REVIEW

The emergence of the cyclopentenone prostaglandins as important, biologically active compounds

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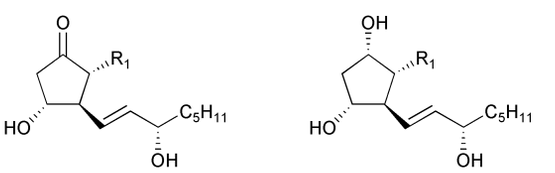
1 Primary prostaglandins and thromboxanes

Prostaglandins (PGs) were discovered almost seventy years ago,[1] but it was not until the 1960s that the area became a 'hot topic' and the focus of attention for many chemists, biochemists and pharmacologists.[2] Then, over a period of about ten years, an immense amount of research was undertaken, concentrating on the chemical synthesis and biological activities of PG-Es (**1**), PG-F_{α}s (**2**) and analogues (Fig. 1).

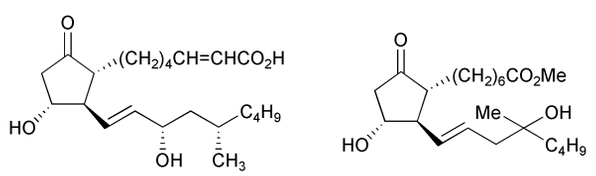


1
PG-E_1, PG-$F_1\alpha$
$R^1 = (CH_2)_6CO_2H$

2
PG-E_1, PG-$F_2\alpha$
$R^1 = CH_2CH{=}CH(CH_2)_3CO_2H$

Fig. 1

In the 1980s it became generally considered that a lot of this effort had been unrewarded. These primary PGs and their analogues often displayed a broad spectrum of biological activity and the requisite selectivity was difficult to achieve. Nonetheless some compounds such as Limaprost (**3**)[3] and Misoprostol (**4**)[4] were taken to the market place and, in the fullness of time, proved to be commercially successful compounds for the treatment of cardiovascular disease and gastrointestinal problems, respectively (Fig. 2).[5]

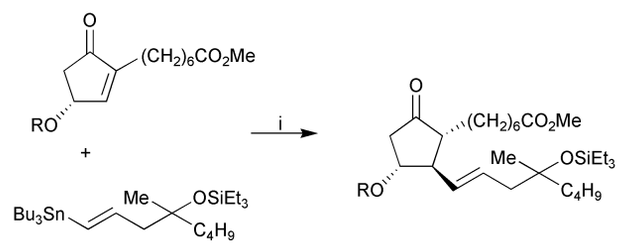


3 **4**

Fig. 2

Misoprostol (**4**)[6] is now produced by Searle Monsanto on a scale of more than 150 kg *p.a.*; a convergent synthesis of this material is summarised in Scheme 1.[7]

Furthermore, PG-E_1 (Alprostadil) and some of its analogues, which induce vasodilatation and inhibit platelet aggregation, are commonly employed to treat infants with congenital heart disease. The continued interest in the biology of PG-Es is reflected in the output from synthetic chemistry laboratories. For example, one of the most elegant and concise approaches to PG-E_1 methyl ester has been reported recently by Feringa and co-workers.[8] The key step, involving the use of a chiral phosphoramidite as a chiral ligand, is featured in Scheme 2.



Scheme 1 *Key reagents and conditions*: (i) stannane added to MeLi and CuCN at 0 °C; temperature raised to ambient (2.5 h) then lowered to −78 °C and enone added; temperature raised to −30 °C for 10 min. R = $SiMe_2{}^tBu$.

Different facets of activity of the primary prostaglandins continue to emerge. For example PG-E_2 has been shown to enhance bone formation, with better penetration to the site of action being achieved with C-15 derivatives.[9] PG-$F_2\alpha$ (Dinoprost) and analogues have been used for some time to induce labour as part of normal childbirth or to terminate pregnancy.[10] More recently the synthetic prostaglandin (+)-16-[3-(trifluoromethyl)phenoxy]-17,18,19,20-tetranor-PG-$F_2\alpha$ and its ester derivatives have been introduced as potent drugs for the treatment of glaucoma and ocular hypertension. Kilogram quantities of the isopropyl ester **6** have been prepared using the tricycloheptanone **5** as the key intermediate (Scheme 3).[11]

Recently, a series of publications has emerged detailing the synthesis of various isoprostanes,[12] compounds in which the C_7- and C_8-side chains of PG-F and PG-E are *cis*-oriented on the five-membered ring. The isoprostanes have been recognised as potentially important biological markers for oxidative stress and oxidative injuries such as atherosclerosis, kidney failure and Alzheimer's disease.[13] The key steps in recent synthetic routes to 12-epi-PG-$F_2\alpha$ and 8-epi-PG-$F_2\alpha$ (isoprostanes **7** and **8**, respectively) are summarised in Scheme 4.[14]

In the late 1970s a second wave of interest in PGs occurred with the discovery and characterisation of PG-I_2 (prostacyclin) **9** and thromboxane-A_2 (Tx-A_2) **10** (Fig. 3).[15] These two compounds were shown to have opposite effects in haemostasis; prostacyclin inhibits the aggregation of blood platelets while Tx-A_2 is a potent thrombus-forming agent. Both Tx-A_2 and PG-I_2 are relatively unstable *in vivo* yet the latter compound (Epoprostanol) is still used, by continuous infusion, for the treatment of primary pulmonary hypertension: metabolically stable analogues of PG-I_2, for example Cicaprost (**11**) and Beraprost (**12**), offer the prospect of more acceptable dosing regimens.[16]

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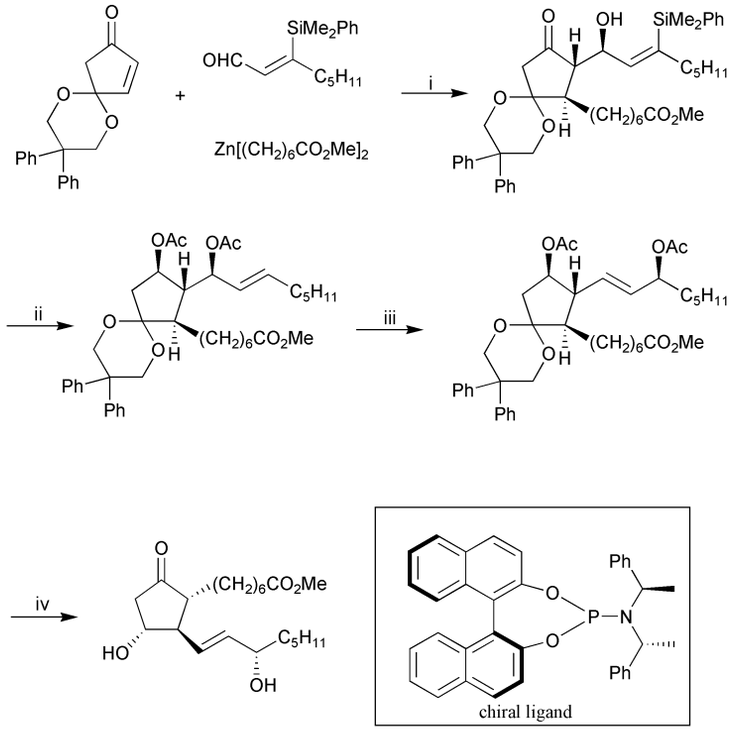
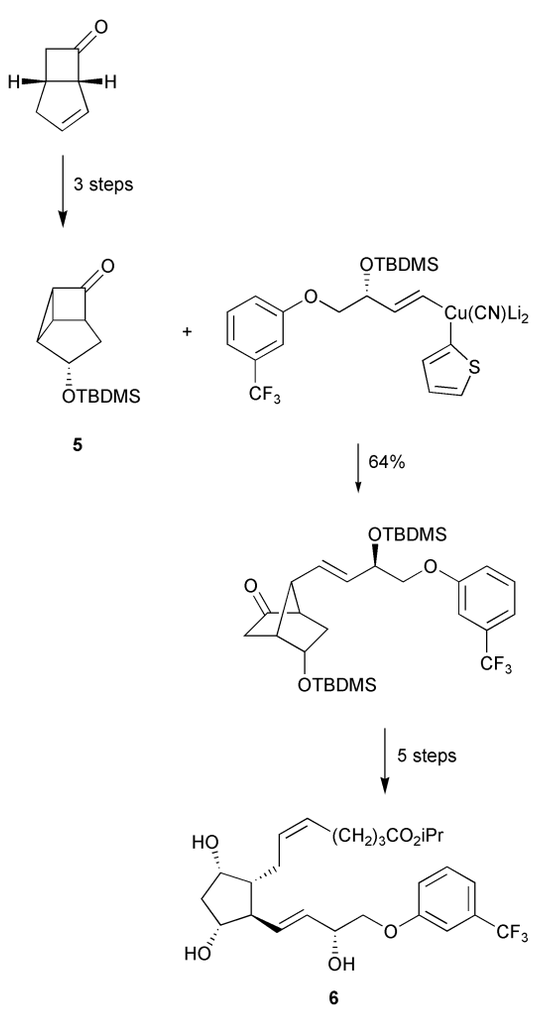


Scheme 2 *Key reagents and conditions*: (i) 3 mol% $Cu(OTf)_2$, 6 mol% chiral ligand, toluene, −40 °C, 18 h, 60%; (ii) $Zn(BH_4)_2$, ether, −30 °C, 3 h, 63% then 3 equiv. Bu_4NF (1 M in THF) methyl propionate, DMSO, 80 °C, 20 min followed by Ac_2O, DMAP, pyridine, 20 min, 71% over 2 steps; (iii) 5 mol% $Pd(CH_3CN)_2Cl_2$, THF, 3 h, 63%; (iv) K_2CO_3, MeOH, 18 h, 90% then $(NH_4)_2Ce(NO_3)_6$, MeCN, borate–HCl buffer (pH = 8), 60 °C, 2 h, 45%.



Scheme 3

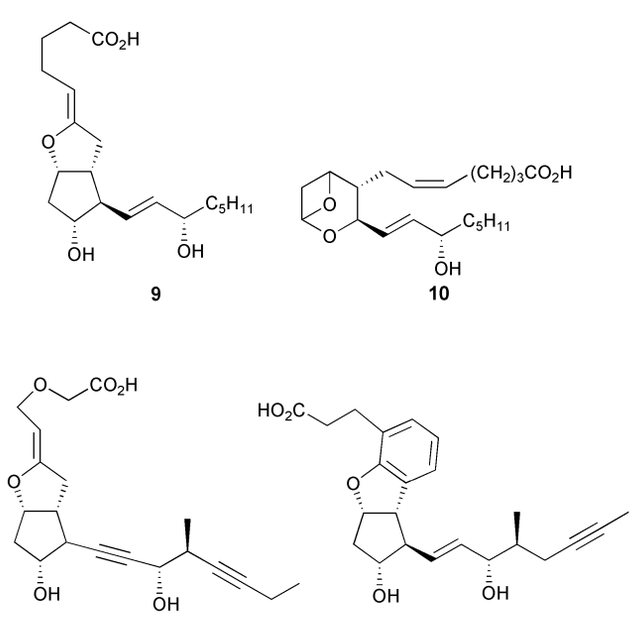
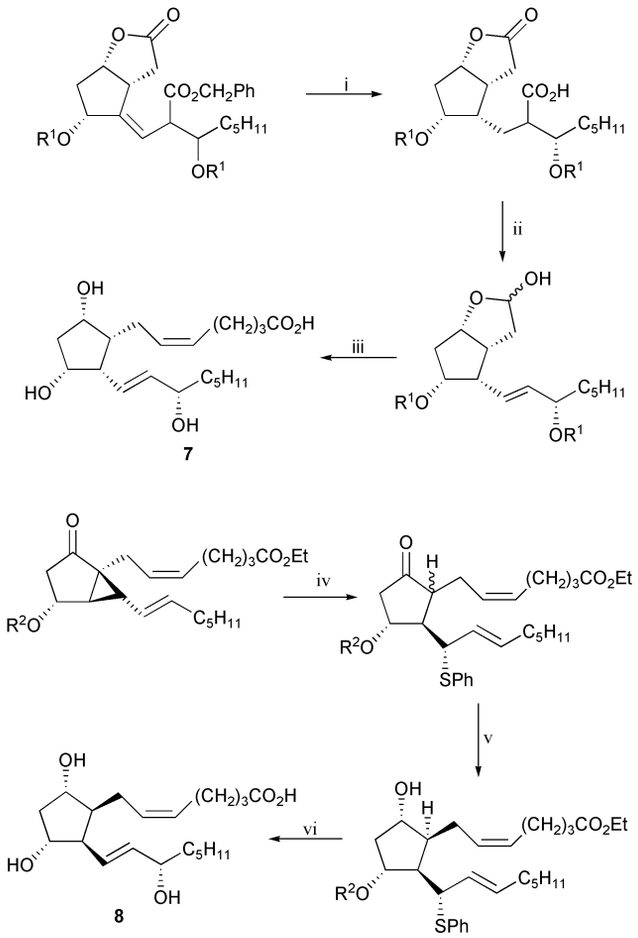


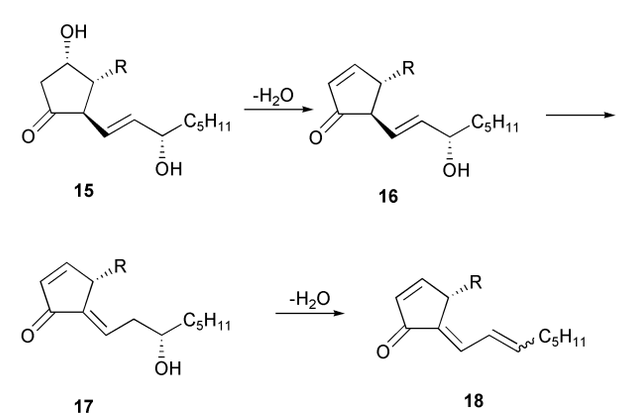
Fig. 3

2 Cyclopentenone prostaglandins

During the early years of prostaglandin research various prostaglandin metabolites were identified and synthesised, including PGs containing a cyclopentenone ring system. Thus PG-As (**13**) and PG-Bs (**14**) (Fig. 4) were formed on treatment of the corresponding PG-E with acid and base respectively. Similarly PG-D_2 (**15**) is dehydrated to PG-J_2 (**16**) *in vivo* and *in vitro*,[17] and this compound in turn, isomerizes to Δ^{12}-PG-J_2 (**17**) before further dehydration furnishes $\Delta^{12,14}$-15-deoxy-PG-J_2 (**18**) (Scheme 5). The biological activities of PG-As and PG-J_2 received relatively scant attention initially but, in recent years, profoundly interesting properties have been revealed.



Scheme 4 *Key reagents and conditions*: (i) H_2 (60 psi), PtO_2, Li_2CO_3, ethyl acetate, 18 h; (ii) $Cu(OAc)_2$, pyridine, chlorobenzene, then $Pb(OAc)_4$, 125 °C (1 h), 125 °C (4 h) followed by DIBAL-H, THF, −78 °C, 97%; (iii) $Ph_3P{=}CH(CH_2)_3CO_2K$, THF, 0 °C, 1 h, 80% then CH_3CO_2H–H_2O–THF (3 : 1 : 1), 2 d, 84%; (iv) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 to −78 °C, 90% (*cis*–*trans*, 9 : 1); (v) $NaBH_4$, MeOH, 0 °C, 74% then *p*-nitrobenzoic acid, Ph_3P, DEAD, benzene; (vi) K_2CO_3, EtOH, 64% then MCPBA, CH_2Cl_2, −78 °C; $(MeO)_3P$, EtOH, −78 °C followed by *n*-Bu_4NF, THF. $R^1 = SiMe_2{}^tBu$; $R^2 = SiPh_2{}^tBu$.



Scheme 5 $R = CH_2CH{=}CH(CH_2)_3CO_2H$.

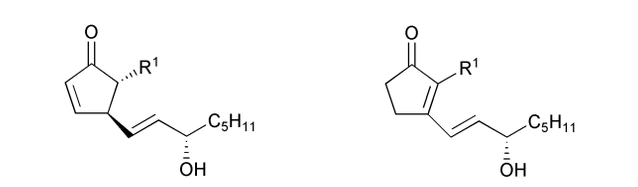


Fig. 4 PG-A_1, PG-B_1: $R^1 = (CH_2)_6CO_2H$; PG-A_2, PG-B_2: $R^1 = CH_2CH{=}CH(CH_2)_3CO_2H$.

PG-As were known to be involved in the control of renal function, hormone regulation, vaso- and broncho-dilatation.[18] Moreover, evidence for the anti-tumour activity of PG-As, PG-Js and the tetraene **18** began to accumulate.[19] One important characteristic of the anti-cancer activity of both enone **18** and the closely related compound Δ^7-PG-A (**19**, Fig. 5)[20] is that

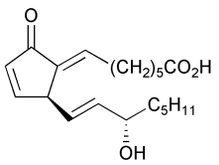


Fig. 5

they have little cross-resistance with *cis*-platin and adriamycin *in vivo*.[21] The anti-tumour activity has been attributed, at least in part, to the potentiation of tumour necrosis factor-α,[22] the inhibition of topoisomerase II[23] and, most recently, to the induction of the cytoprotective enzyme glutathione-5-transferase.[24]

In another important discovery it was found that the cyclopentenone prostaglandins inhibited viral replication by induction of heat-shock protein synthesis *via* activation of heat shock factors (HSF),[25] and inhibition of nuclear factor (NF) κ-B-dependent transcription.[26] A range of viruses including influenza virus,[27] polio virus[28] and human immunodeficiency virus (HIV)[29] were inhibited due to the cytoprotective effect of the PG-As and PG-Js.[30] *in vivo* Activity was demonstrated in an influenza screen.[31] Some of these activities have been associated with binding of the cyclopentenone PGs with the thiol groups of key proteins.[32] In related studies, Noyori and co-workers have studied Michael-type addition of thiols to PG-A_1 (**13**) and Δ^7-PG-A_1 (**19**) *in vitro*, in an endeavour to explain the difference in the anti-tumour and the anti-viral activity between these two compounds.[33] Interestingly PG-A_2 (**13**), PG-J_2 (**16**) and Δ^{12}-PG-J_2 (**17**) are known to conjugate, stereoselectively, to glutathione[34] and this may be an important event for the transport, inactivation and/or elimination of the cyclopentenone PGs *in vivo*. Indeed, it has been mooted that the interaction of PG-As and PG-J_2 with glutathione may underlie the well-documented anti-tumour activities of these PGs.[35]

Another important activity associated with PG-J_2 (**16**) and the prostanoid **18** was reported by two research groups in 1995.[36] It was demonstrated that PG-J_2 and its derivatives were efficacious activators of peroxisome proliferator associated receptors-α and -γ (PPAR-α, PPAR-γ), *inter alia*, generating the hypothesis that compounds in this group could act as adipogenic agents, in turn giving rise to the hope that novel anti-diabetics could be designed. Some data have suggested that the transcription factor PPAR-γ and thus the associated PGs may be involved in the regulation of inflammatory processes,[37] leading to the possibility that PG-J analogues may be useful in controlling atherosclerosis and rheumatoid arthritis.[38]

Rheumatoid arthritis is a disease associated with massive synovial proliferation, inflammation and angiogenesis. $\Delta^{12,14}$-15-Deoxy-PG-J_2 suppresses chronic inflammation of adjuvant-induced arthritis in rats. Part of the activity of the prostaglandin **18** may be PPAR-γ independent,[39] acting through inhibition of COX-2 and hence providing a negative feedback control on the production of the pro-inflammatory PG-Es.[40] That the anti-inflammatory activity of the cyclopentenone PGs is due to control of the production of pro-inflammatory primary prostaglandins by indirect action on COX-2 receives backing from other experimental evidence.[41]

The possibility that cyclopentenone prostanoids could be good candidates for a novel class of anti-inflammatory drugs has been strongly enhanced by the recent discovery of the ability of these molecules to inhibit the IκB kinase IKK. The

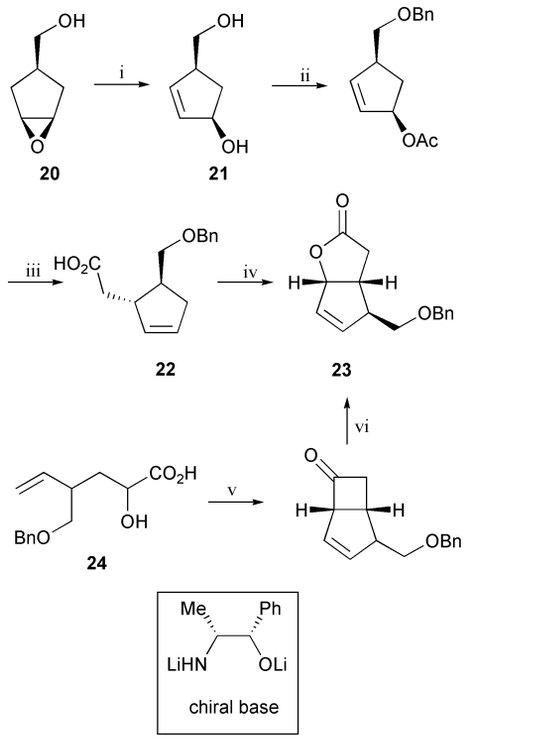
cyclopentenone PG-A_1 and Δ^{12}-14,15-deoxy-PG-J_2 have been shown to be direct inhibitors of IKK, by binding to cysteine 179 in the activation loop of the β subunit of the enzyme.[32] IKK is the key enzyme in triggering the activation of the pro-inflammatory transcription factor NF-κ-B, by catalysing phosphorylation and consequent degradation *via* the proteasome of the NF-κ-B inhibitory protein IκBα. NF-κ-B is a critical regulator of inflammation and the immune-response, controlling the expression of a variety of pro-inflammatory and chemotactic cytokines, cytokine receptors and enzymes involved in the production of inflammatory mediators. NF-κ-B also controls the expression of selected viral genes,[42] so that inhibitors of IKK and NF-κ-B are considered to have interesting potential as novel anti-inflammatory[43] and antiviral drugs.[26]

In addition, PPAR-γ ligands such as the didehydro-PG-D_2 (**18**) are potent inhibitors of angiogenesis *in vitro* and *in vivo* and this indicates that PPAR-γ may be an important molecular target for small molecule inhibitors of angiogenesis.[44] Other studies have focussed on PG-mediated apoptosis. For example, it was found that compound **18** inhibited the growth of human pancreatic cancer cells[45] and the growth of lung cancer cell lines through the induction of apoptosis.[46] In some instances prostanoids of the J-series have unique efficacy as apoptotic agents and it has been shown that these PGs are efficacious inhibitors of ubiquitin isopeptidase, an enzyme within the proteasome pathway. Disruption of this pathway by proteasome inhibitors can cause apoptosis. This recent work identifies isopeptidases as novel targets for the development of anti-neoplastic agents.[47] Neuronal apoptosis associated with PPAR-γ activation may contribute to the onset of certain neurodegenerative disorders including Alzheimer's disease.[48] Non-apoptotic (autophagic) cell-death associated with S-phase arrest was observed with PG-treated prostate cancer cells.[49] Enhanced PPAR-γ levels have been found in thyroid carcinoma cell lines and colonic tumours.[50] On the other hand, PG-J_2 (**16**) and Δ^{12}-14,15-deoxy-PG-J_2 (**18**) induce proliferation of cyclo-oxygenase depleted colorectal cancer cells.[51] Once again control of the transcription factor may provide a novel target for the chemoprevention of colorectal cancer.

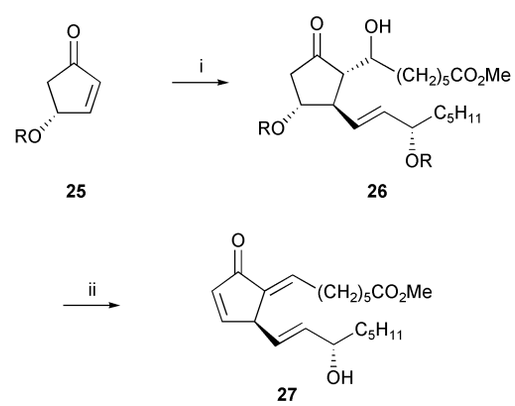
Given the volume of biological research in the area of the cyclopentenone prostaglandins, it is surprising that only a few new synthetic approaches to these PGs and analogues have appeared in the chemical literature. Hodgson and Gibbs[52] have used an optically active base to effect the stereoselective rearrangement of the epoxide **20** to afford the diol **21** (95% ee). Benzylation of the primary alcohol unit, acetylation of the secondary hydroxy group and then Claisen rearrangement of a silyl ketene acetal furnished the carboxylic acid **22**, which was converted into the prostaglandin intermediate **23**, used initially by Corey and Grieco to produce PG-A_2.[53] An alternative approach to the PG intermediate **23** involves the intramolecular cyclization of the hydroxy acid **24** followed by chemo- and regio-selective Baeyer–Villiger reaction (Scheme 6).[54]

Δ^7-PG-A_1 Methyl ester has been prepared from the enone **25** by adaptation of Noyori's elegant three-component coupling protocol, which was invented to gain more efficient access to the primary prostaglandins.[55] Thus a Michael reaction using an organometallic reagent followed by the trapping of the resultant enolate with methyl 6-formylhexanoate provided the key intermediate **26**, which was readily dehydrated and deprotected to provide the trienone **27** (Scheme 7).[56] 13,14-Dihydro-15-deoxy-Δ^7-PG-A_1 methyl ester is a candidate for clinical trial as an anti-cancer agent.[57]

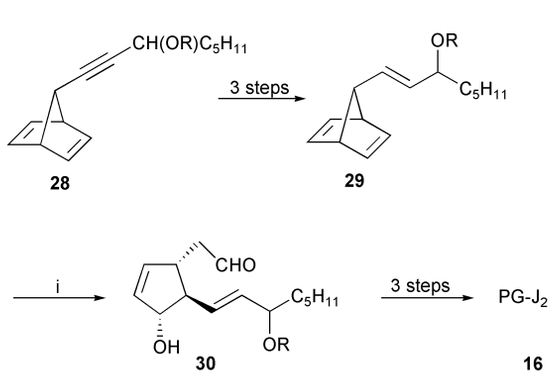
One of the best ways to proceed directly to PG-J_2 involves reaction of an alkyne Grignard with 7-chloronorbornadiene, furnishing the alkyne **28**. Reduction of the alkyne to the (*E*)-alkene **29**, followed by a two-step oxidation–hydrolysis sequence, affords the hydroxyaldehyde **30**, a late-stage precursor to the target PG **16** (Scheme 8).[58]



Scheme 6 *Key reagents and conditions*: (i) chiral base, benzene–THF, 0 °C, 57%, 95% ee; (ii) NaH, BnBr, DMF, −60 °C (3 h), 25 °C (14 h), 81% then CH_3COOH, PPh_3, DEAD, Et_2O, −10 °C (3 h), 25 °C (14 h); LDA, TMSCl, HMPA, THF, −78 °C, 30 min, then 190 °C (sealed tube), xylenes, 18 h, 64%; (iv) I_2, $NaHCO_3$, MeCN, 24 h, then DBU, THF, reflux, 3 h, 87%; (v) CH_3COOK, Ac_2O, rt (2 h); Δ (3 h), 93%; (vi) H_2O_2, CH_3COOH, 10% aq. $Na_2S_2O_6$, 90%.



Scheme 7 *Key reagents and conditions*: (i) (1*E*,3*E*)-LiCH=CHCH(OR)-C_5H_{11}, $ZnMe_2$, THF, −78 °C then $HCO(CH_2)_5CO_2Me$, −78 to 30 °C, 92%; (ii) CH_3SO_2Cl, DMAP, CH_2Cl_2, 80% then CH_3COOH–THF–H_2O (2 : 1 : 1), 60 °C, 72%. R = $SiMe_2{}^tBu$.



Scheme 8 *Key reagents and conditions*: (i) CH_3CO_3H, CH_3CO_2H, CH_3CO_2Na, CH_2Cl_2, 0 °C then HCl, CH_2Cl_2, 61%. R = $SiMe_2{}^tBu$.

Interest in the synthesis of compounds of the cyclopentenone-PG type was refreshed by the isolation and structure elucidation of three new series of natural products, the punaglandins,[59] the clavulones[60] and the chlorovulones (Fig. 6).[61] The punaglandin **33** is an order of magnitude more

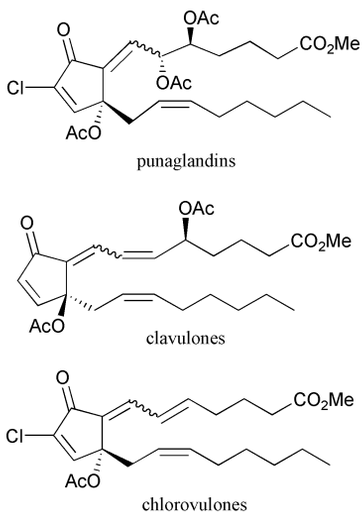
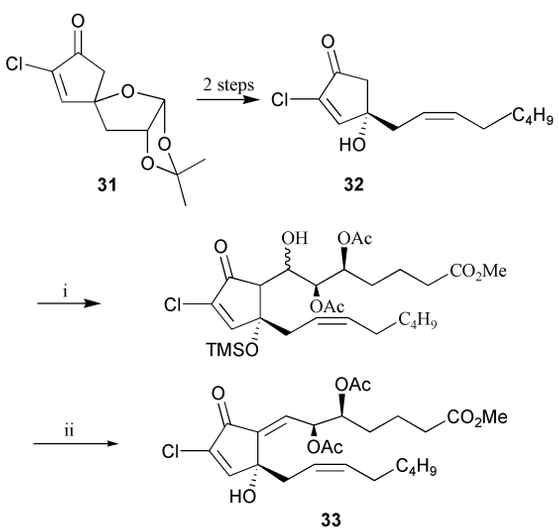


Fig. 6

potent than Δ^7-PG-A_1 (**19**) in anti-neoplastic assays *in vitro* and *in vivo*. Florent and Kuhn have developed a highly efficient and stereoselective synthesis of a chiral precursor **31** of 2-chloro-4-hydroxy-4-alkylcyclopent-2-enone **32** from 1,2-*O*-isopropylidene-α-D-glucose (Scheme 9).[62] This chiral intermediate has been elaborated to give punaglandin IV (**33**).

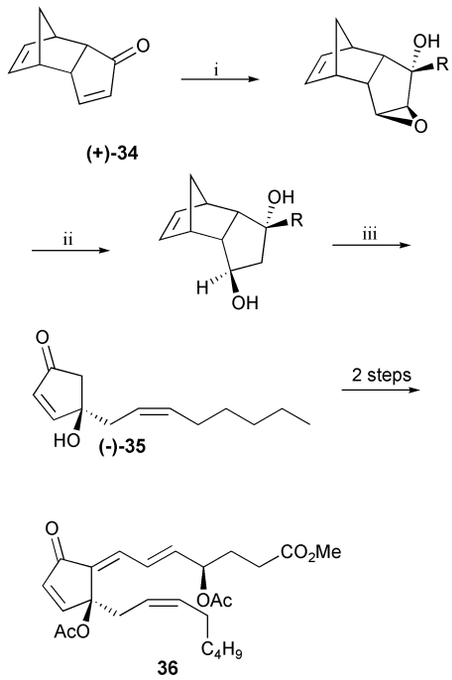


Scheme 9 *Key reagents and conditions*: (i) TMSOTf, diisopropylethylamine, CH_2Cl_2, 0 °C, 86%, then LDA, THF, −78 °C followed by addition of $HCOCH(OAc)CH(OAc)(CH_2)_3CO_2Me$, 58%; (ii) Ac_2O, DMAP, CH_2Cl_2, 4 °C, 28 h then CH_3COOH–H_2O–THF (2 : 1 : 1), 16 °C, 6 h.

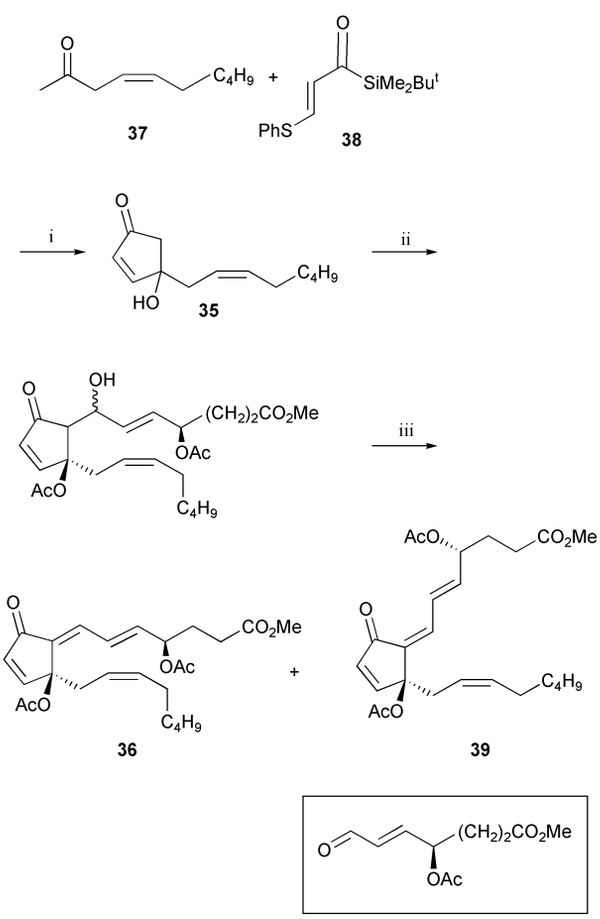
The clavulones have been the target of synthetic endeavours over the years. Zwanenburg has described an enantio- and stereo-selective synthesis of clavulone II (**36**) from γ-hydroxycyclopentenone (−)-**35**, in turn derived from enantiopure *endo*-tricyclo[5.2.1.$0^{2,6}$]decadienone **34** (Scheme 10).[63]

Furthermore, syntheses of clavulone II (**36**) and III (**39**) have been achieved using a [3+2] annulation strategy in which the lithium enolate of methyl ketone **37** condensed with [β-(phenylthio)acryloyl]silane **38** to give the functionalised cyclopentenone **35**, which was converted into the polyenes **36** and **39** (Scheme 11).[64]

While the punaglandins and clavulones have attracted much interest from synthetic organic chemists and biologists alike, it



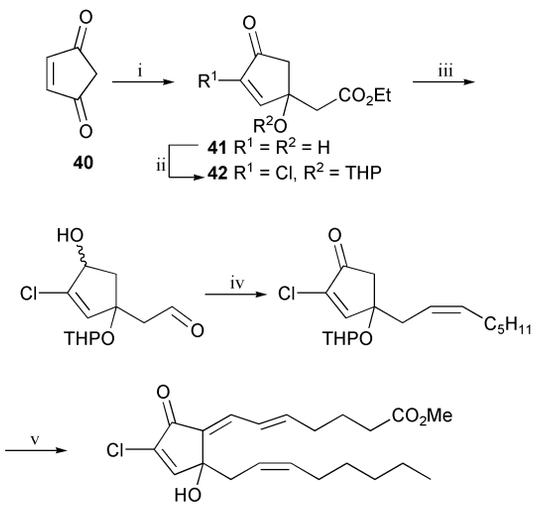
Scheme 10 *Key reagents and conditions*: (i) H_2O_2, aq. NaOH, 30 min, 95% then $BrZnCH_2CC(CH_2)_4CH_3$, 12 h, 90%; (ii) $LiAlH_4$, THF, 3 d, 83%; (iii) FVT, 3×10^{-2} mbar, 550 °C, 72% then PCC, CH_2Cl_2, 4 h, 90% followed by H_2, Lindlar cat., toluene, 84%.



Scheme 11 *Key reagents and conditions*: (i) compound **37** treated with lithium 2,2,6,6-tetramethylpiperidide, then added to a THF solution of **38** at −98 °C; warm to −30 °C followed by treatment with TBAF; (ii) LDA, THF, −80 °C then aldehyde and warm to −30 °C, 34%; (iii) Ac_2O, DMAP, pyridine, 50 °C, 30 min.

is the halogen-containing chlorovulones which might prove therapeutically most useful, showing pronounced anti-tumour activity. (±)-Chlorovulone II (**43**), one of the most active

members of this class of compounds, has been synthesised in nine steps from simple precursors.[65] Aldol addition of the enolate of ethyl acetate to cyclopent-4-ene-1,3-dione (**40**) gave the key intermediate **41** in 86% yield. Introduction of the chlorine atom into compound **41** proceeded uneventfully and the resultant chloroenone **42** was transformed into chlorovulone II (**43**) (Scheme 12). Recently, attention has also been



Scheme 12 *Key reagents and conditions*: (i) enolate from ethyl acetate and LDA, THF, −78 °C, 86%; (ii) Cl_2 gas, CCl_4, Et_3N, 77%; then DHP, CSA, CH_2Cl_2, rt, 100%; (iii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 88% then DIBAL-H, THF, −78 °C, 79%; (iv) $Ph_3PCH_2(CH_2)_4CH_3Br$, BuLi, THF, DMPU, −40 °C, 80% then PDC, DMF, 83%; (v) LDA, THF, then $MeO_2C(CH_2)_3CH{=}CHCHO$, 82% followed by TsOH, MeOH, 88%.

given to the synthesis of hybrid structures such as Δ^7-10-chlorodeoxy-PG-A derivatives (**44**, Fig. 7).[66]

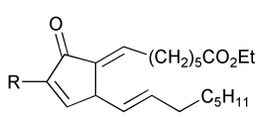


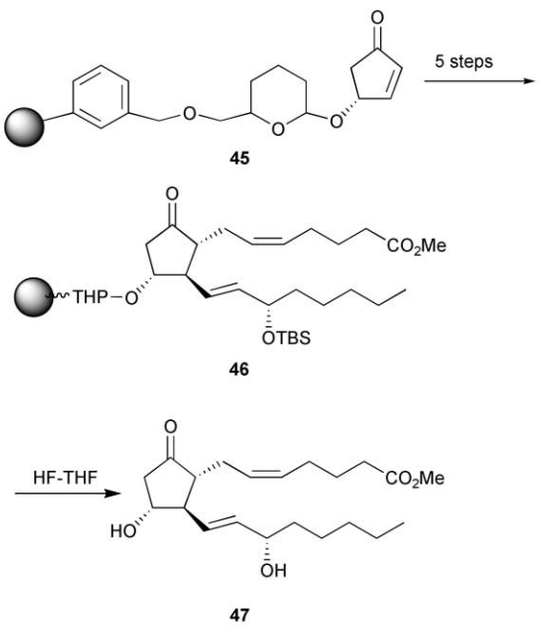
Fig. 7 R = Cl, OH, OAc and $C(S)NMe_2$.

The emergence of cyclopentenone prostaglandins and related structures as potential therapeutic agents has presented synthetic chemists with the challenge of producing structural variants of these compounds for high-throughput screening. While no published approaches to small libraries of cyclopentenone PGs have been reported, Janda and Chen have shown that it is possible to prepare PG-E_2 methyl ester **47** using liquid phase synthesis on a soluble non-cross linked chloromethylated polystyrene support (NCPS).[67] Thus attachment of (*R*)-(+)-4-hydroxycyclopent-2-en-1-one to the polymer gave **45** which was subjected to a three-component coupling strategy to give the fully elaborated prostaglandin framework linked to NCPS (**46**). Treatment of **46** with an aqueous solution of HF–THF liberated the PG-E_2 methyl ester **47** (Scheme 13).

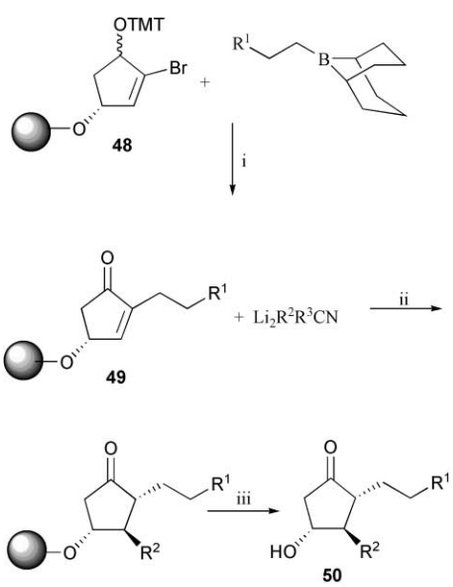
Recently Ellman and co-workers have described the parallel synthesis of PG-E_1 analogues (**50**).[68] Thus α-side chain diversity was introduced into the solid-supported cyclopentenone core **48** by Suzuki coupling of hydroborated alkenes. Conversion to the corresponding enones **49** was followed by cuprate addition of the ω-side chain. Finally cleavage from the support provided twenty-six PG-E_1 analogues (**50**) in high purity (Scheme 14).

3 Conclusions and outlook

Biology and pharmacology laboratories are continuing to investigate the actions of the primary prostaglandins and



Scheme 13



Scheme 14 *Key reagents and conditions*: (i) $Pd(PPh_3)_4$, 2 M Na_2CO_3, THF, 70 °C, 12 h, then 1 M HCO_2H, CH_2Cl_2, 5 min followed by Dess–Martin periodinane, CH_2Cl_2, 54 °C, 2 h; (ii) cuprate added to resin at −78 °C, temp. raised to −20 °C for 1 h then cooled to −78 °C again, then 10% CH_3COOH–THF added; (iii) HF–pyridine, THF then TMSOMe. TMT = $C(C_6H_4\text{-}p\text{-}OMe)_3$; R^3 = thiophene.

thromboxanes. For example, prostanoid[69] and thromboxane receptors[70] are now characterised as members of the G-protein coupled receptor superfamily and work has continued in cloning and characterising these materials with a view to finding compounds which act selectively on one (or a limited number) of these units.[71]

However, it is the explosion of interest in the cyclopentenone prostaglandins in biology laboratories worldwide that is eye-catching. Synthetic organic chemists should be attracted to this area, since new, efficient pathways to cyclopentenone prostaglandins and analogues are now required to define further the therapeutic potential of these fascinating materials in a host of disease areas.[72]

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