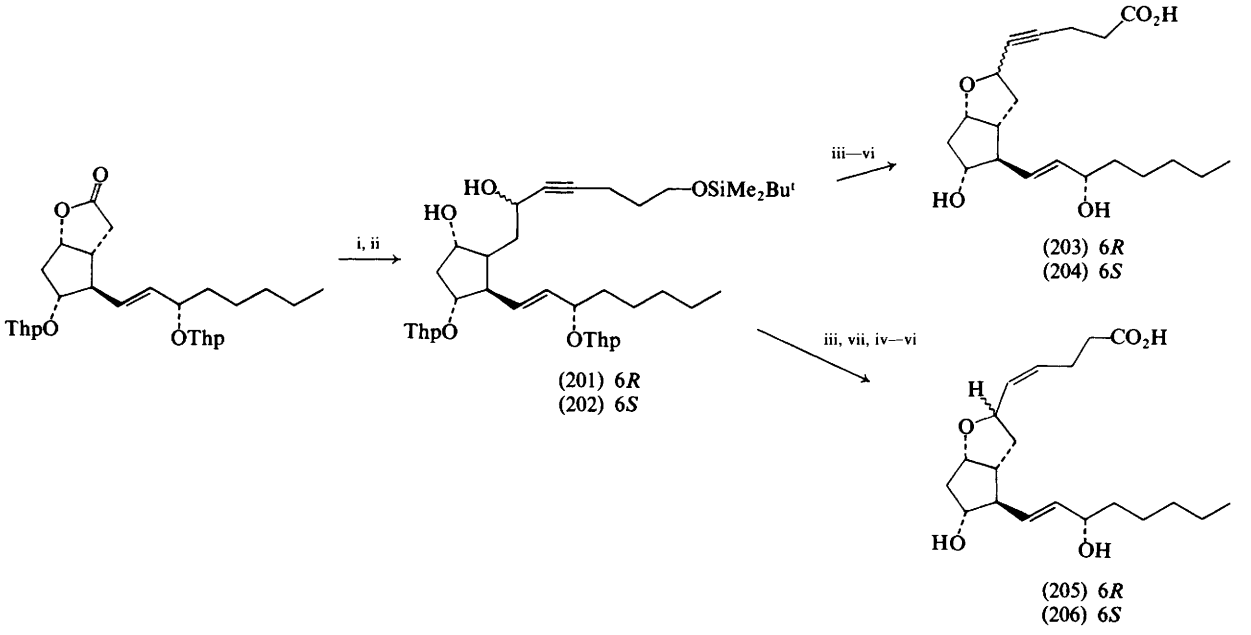
Scheme 34



(208). Treatment of (208) with 2-(methoxycarbonyl)ethylsulphenyl chloride then furnished both the 6α- and the 6β-isomer, (209) and (210) respectively, after deprotection. Both (209) and (210) were inactive in the platelet-aggregation assay, although (209) showed some inhibition of ethanol-elicited gastric lesions.

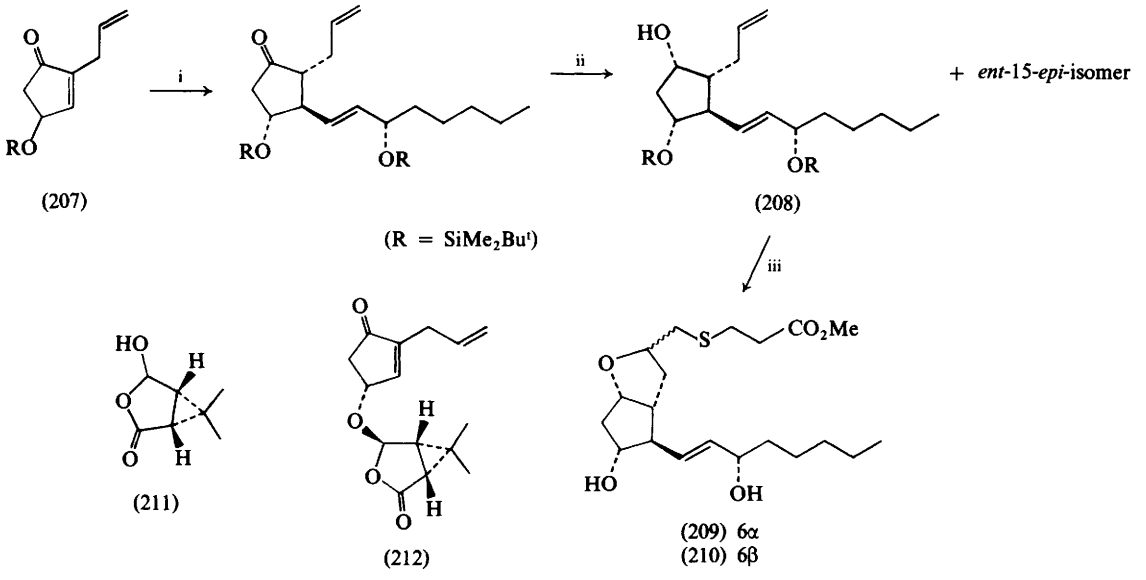
Szántay *et al.*[116] have reported syntheses of the 13-oxa- and 13-thia-prostacyclins (215) and (216). These were prepared from the optically active and readily available epoxy-alcohol (213) *via* the intermediate (214). Both of these prostacyclin analogues were hypotensive and potent inhibitors of the ADP-induced aggregation of blood platelets. The 13-oxaprostacyclin analogue (215) was equipotent to PGI_2 in the latter assay, indicating the isosteric relationship between their ω-side-chains.

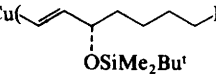
The fused tricyclic analogue (219) that has been reported by the Upjohn research group combines ring and side-chain modifications of PGI_2 in one (Scheme 37).[117] Intramolecular alkylation of (217) through to the phenol (218) occurred predominantly at the *ortho*-position. However, the aldol-type cyclization of the precursor (220) could be directed to provide the *ortho*- (222) or the *para*- (223) aldol products, depending on the reaction conditions. For example, the treatment of (220)



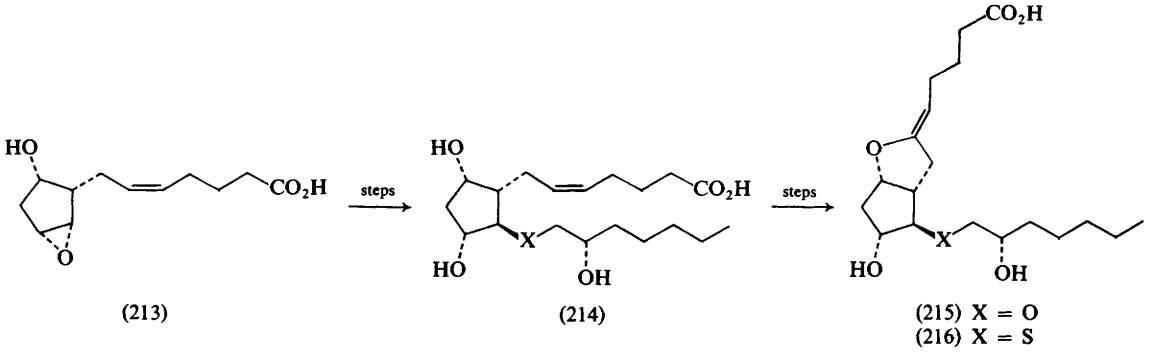
Reagents: i, $LiC{\equiv}C[CH_2]_3OSiMe_2Bu^t$; ii, $NaBH_4$; iii, TsCl, pyridine; iv, $Bu^n_4N^+F^-$; v, Jones oxidation; vi, acid; vii, H_2, 5% $Pd/BaSO_4$, pyridine

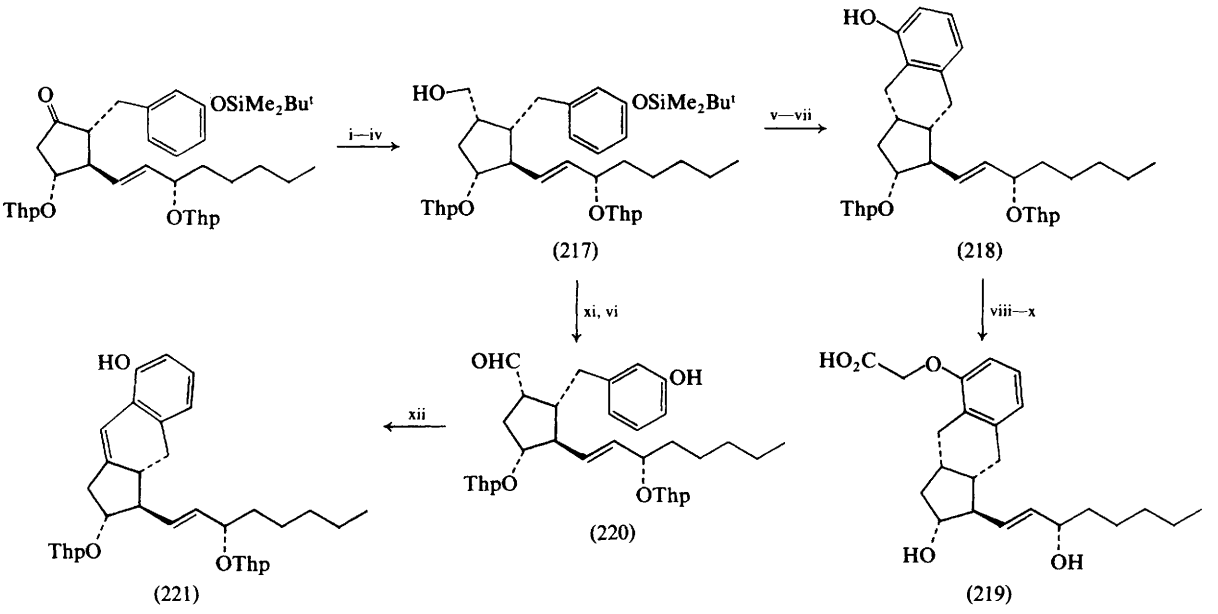
Scheme 35



Reagents: i, $LiCu(\text{  }Me)_2$; ii, L-Selectride; iii, $MeO_2CCH_2CH_2SCl$

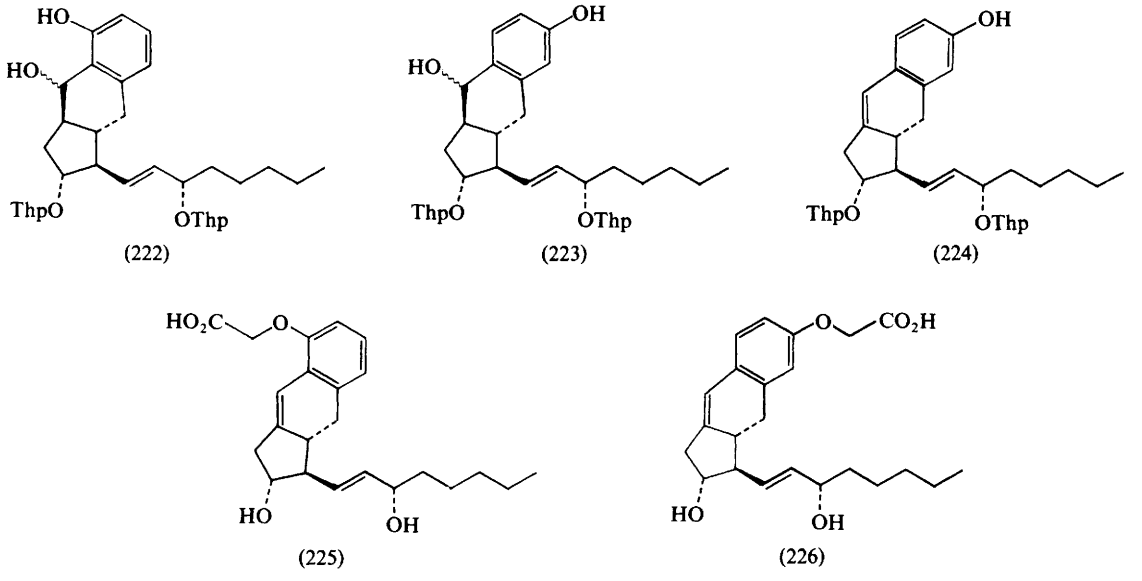
Scheme 36





Reagents: i, *S*-methyl-*S*-phenyl-*N*-methylsulphoximide; ii, Al/Hg, AcOH; iii, 9-borabicyclononane; iv, H_2O_2; v, $MeSO_2Cl$, Et_3N; vi, $Bu^n_4N^+F^-$; vii, NaH, glyme, heat; viii, $BrCH_2CO_2Et$, NaH, glyme; ix, AcOH; x, KOH, MeOH; xi, Collins oxidation; xii, MeMgCl, glyme

Scheme 37



with methylmagnesium chloride in glyme afforded exclusively the *ortho*-adduct (222), which was further dehydrated to the *ortho*-vinylphenol (221) under the reaction conditions. Alternatively, the tetra-n-butylammonium phenoxide of (220), in refluxing THF, furnished exclusively the *para*-aldol product (223), which was subsequently dehydrated to (224). The phenols (221) and (224) were then elaborated to (225) and (226) respectively.

The prostacyclin analogues (219) and (225) were found to be potent inhibitors of the aggregation of blood platelets, the former being twice as active as 6a-carbaprostacyclin (154).

5 Leukotrienes

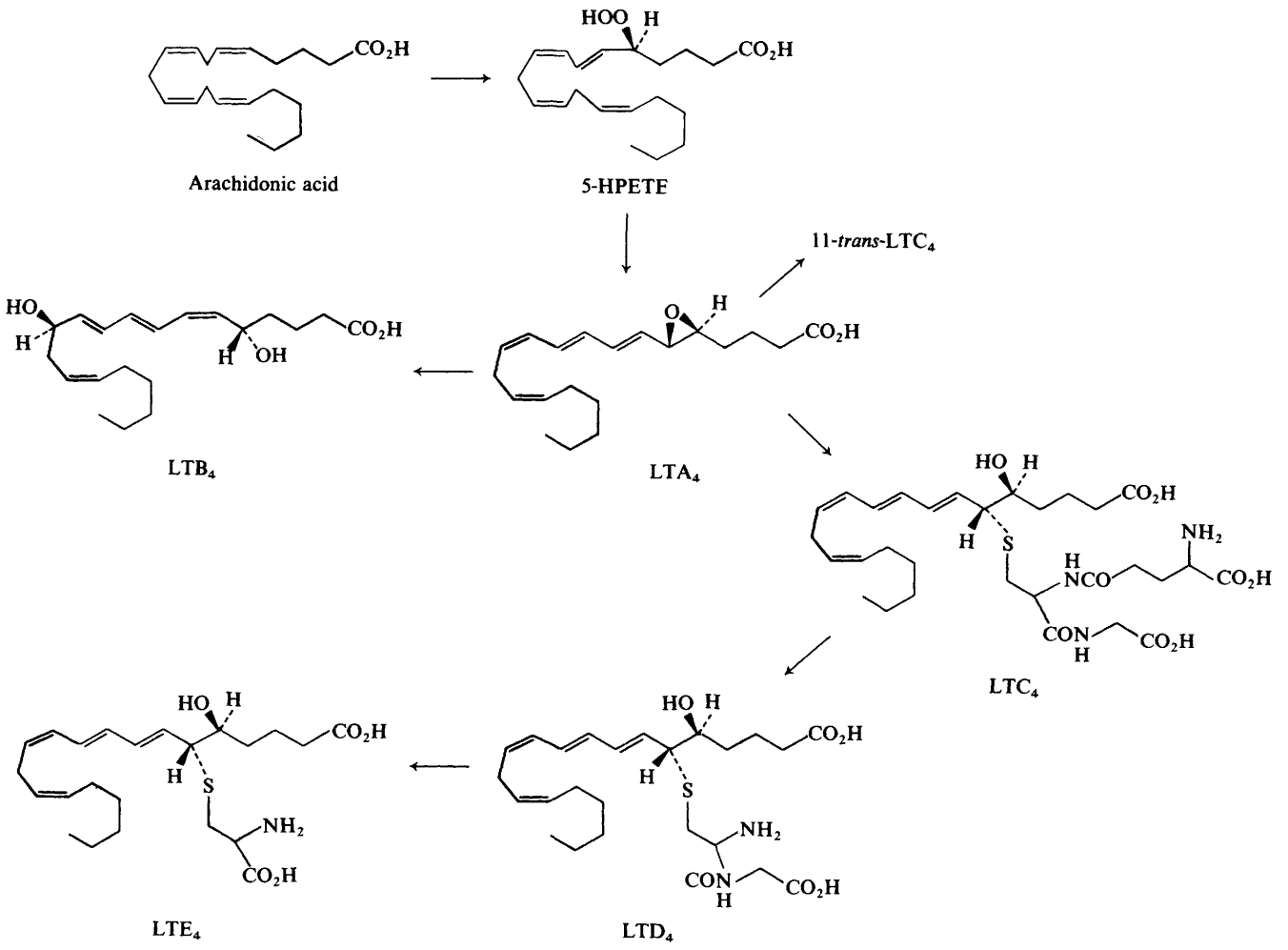
5.1 General

Several reviews on the chemical synthesis[118,119] and on biochemical[120–123] and pharmacological[124,125] aspects of leukotrienes have been published. A book reviewing the biosynthesis and biological actions of leukotrienes has also appeared.[126]

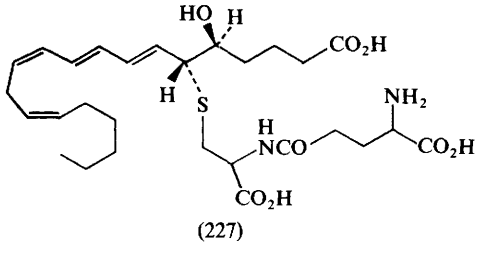
This class of arachidonic acid metabolites is derived from the 5-lipoxygenation of arachidonic acid, leading to (5*S*)-5-hydroperoxyicosa-6,8,11,14-tetraenoic acid (5-HPETE). The latter is then acted upon by a dehydrase and converted into the pivotal intermediate leukotriene A_4 (LTA_4). At this point, LTA_4 is metabolized along three pathways. The action of a hydrolase on LTA_4 results in the formation of leukotriene B_4 (LTB_4), while conjugation of glutathione in the presence of glutathione-*S*-transferase affords leukotriene C_4 (LTC_4) and 11-*trans*-LTC_4. Leukotriene D_4 (LTD_4) and leukotriene E_4 (LTE_4) are formed by sequential enzymic cleavage of the glutathione group of LTC_4 (Scheme 38).

The isolation and purification of 5-lipoxygenase and leukotriene-forming enzymes have been fully described.[127] In particular, it has been shown that the enzymes that are responsible for the formation of LTC_4 and LTD_4 are located on the cell membrane.[128] The more labile LTA_4 has been reported to be stabilized, in aqueous medium, by vertebrate albumins.[129] Under this condition, LTA_4 can be converted into LTD_4, using a cell-free epoxide hydrolase from rat basophilic leukaemia cells.[130]

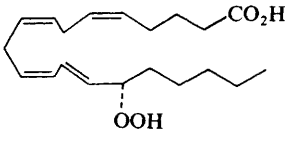
The levels of the glutathione-*S*-transferase and the γ-glutamyl transpeptidase activity in guinea-pig lung and rat basophilic leukaemia cells have been reported.[131] The inter-



Scheme 38



(227)



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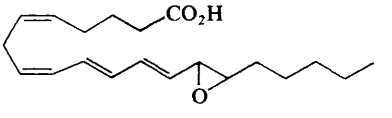

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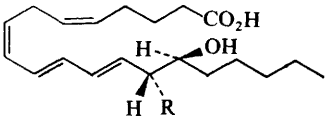
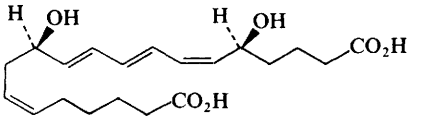
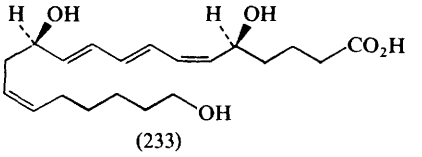


(230) R = glutathion-*S*-yl
(231) R = 1-glycinocystein-*S*-yl



(232)



(233)

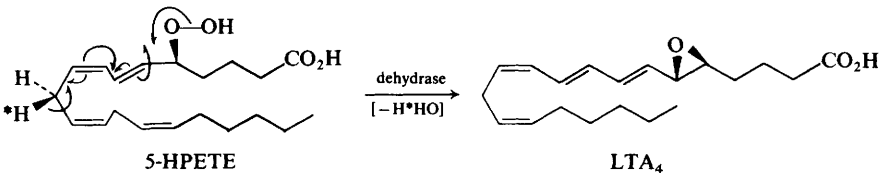
conversion of LTC_4 and LTD_4 by highly purified γ-glutamyl transpeptidase and glutathione has been studied.[6] In addition, incubation of LTE_4 with γ-glutamyl transpeptidase and glutathione has led to the isolation of a new leukotriene, LTF_4 (227).

Two other classes of leukotrienes have been reported. The proposed 14,15-LTA_4 (229), derived from the 15-HPETE (228), has been isolated, and the corresponding 14-glutathion-*S*-yl conjugate LTC_4 (230) and the related metabolite LTD_4 (231) have been identified.[7] The other class of novel leukotrienes (232) and (233) has been isolated from stimulated human polymorphonuclear leukocytes. These metabolites are derived from ω-oxidation of LTB_4 and possess chemotactic properties.[8]

A comparative study of eight synthetic isomers of 6-(1-glycinocystein-*S*-yl)-5-hydroxyicosa-7,9,11,14-tetraenoic acids with authentic guinea-pig slow-reacting substance of anaphylaxis (SRS-A) has confirmed the findings of other workers that its structure is (7*E*,9*E*,11*Z*,14*Z*)-(5*S*,6*R*)-6-(1-glycinocystein-*S*-yl)-5-hydroxyicosa-7,9,11,14-tetraenoic acid (LTD_4).[132]

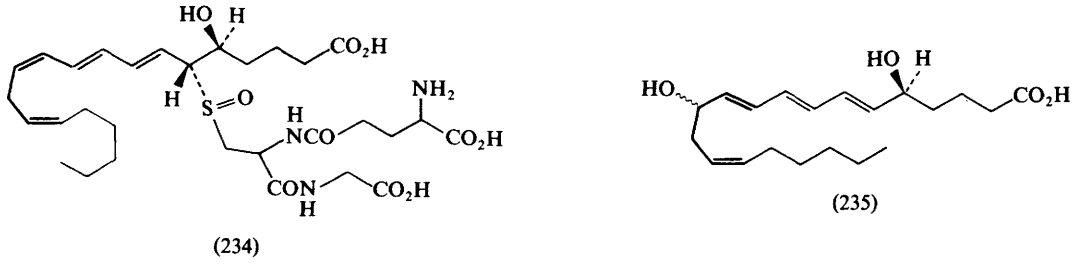
Independent reports by Oates *et al.*[133] and by Samuelsson *et al.*[134] have demonstrated the stereospecific removal of the *pro-R* hydrogen at C-10 during the enzymatic formation of LTA_4 from 5-HPETE (Scheme 39).

The metabolism of leukotrienes has been reviewed.[126] More recently, it has been shown that LTC_4 is metabolized in stimulated human polymorphonuclear leukocytes into three classes of physiologically inactive products.[9] Two of these have

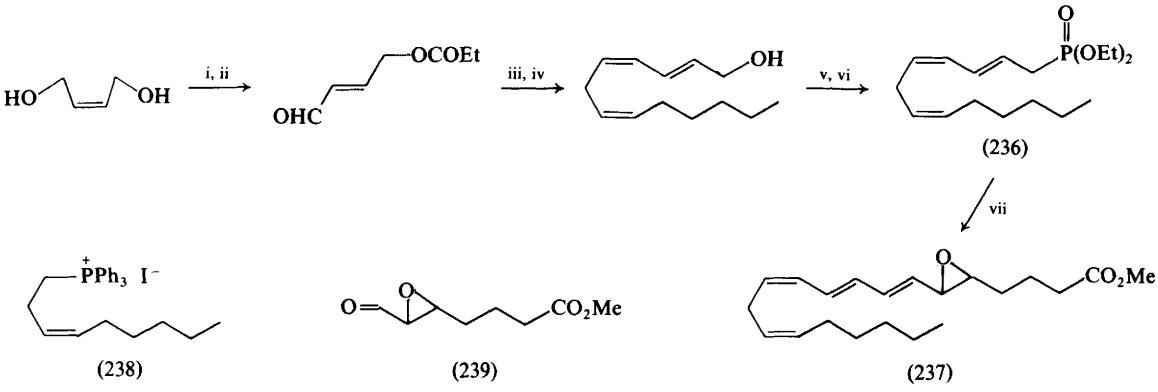


5-HPETE LTA_4

Scheme 39



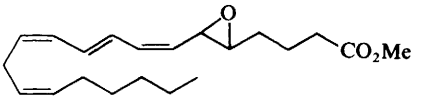
(234) (235)



(238) (239) (236) (237)

Reagents: i, $(EtCO)_2O$, Me_3COMe; ii, pyridinium chlorochromate; iii, Bu^nLi, HMPA, (238); iv, K_2CO_3, MeOH; v, CBr_4, PPh_3; vi, $P(OEt)_3$; vii, (239), NaH, THF, 15-crown-5

Scheme 40



(240)

been identified as the diastereoisomers of LTC_4 sulphoxide (234) and 6-*trans*-LTB_4 (235). Further chemical evidence presented by Corey *et al.*[135] indicated an identical conversion of LTC_4 into diastereoisomeric (234) and (235) in the presence of hypochlorous acid.

High-resolution ^1H n.m.r. studies of LTA_4 methyl ester, LTB_4 methyl ester diacetate, and 12-*epi*-(6*E*,8*Z*)-LTB_4 methyl ester diacetate have been reported.[136]

5.2 The Synthesis of Leukotrienes

5.2.1 Leukotriene A_4

A stereospecific synthesis of the (±)-LTA_4 methyl ester (237), based on the Wadsworth–Emmons olefination of the C_7 epoxy-aldehyde (239) and the C_{13} olefinic phosphonate ester (236), has been reported by the Glaxo research group (Scheme 40).[137] Under the reaction conditions, the tetraene epoxide (237) was formed in 34% yield and free from contamination by geometric isomers. The (±)-7-*cis*-LTA_4 methyl ester (240) was prepared by Wittig olefination of (239), using the phosphonium salt corresponding to (236).

An alternative synthesis of LTA_4 methyl ester and 7-*cis*-LTA_4 methyl ester has been described by the Ciba–Geigy research group (see Section 5.2.3).[144]

5.2.2 Leukotriene B_4

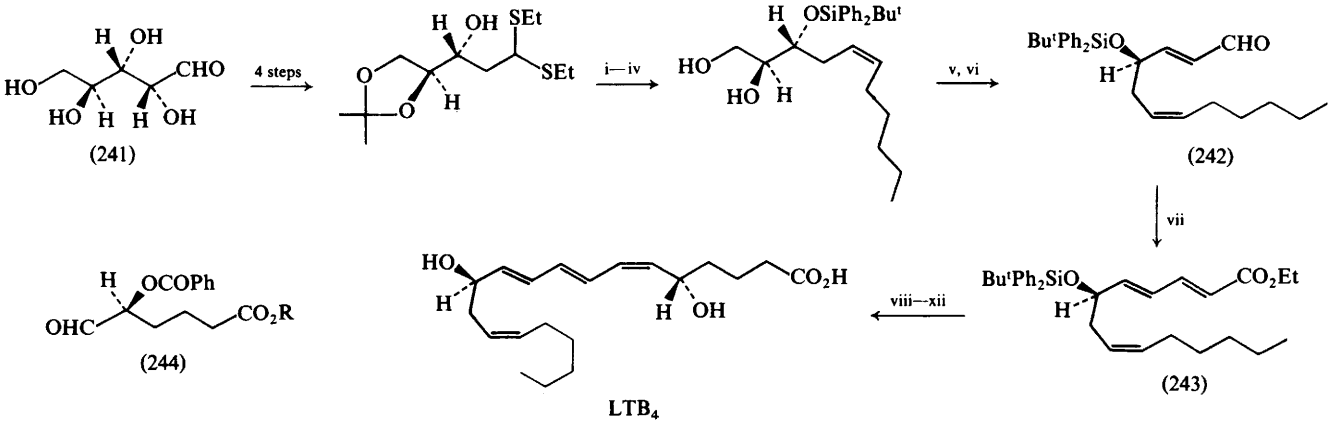
The Merck research group has reported a versatile stereospecific synthesis of LTB_4 (Scheme 41).[138] The C_{12} chiral alcohol (242), prepared from L-arabinose (241), was elaborated to give the C_{14} chiral ester (243). Reduction of (243), followed by bromination, conversion into the corresponding phosphonium salt, and subsequent olefination with (244; R = Et), then furnished LTB_4 after saponification. The C_6 chiral aldehyde (244; R = Et) was readily available either from 2-deoxy-D-ribose, in six steps,[139] or by a semi-microbial procedure (see Section 6.2).[140] The 12-*epi*-LTB_4 (245) was prepared in a similar fashion from D-arabinose by the same route.

The triene intermediate (243) has also been prepared from 2-deoxy-D-ribose (246) *via* the *C*-glycoside (247), which is unmasked by base-promoted ring-opening (Scheme 42).[141] The 12-*epi*-LTB_4 (245) was found to be about 16 times less potent than the natural LTB_4 in a rat neutrophil aggregation assay.[138]

A synthesis of the recently reported LTB_4 metabolites (232) and (233)[134] has been reported by the Merck research group.[142] The synthesis utilizes the chiral intermediate (248) (Scheme 43).

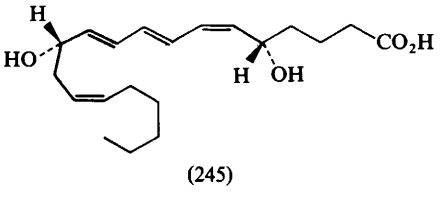
5.2.3 Leukotrienes C_4, D_4, E_4, and F_4 and Related Metabolites

Corey *et al.*[143] have reported a biomimetic synthesis of chiral LTC_4 and LTD_4 from readily available racemic 5-HPETE. This method is useful for providing small quantities of SRS-A for biological studies.

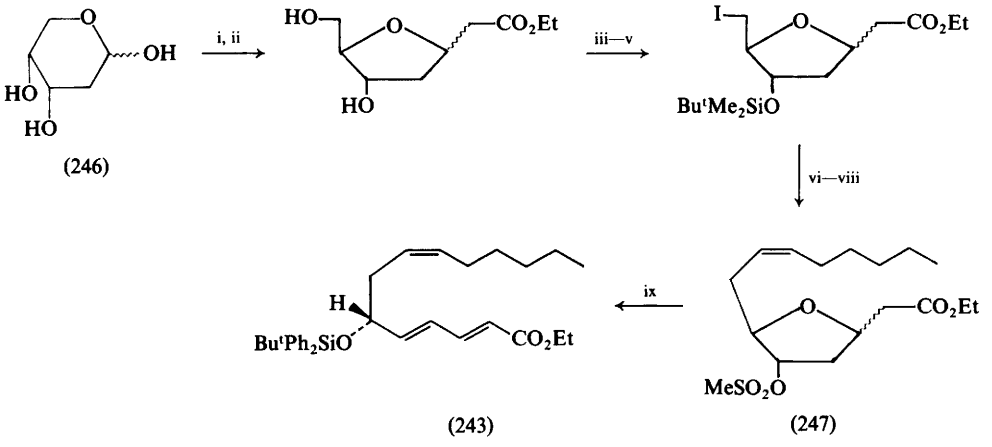


Reagents: i, Bu^tPh_2SiCl, 4-dimethylaminopyridine, NEt_3; ii, *N*-chlorosuccinimide, $AgNO_3$, MeCN; iii, $Ph_3P{=}CH[CH_2]_4Me$; iv, CF_3CO_2H; v, $Pb(OAc)_4$, Na_2CO_3; vi, $Ph_3P{=}CHCHO$; vii, $(EtO)_2P(O)CH_2CO_2Et$, NaH; viii, AlH_3; ix, CBr_4, PPh_3; x, Bu^nLi, HMPA, (244; R = Et); xi, $Bu^n_4N^+\ F^-$; xii, saponification

Scheme 41

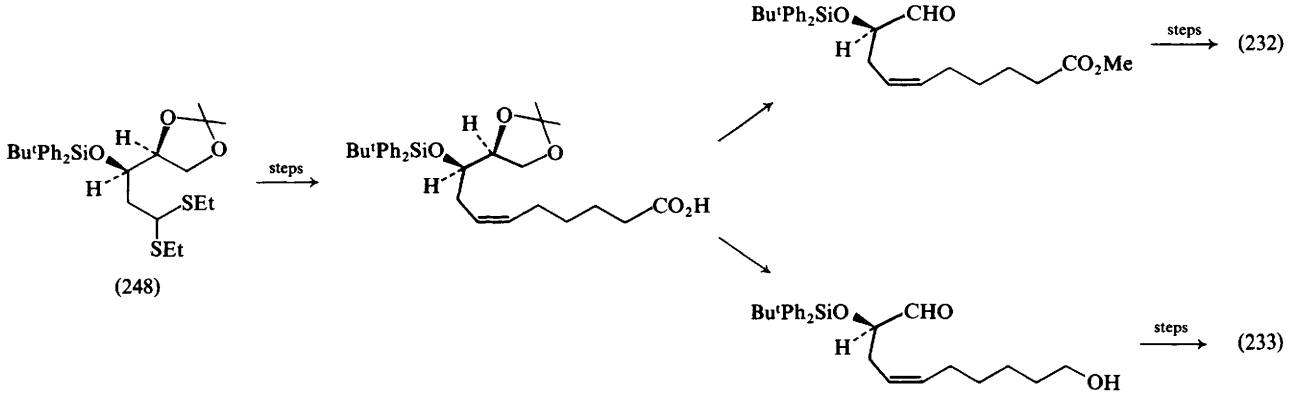


The Ciba–Geigy research group[144] has reported the synthesis of the novel 7-*cis*-LTD_4 (253). The 7-*cis* double-bond (using the prostaglandin numbering) is introduced *via* olefination of the known epoxy-aldehyde (239) with triphenylphosphoranylidenecrotonaldehyde (249) at an early stage. A second olefination of (250) gave 7-*cis*-LTA_4 methyl ester (252). Subsequent conjugation of (252) with a protected cysteinylglycine and deprotection afforded 7-*cis*-LTD_4 (253) (Scheme 44).

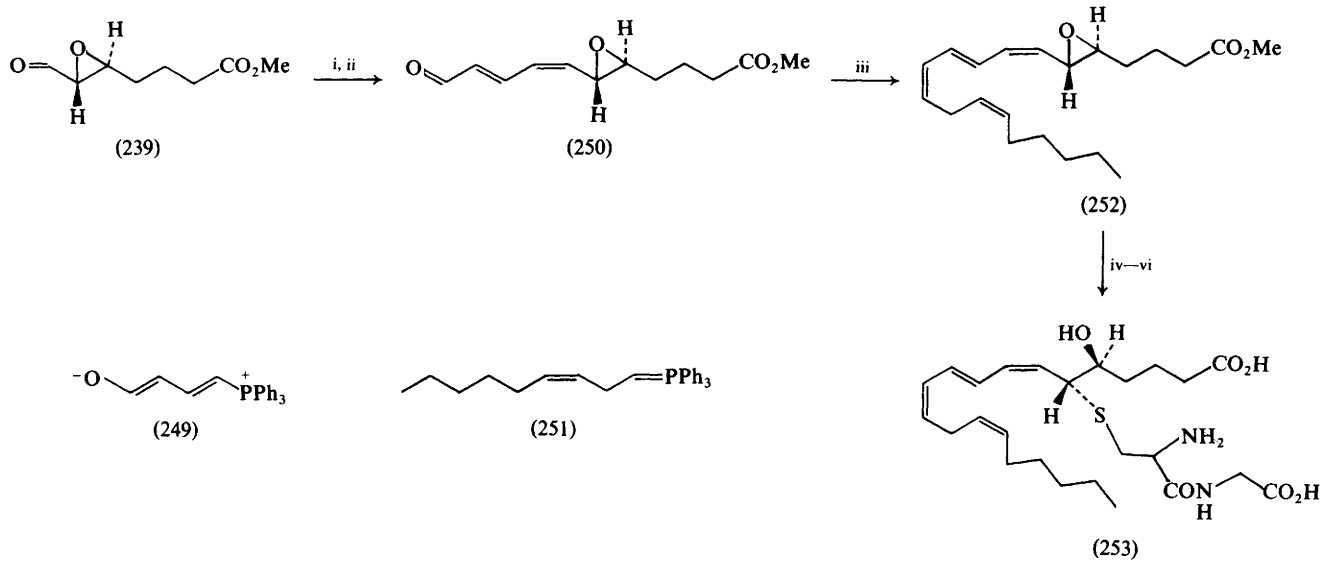


Reagents: i, $Ph_3P{=}CHCO_2Et$; ii, NaOEt; iii, TsCl, pyridine; iv, Bu^tMe_2SiCl, 4-dimethylaminopyridine, Et_3N; v, NaI, MeCOMe; vi, $Me_3CC{\equiv}C\text{-}CuCH{=}CH[CH_2]_4Me$, $CuBr{\cdot}Me_2S$; vii, $Bu^n_4N^+\ F^-$; viii, $MeSO_2Cl$, Et_3N; ix, NaOEt, EtOH; x, Bu^tPh_2SiCl, Et_3N

Scheme 42

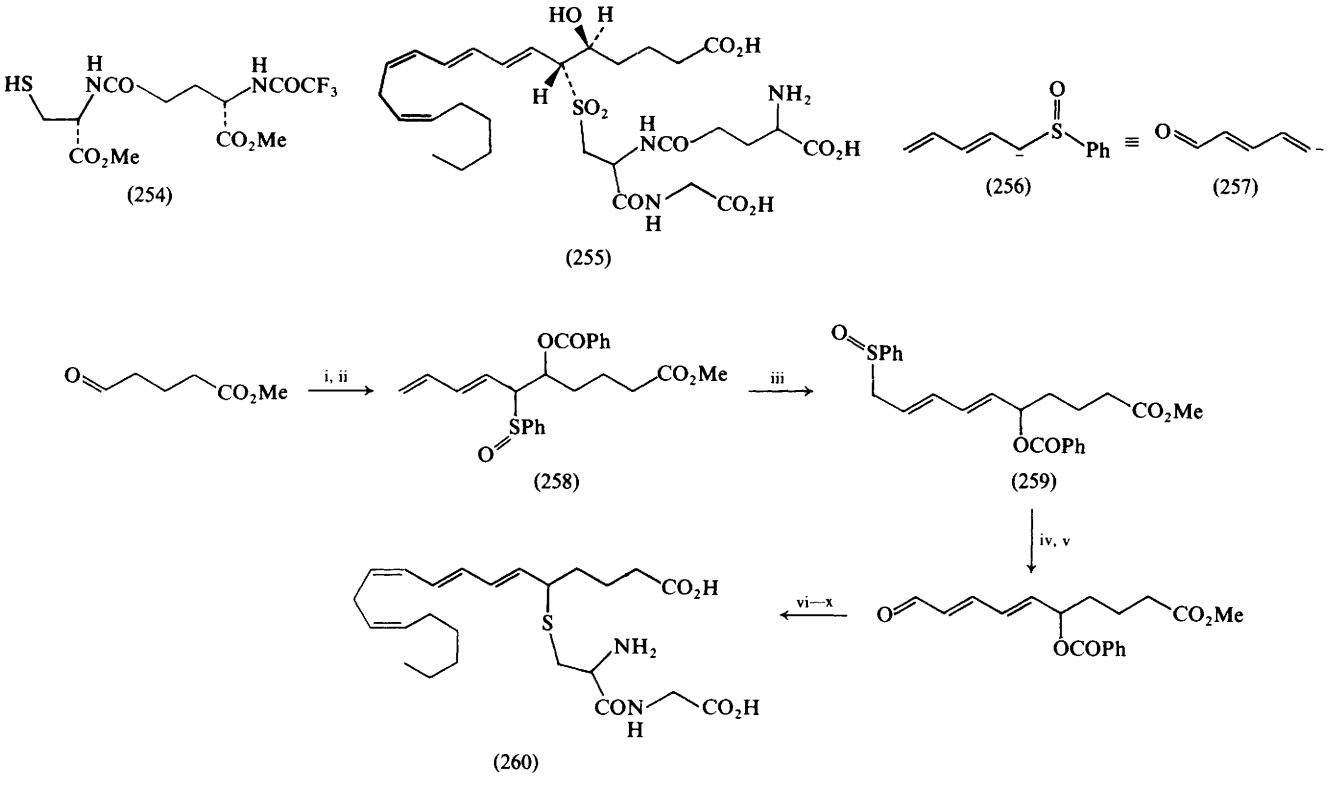


Scheme 43



Reagents: i, (249), ii, I_2, CH_2Cl_2; iii, (251), HMPA; iv, *N*-trifluoroacetyl-L-cysteinylglycine, NEt_3, MeOH; v, K_2CO_3; vi, h.p.l.c.

Scheme 44



Reagents: i, (256); ii, PhCOCl; iii, heat at 25 °C for 3 hours; iv, Ac_2O, $(CF_3CO)_2O$, NaOAc, 2,6-lutidine; v, $CaCO_3$, $HgCl_2$; vi, (251), HMPA; vii, K_2CO_3, MeOH; viii, $MeSO_2Cl$, NEt_3; ix, *N*-trifluoroacetyl-L-cysteinylglycine methyl ester, potassium thiolate, HMPA; x, LiOH, MeOH

Scheme 45

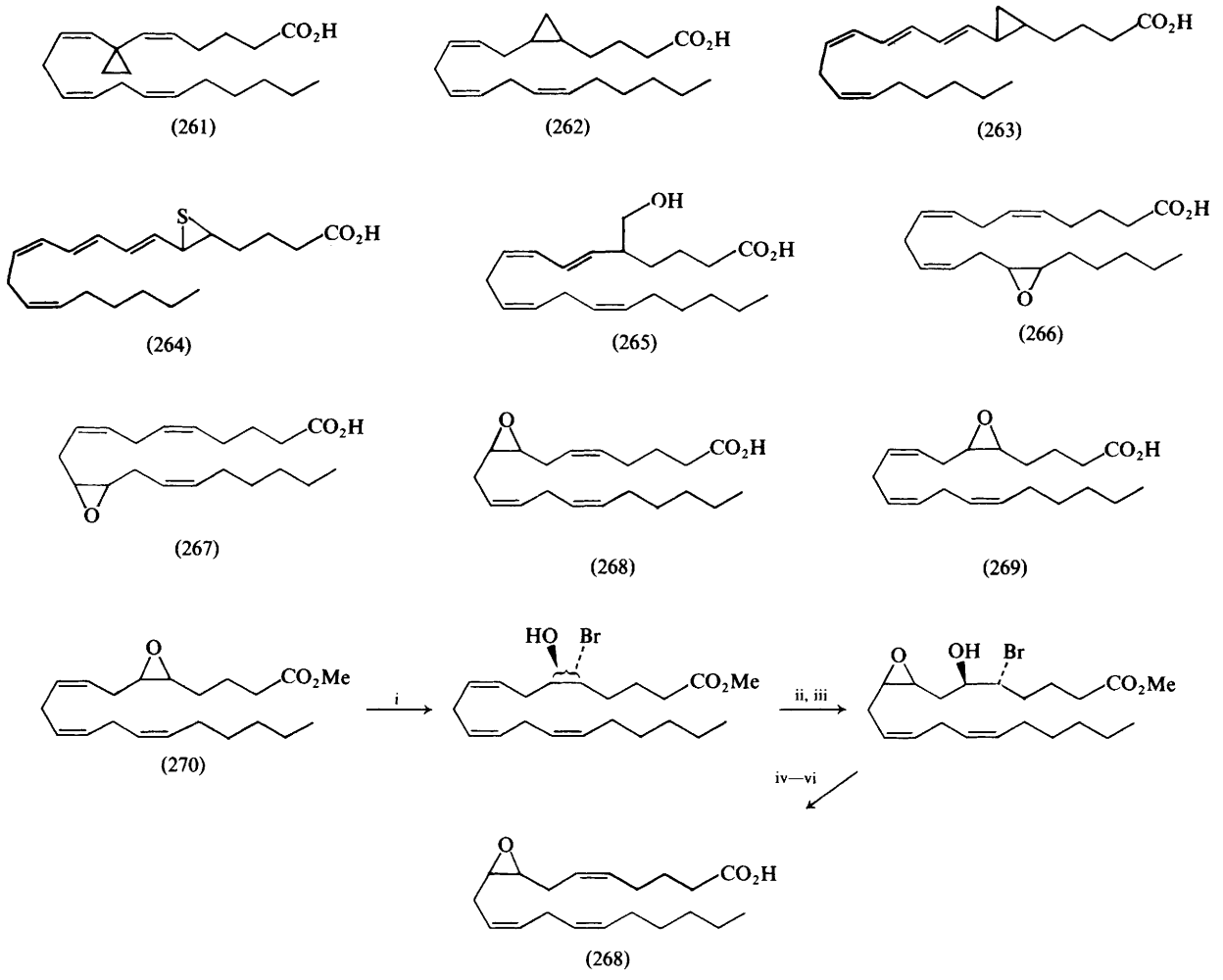
The 7-*cis*-LTD_4 (253) showed contractile activity on isolated guinea-pig ileum and induced bronchoconstriction in the anaesthetized guinea pig; for both effects, the compound showed one tenth the potency of LTD_4.

The total synthesis of the LTF_4 (227) has been reported by the Glaxo research group.[145] The protected glutamylcysteine diester (254) (prepared in six steps) was coupled to (±)-LTA_4 methyl ester by an established method to afford, on deprotection, a diastereoisomeric mixture of LTF_4.

More recently, the Merck research group has reported the synthesis of pure LTF_4 *via* coupling of *N*-(L-γ-glutamyl-α-benzyl ester)-L-cysteine methyl ester with LTA_4.[146]

Reports indicate that LTF_4 is less potent than LTD_4 in causing the contraction of guinea-pig bronchus and ileum.[145,146]

The synthesis of leukotriene sulphones by selective oxidation of the thioether function of the corresponding leukotrienes has been reported by the Merck research group.[147] The oxidant of choice is potassium hydrogen persulphate ($KHSO_5$). Under controlled conditions, the reactive 14–15 double-bond is not significantly oxidized. These sulphones are of some interest as they show a similar biological profile to their parent sulphides and are nearly as potent.[146,148] Leukotriene C_4 sulphone (255) has been isolated from rat peritoneal cells.[149]



Reagents: i, AcOH, KBr, H_2O; ii, $VO(acac)_2$, Bu^tO_2H; iii, chromatography, separation of isomers; iv, $(CF_3CO)_2O$, pyridine; v, $P(NMe_2)_3$; vi, saponification

Scheme 46

5.2.4 Analogues and Inhibitors of Leukotrienes

Several leukotriene analogues have been reported by the Ono research group.[150] These analogues incorporate variations in the peptide moiety and in the position of the hydroxy-group, derivatives of the carboxyl group, and alterations in the number and geometry of the double-bonds. In general, it was shown that the free amino-group of LTC_4 and LTD_4 was not critical for contractile activity (guinea-pig pulmonary and parenchymal strip assays). However, the presence of a hydroxy-group at C-5 and of the carboxy-groups, and the conjugation of the double-bonds, appear to be critical for activity.

Corey *et al.*[151] have reported a novel synthetic approach to 5-deoxy-LTD_4 (260). The synthesis utilizes the conjugate base (256) as a synthon for the 4-formyl-*trans*,*trans*-buta-1,3-dienyl anion (257), as shown in Scheme 45. The ease of the double [2,3] sigmatropic shift of (258) to (259) is noteworthy. Each of the diastereoisomers of 5-deoxy-LTD_4 (260) was found to have less than 1% of the activity of LTD_4 in guinea-pig ileum and pulmonary parenchymal strip assays. This establishes the importance of the 5-hydroxy-group for bioactivity.

Short syntheses of the analogues (261)—(265) of LTA_4 and 5-HPETE have been reported by the Ono research group.[152] These stable analogues are inhibitors of 5-lipoxygenase from polymorphonuclear leukocytes of guinea pig, with an order of activity (263) > (264) > (261) > (262). In particular, (263) selectively inhibited 5-lipoxygenase activity (IC_{50} = 3 μmol dm^{-3}) without inhibiting the cyclo-oxygenase and the 12-lipoxygenase activities of blood platelets of the guinea pig and rabbit.

6 Miscellaneous

6.1 Analogues of Arachidonic Acid and Related Metabolites

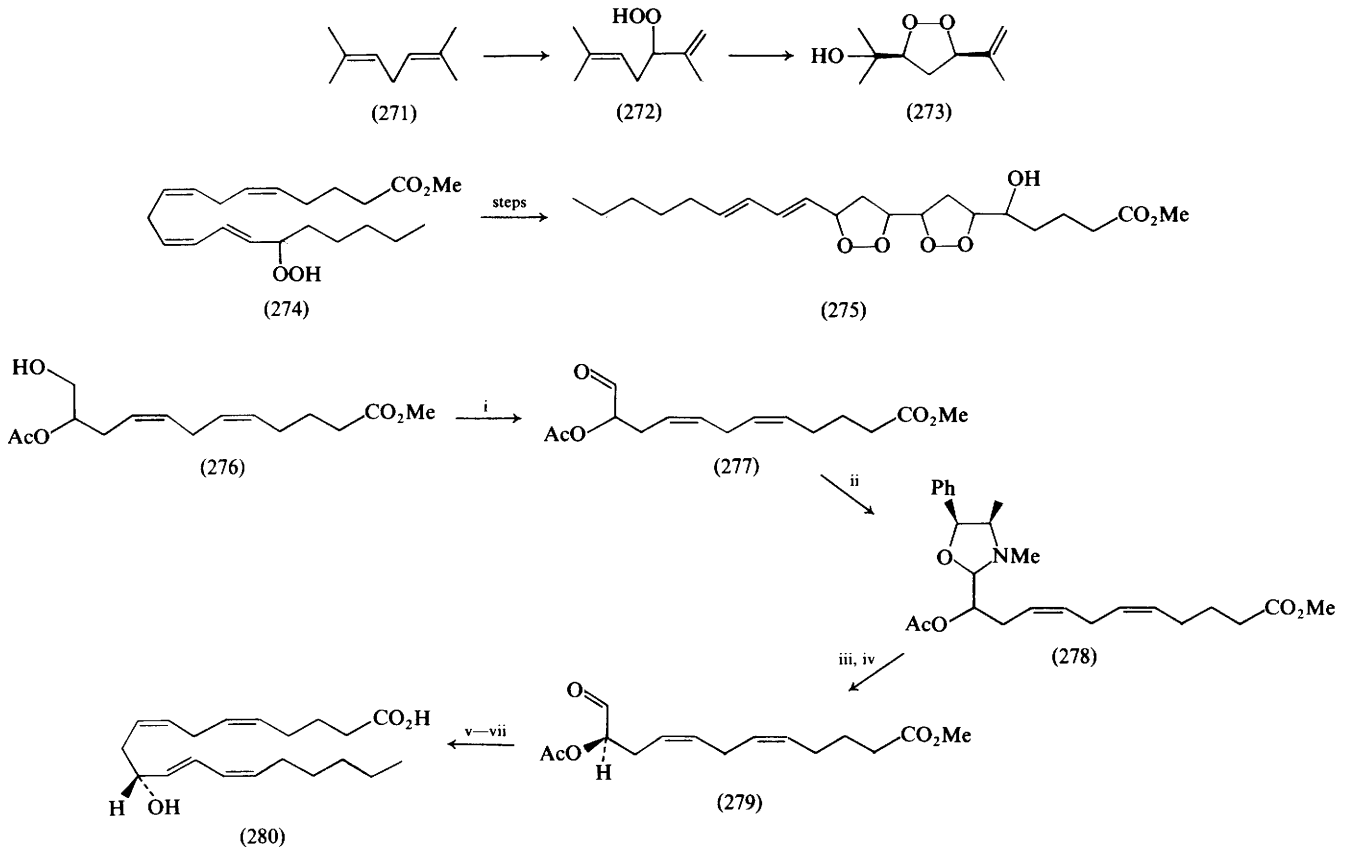
Free arachidonic acid is not normally present in mammalian cells. It is mainly stored as phosphatidyl esters and its release is controlled by the action of specific phospholipases.[153] The arachidonic acid is then immediately oxidized by specific enzyme complexes into prostaglandins, prostacyclins, thromboxanes, leukotrienes, and other C_{20} hydroxylated acids.

Like leukotrienes, the C_{20} hydroxylated acids are derived from mono-oxygenation of arachidonic acid. It has been demonstrated recently that hepatic mono-oxygenase *P*-450 enzymes metabolize arachidonic acid to a variety of *cis*-epoxyarachidonic acids (266)—(269).[154]

The *cis*-epoxide (268) has been synthesized from the known methyl ester *cis*-epoxide (270) in five steps (Scheme 46).[155]

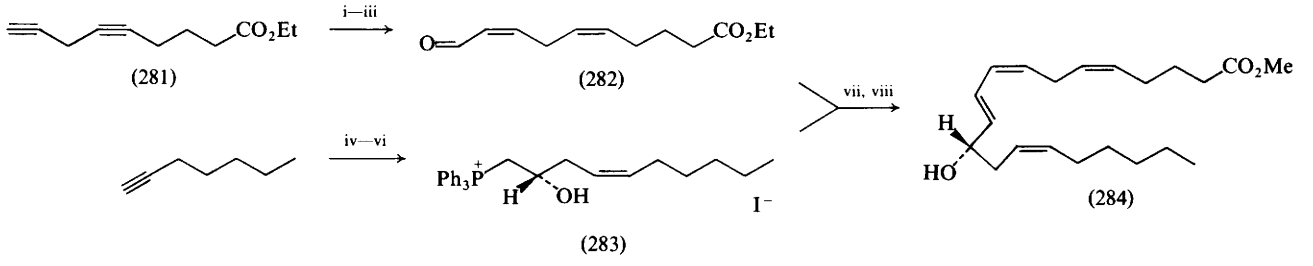
Several hydroperoxy-arachidonic acids have been implicated in the leukotriene and prostaglandin metabolic pathways. A model study of the peroxidation of the 1,4-diene system has been described.[156] The hydroperoxide (272), which was formed from the reaction of (271) with singlet oxygen, further reacted in the presence of di-t-butyl peroxyoxalate and oxygen to give the *cis*-1,2-dioxolane (273) after reduction. More recently, Porter and Khan have reported that (5*Z*,8*Z*,11*Z*,13*E*)-15-hydroperoxyicosa-5,8,11,13-tetraenoic acid (15-HPETE) methyl ester (274) was similarly converted into the dioxolane (275) when treated with di-t-butyl hyponitrite and oxygen, followed by reduction.[157,158]

Two syntheses of (5*Z*,8*Z*,12*E*,14*Z*)-11-hydroxyicosa-5,8,12,14-tetraenoic acid, 11-HETE, which is an interesting



Reagents: i, Swern oxidation; ii. *l*-ephedrine; iii, chromatography, separation of (*R*)- and (*S*)-isomers; iv, acid; v, $Ph_3P{=}CHCHO$; vi, $Ph_3P{=}CHC_5H_{11}$; vii, NaOMe, NaOH

Scheme 47



Reagents: i, $CH(OEt)_3$, ZnI_2; ii, H_2, Lindlar catalyst; iii, $(CO_2H)_2$, MeCOMe; iv, Li, NH_3 (liq), then (*R*)-epichlorhydrin; v, NaI, NaOAc, Et-CO_2H; vi, PPh_3; vii, MeLi, HMPA; viii, K_2CO_3, MeOH

Scheme 48

metabolite in the biosynthesis of PGH_2, have appeared.[159,160] In one synthesis of (11*R*)-11-HETE (280) (Scheme 47),[160] the ester (276) was oxidized to (277), which was then condensed with *l*-ephedrine to furnish the oxazolidine (278). This key intermediate was separated into its (*R*)- and (*S*)-isomers by chromatography. The former was re-converted into the chiral aldehyde (279), which was elaborated to (280) by established methods.

The synthesis of (12*S*)-12-HETE methyl ester (284) has been reported by the Unilever research group (Scheme 48).[161] The chiral phosphonium salt (283) was prepared from (*R*)-epichlorohydrin, while the C_{10} aldehyde (282) was readily prepared from the known diacetylenic ester (281). Assembly of the C_{10} aldehyde (282) and the C_{10} phosphonium salt (283) by Wittig olefination then furnished the methyl ester (284), after transesterification.

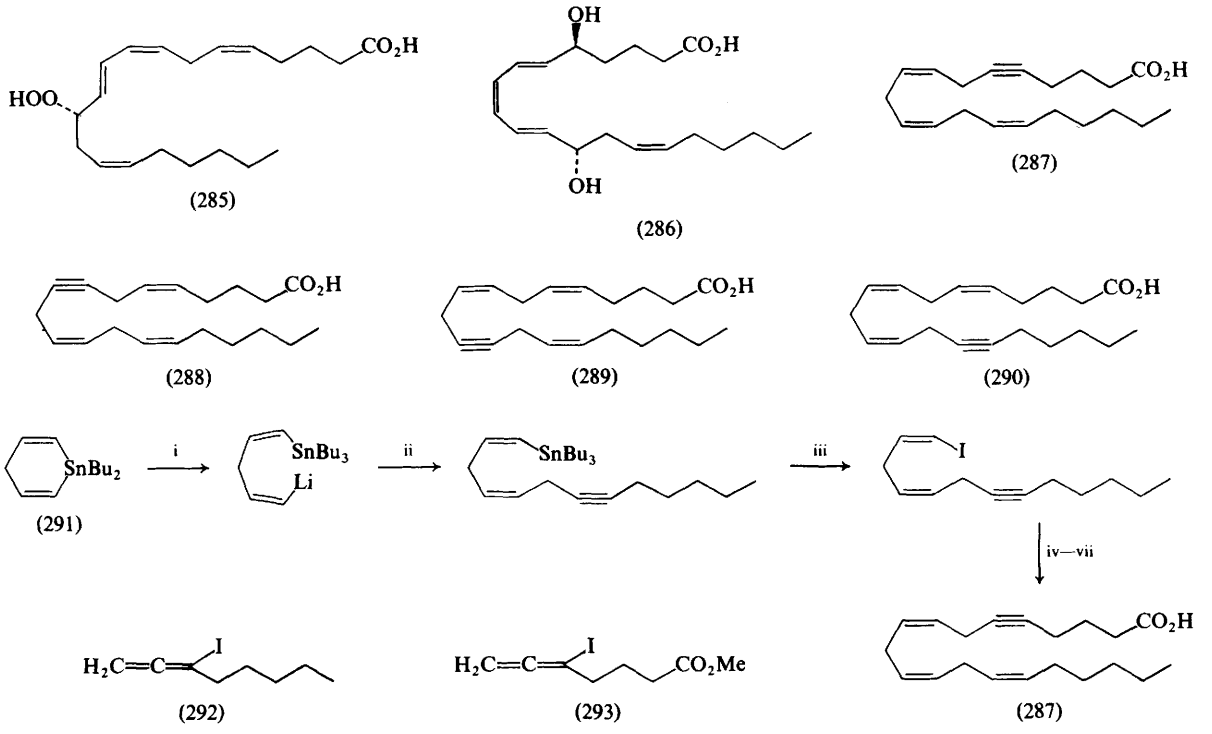
The corresponding (12*S*)-12-HPETE (285), which is an important metabolite of arachidonic acid that is produced by human blood platelets, has recently been shown to stimulate the biosynthesis of leukotrienes in human blood leukocytes.[162]

The mechanism of formation of (5*S*,12*S*)-5,12-diHETE (286) in blood leukocytes has been reported.[163] Using ^{18}O-labelling experiments, it has been shown that (286) is not derived from LTA_4, but is a product of successive reactions of arachidonic acid with two lipoxygenases of different positional specificities.

The stereochemical assignment of 5,12-diHETE has been reported,[164] and the preparation of (5*Z*,8*Z*,11*Z*)-icosa-5,8,11-trienoic acid from arachidonic acid by reduction with hydrazine has been described.[165]

The dehydroarachidonic acids (287), (288), (289), and (290) have been synthesized by Corey *et al.*[166–168] These derivatives of arachidonic acid were designed as position-selective inhibitors that could selectively block any of the arachidonate oxidation pathways. It was shown that (287)[167] and (290)[166] are irreversible inhibitors of 5- and 15-lipoxygenases respectively, while (288) and (289) are inhibitors of the synthesis of prostaglandins.[167]

The synthesis of the trienynoic acid (287) (Scheme 49) that has been described by Corey *et al.*[168] is particularly noteworthy, since the strategy depends on the use of the dibutylstanna-



Reagents: i, Bu^{n}Li, CuBr·Me$_2$S; ii, (292); iii, I_2; iv, disiamylborane; v, Bu^{t}Li, CuBr·Me$_2$S; vi, (293); vii, LiOH

Scheme 49

cyclohexa-2,5-diene (291) as a nucleophilic 'skipped' diene and the iodo-allenes (292) and (293) as electrophilic acetylene synthons.

6.2 Synthons

Several reports on the synthesis of various synthons that are useful for the preparation of prostaglandins and their analogues have appeared. In particular, the useful synthons (295) and (296) have been prepared from the naturally occurring iridoid glucoside aucubin (294).[169–171] Similarly, the related iridoid glycoside asperuloside tetra-acetate (297) has been converted into the lactone (298).[172]

The fragmentation of the norborn-5-en-2-ols (299) with mercury(II) acetate, followed by oxidation, afforded the lactone (300).[173] The latter is a useful synthon in prostaglandin synthesis.

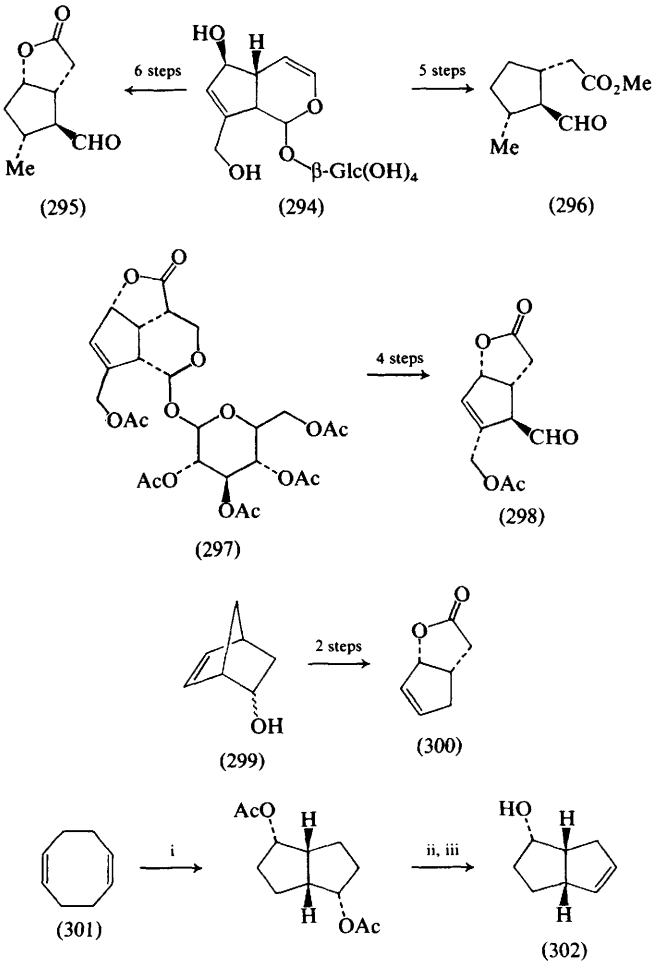
The *endo-cis*-bicyclo[3.3.0]oct-6-enol (302), which is a key intermediate in the synthesis of 11-deoxy-PGF$_2$, has been prepared by a short synthetic route from the readily available cyclo-octadiene (301) (Scheme 50).[174] The cyclopentenone (303) has also been prepared from the cyclo-octadiene (301) in good yield.[175] The related cyclopentanone (305) has been prepared from the sulphone (304) in 6 steps.[176]

The synthesis of the thromboxane synthon (148) has been reported (see Section 3.2).[90]

The base-catalysed epimerization of a variety of 7-substituted bicyclo[3.2.0]hept-2-en-6-ones (306) and its bearing on the 'orthogonal approach' in the cycloaddition of ketenes to olefins has been reported by Dreiding and co-workers.[177]

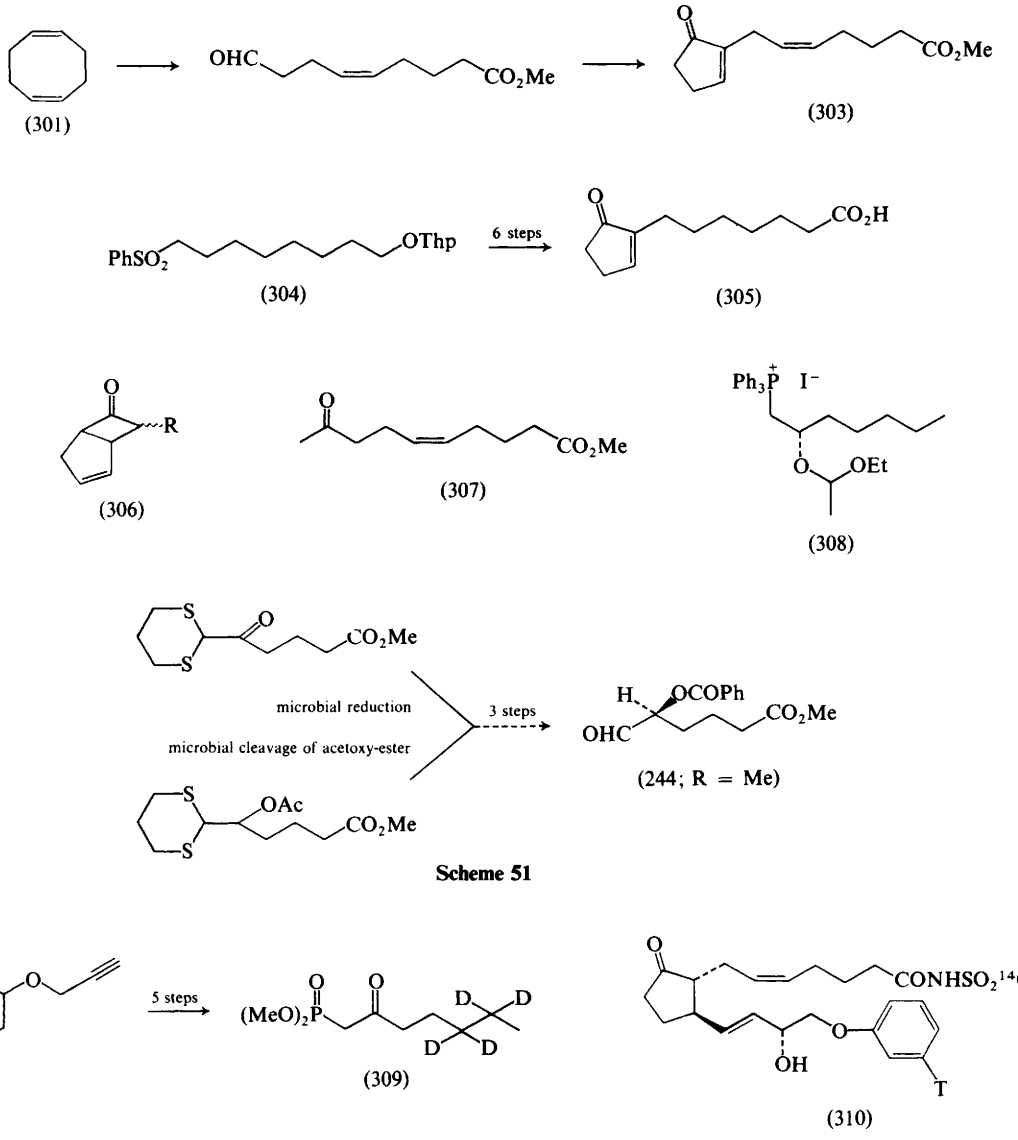
The synthesis of the useful keto-ester (307) from the cyclo-octadiene (301) has been described[178] and a semi-microbial procedure for the preparation of the chiral ω-side-chain synthon (308) has been communicated by Schick and co-workers.[179]

Sih *et al.* have described a semi-microbial procedure for the preparation of the leukotriene synthon (244; R = Me) (Scheme 51).[140]



Reagents: i, Pd/C, Pb(OAc)$_4$, AcOH, LiCl; ii, 600 °C, argon, at 38 Torr; iii, NaOH

Scheme 50



Scheme 51

6.3 Labelled Compounds

Specific reports on the preparation of deuteriated[180] and ^{18}O-labelled derivatives[181] of icosanoids have appeared and general reports on labelled prostaglandins[182,183] are available.

The synthesis of dimethyl 2-oxo[5,5,6,6-$^2H_4$]heptylphosphonate (309) has been described[184] and the preparation of deuteriated metabolites of $PGF_{2\alpha}$ has been reported.[185] Reports on the synthesis of tritium-labelled PGA[186,187] and PGE_1[187] have also appeared.

The synthesis of doubly labelled 'Sulprostone' (310), which is an abortifacient 11-deoxy-PGE_2 analogue, has been reported by the Pfizer research group.[188]

6.4 The Analysis of Arachidonic Acid Metabolites

Fast atom bombardment (FAB) mass spectrometry (m.s.) has been used to compare biologically derived LTC_4 directly with synthetic material, thereby confirming the structure of the former material.[189] Previous conventional mass-spectrometric investigations of LTC_4 and LTD_4 relied on chemical modification, which, combined with the extensive fragmentation that is inherent with the technique, leads to ambiguous results.

A new sensitive radioimmunoassay for 6-keto-$PGF_{1\alpha}$ has been reported.[190]

The high-performance liquid chromatography (h.p.l.c.) of prostaglandins, leukotrienes, and other arachidonic acid metabolites has been reviewed.[191] Several new methods for reverse-phase h.p.l.c. of underivatized prostaglandins and hydroxyicosatetraenoic acids have been described.[192–195]

More sensitive methods for the determination of prostaglandins by h.p.l.c. have been reported which involve the preparation of u.v.-fluorescent ester derivatives.[196–198]

Argentation h.p.l.c. has been used for the separation of prostaglandins and related fatty acids and is reported to give better separations than reverse-phase h.p.l.c.[199] This method also has the advantage of employing easily removed, volatile organic solvents.

Methods for the reverse-phase h.p.l.c. determination of intact leukotrienes have now been reported.[200,201]

Further methods for the gas–liquid chromatographic separation of prostanoids have appeared[202,203] and a review[204] and a number of papers[205–213] have been published on the use of m.s. in the quantification of various prostanoids.

The determination of prostaglandins and thromboxanes in biological fluids has been carried out, using negative-ion chemical-ionization mass spectrometry (NICI m.s.) by several groups.[94,214–218] Whereas conventional electron-impact m.s. causes considerable fragmentation, leaving few suitable ions for sensitive selected ion monitoring (SIM), NICI m.s. of prostaglandins, suitably derivatized to improve electron capture (*e.g.* as pentafluorobenzyl esters), shows greatly enhanced sensitivity and good selectivity.

Several analytical thin-layer chromatography techniques for arachidonic acid metabolites have been described.[219–222]

7 Bibliography

7.1 Chemical Reviews

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