The conjugate addition–Peterson olefination reaction for the preparation of cross-conjugated cyclopentenone, PPAR-γ ligands†

Mazhar Iqbal,‡[a] Patricia Duffy,[b] Paul Evans,*[b] George Cloughley,[c] Bernard Allan,§[c] Agustí Lledó,[d] Xavier Verdaguer[d] and Antoni Riera[d]

Received 21st August 2008, Accepted 23rd September 2008
First published as an Advance Article on the web 4th November 2008
DOI: 10.1039/b814619e

5-Alkylidenecyclopent-2-enones **15a–q** may be prepared *via* a conjugate addition–Peterson olefination sequence, best achieved in one-pot, using *exo*-2-trimethylsilyl-3*a*,4,7,7*a*-tetrahydro-4,7-methanoinden-1-one **12**, followed by a *retro*-Diels–Alder reaction. The geometry of the exocyclic alkene may be controlled according to the use of organometallic species in the conjugate addition step; organocuprate reagents are found to selectively lead to the formation of *E*-exocyclic alkene adducts, whereas Grignard reagents favour the formation of *Z*-alkenyl isomers. The use of enantiomerically enriched **12**, accessed from an asymmetric Pauson–Khand reaction, affords the corresponding enantioenriched 5-alkylidenecyclopent-2-enones and this approach is exemplified by the short, stereoselective total syntheses of two cyclopentenone phytoprostanes **51** and 13,14-dehydrophytoprostane J_1 **65**. The ability of this family of synthetic compounds to activate the peroxisome proliferator activated receptor-γ is reported.

Introduction

Natural products possessing the cyclopentane structure are widely distributed throughout the animal, bacterial and plant kingdoms. A subset of this broader class is the family of compounds derived from fatty acids that possess a cyclopentenone group (see Fig. 1). These compounds are intimately involved in several important and related cellular processes, including mediation of the inflammatory response and involvement in cellular defence pathways.[1] Evidence indicates that these biological effects may directly result from the covalent modification of cysteinyl groups present in proteins following conjugate addition to the electrophilic α,β-unsaturated ring.[2] Biosynthetically, however, the origins of these structurally related compounds appear to be different. PGA_2 **2** and J_2 **3**, for example, may be formed in mammalian systems following the oxidation and subsequent dehydration of $PGF_{2\alpha}$ **1**.[1] $PGF_{2\alpha}$ **1** itself being derived from the arachidonic acid-cyclooxygenase cascade.[3] Further allylic dehydration of PGJ_2 **3**, which has been reported to occur in serum albumin, generates $\Delta^{12,14}$-15-deoxy-PGJ_2 **4**.[4] Another facet to this story concerns the recent discovery that structurally similar, albeit racemic, prostanoid natural products are also formed, particularly during events of cellular (oxidative) stress. Such compounds, termed isoprostanes to distinguish them from the enzymatically derived prostaglandins, are thought to be derived from the non-enzymatic oxidation of membrane-bound polyunsaturated fatty acids.[5] These natural products provide a link to the popular current concept that dietary manipulation of the levels of polyunsaturated fatty acids might protect cells from the destructive influence of reactive oxygen species.[6]

The cross-conjugated juxtaposition of the dienone unit present in **4** is also found in several other, structurally related, naturally occurring compounds. Again these compounds, from different biological sources, appear to possess interesting biological properties.[1] In plants, 12-oxophytodienonic acid **5**, the biosynthetic precursor to jasmonic acid, is derived from linolenic acid *via* the allene oxide synthase pathway.[7] Dehydrophytodienoic acid **6** (13,14-dehydrophytoprostane J_1 originally also called chromomoric acid)[8] has been isolated from several plant sources and, despite the structural similarity to **5**, it is not known whether this compound is derived enzymatically, or from the plant version of the isoprostane pathway.[9] The plant congeners of the mammalian isoprostanes are termed phytoprostanes.[9] Marine derived natural products related to **4** and **6** are also known and clavulone **7** is a representative example.[10] These compounds typically display greater oxidation than their terrestrial counterparts and often include halogenation.[10] Recently a new class of cross-conjugated cyclopentenone has been discovered that possesses an allylic epoxide in the alkylidene side chain. Such racemic compounds, exemplified by **8**, are, again believed to be derived *via* the isoprostane pathway.[11]

Primary prostaglandins, such as the historic $PGF_{2\alpha}$, elicit their potent biological activities *via* their direct interaction with specific receptors on the surface of the cell plasma membrane.[1]

[a]*Department of Chemistry, University of Liverpool, Liverpool, UK L69 7ZD*
[b]*Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Dublin 4, Ireland. E-mail: paul.evans@ucd.ie*
[c]*Conway Institute, University College Dublin, Dublin 4, Ireland*
[d]*Unitat de Recerca en Síntesis Asimètrica, Institute for Research in Biomedicine (IRB Barcelona), Departament de Química Orgànica, Universitat de Barcelona, Parc Científic de Barcelona, c/Baldiri Rexiac 10, 08028, Barcelona, Spain*

† Electronic supplementary information (ESI) available: Full experimental details and spectroscopic data. CCDC reference number 219462. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b814619e

‡ Current address: National Institute for Biotechnology & Genetic Engineering (NIBGE), PO Box 577, Jhang Road, Faisalabad, Pakistan.
§ Current address: Dept. Molecular Biology, Genentech Inc. 1 DNA Way, MS 37, South San Francisco, Ca 94080-4990, USA.

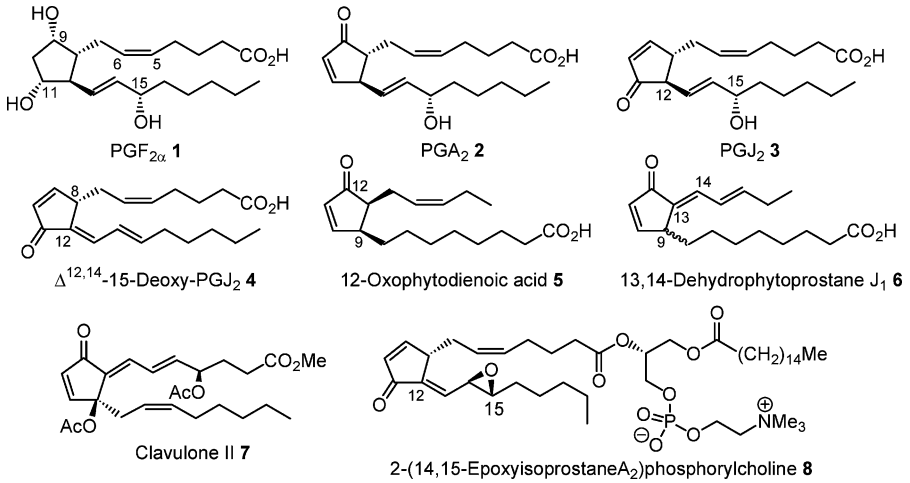


Fig. 1 Representative cyclopentenone fatty acid derived natural products.

Typically such C20 arachidonic acid derivatives possess pro-inflammatory and muscle contracting effects.[1,3] In contrast, the latter, cyclopentenone-containing members of the prostaglandin family, such as **2**, **3** and particularly **4**, appear to counteract these pro-inflammatory effects.[1] Evidence indicates that they may do this by interfering with the processes of gene transcription and ultimately protein translation *via* their interaction with several transcription factors.[1,3]

Nuclear factor kappa B (NF-κB), discovered by Baltimore in 1986,[12] plays a pivotal role in the inflammatory response and its downstream gene products include *i*-NOS, COX-2 and various cytokines responsible for initiating and perpetuating the effects of inflammation.[13] For this reason NF-κB has emerged as a promising target for the development of compounds aimed at inhibiting the excessive inflammation associated with various conditions.[13] In 2000 it was shown by Karin and Santoro that unsaturated prostanoids inhibit NF-κB by binding to a thiol residue contained in the activation loop of the β-subunit of the IκB kinase IKK.[14] This kinase is responsible for the activation of NF-κB in the cytoplasm of the cell, which, following activation, relocates to the nucleus and initiates gene transcription.[13,14] Cyclopentenone prostaglandins also interfere with the heat shock response process, which is a protective mechanism that cells use under stressful conditions including, but not exclusively, extremes of temperature.[1,15] This process is mediated by a transcription factor (heat shock factor) the activation of which leads to the accumulation of proteins termed heat shock proteins (HSP), in particular HSP70, whose role as a molecular chaperone has been documented.[15]

The final important cyclopentenone prostaglandin target is another transcription factor; peroxisome proliferator activated receptor γ (PPAR-γ). This, so-called, orphan nuclear receptor was discovered in the late eighties[16] and soon after was reported to be the molecular target for a clinically useful class of drugs for the treatment of the symptoms of type 2 diabetes.[17] Several members of this class of compounds, known as the thiazolidindiones (TZDs), ultimately became medicines for the treatment of this steadily growing worldwide condition (see later). PPAR-γ's role appears to be in the control of lipid and glucose homeostasis and its gene products include enzymes involved in lipid oxidation and the peptide adiponectin, which controls formation of adipocytes (fat cells). In 1995 it was demonstrated that the unsaturated cyclopentenone, $\Delta^{12,14}$-15-deoxy-PGJ$_2$ **4**, bound to and activated PPAR-γ and consequently the suggestion was made that **4** was the natural ligand for this orphan receptor.[18] This proposal, however, has remained a contentious matter of debate, primarily since the natural detectable levels of **4** have never been in the same range as the levels needed to activate PPAR-γ appreciably.[19] One plausible proposal explaining these detection problems and the apparent low *in vivo* concentration of **4** concerns its reactivity and the fact that free $\Delta^{12,14}$-15-deoxy-PGJ$_2$ **4** may be removed from circulation *via* either conjugation to reduced glutathione (GSH)[1,2,20] and/or by association with serum albumin.[20] The reactivity of **4** with GSH and the stability of the corresponding glutathione adduct has been investigated by Noyori and co-workers.[2] Furthermore, a relationship and interplay between NFκB and PPAR-γ has recently been uncovered which seems to demonstrate that activation of PPAR-γ leads directly to inhibition of NFκB possibly by a nuclear export mechanism.[21]

Although the precise mechanisms are different, in plant species the cyclopentenoid natural products, exemplified by **5** and **6**, appear to play important roles involving the defence and homeostasis of their host.[9] For example, it has been reported that either wounding of the plant, or pathogen attack, induces the accumulation of cyclopentanoid compounds. These compounds activate defence related genes and induce detoxification responses. Even the exogenous application of phytoprostanes **5** and **6** initiates the biosynthesis of secondary metabolites such as phytoalexins.[22]

Based on the interesting profile of biological activities demonstrated by natural products possessing the cross-conjugated cyclopentenone structural motif we became interested in developing a modular synthetic method that enabled the straightforward preparation of analogues.[23] The ultimate aim was to evaluate these analogues in terms of their ability to activate PPAR-γ in the hope that a relationship between structure and activity could be uncovered. We envisaged that the structural motif present in this class of compounds could be efficiently accessed *via* a conjugate addition–Peterson olefination sequence performed on a suitable masked α-silyl cyclopentadienone synthon **9** (see Fig. 2). This process would serve to install both the alkyl and alkylidene (C-8

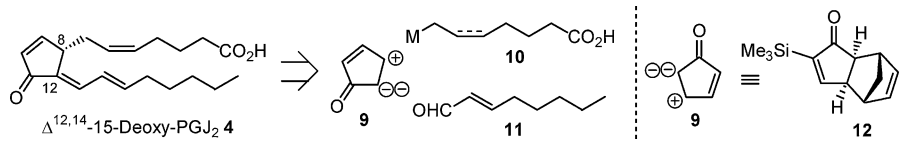


Fig. 2 Retrosynthetic analysis of cross-conjugated cyclopentenones based on a conjugate addition–Peterson olefination approach (M = metal).

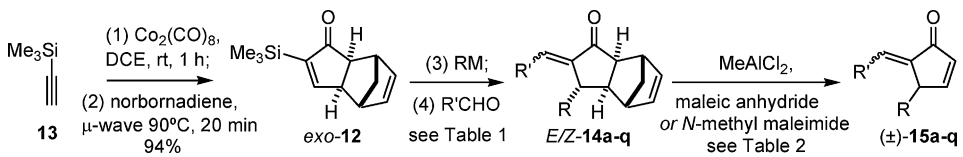
and C-12) side-chains, the latter being at the desired oxidation level. The reaction partners for this proposed sequence would be a functionalised organometallic species represented by **10** and an α,β-unsaturated aldehyde **11** and **9**. A cyclopentene unit was chosen to mask the endocyclic carbon–carbon double bond in the cyclopentenone moiety, since, based on seminal studies by Stork and Roussec,[24] this group may be readily removed by a *retro*-Diels–Alder process either under Lewis acidic, or flash vacuum pyrolysis conditions. Furthermore due to its rigid, conformationally locked molecular architecture high levels of stereoselectivity have been observed following related conjugate addition reactions.[25] Obvious advantages in this approach include expediency and the ability to readily vary the structures of the pendant groups in a modular fashion. We also felt that there was a high possibility that the conjugate addition reaction and the Peterson olefination could be carried out sequentially, in the same reaction vessel. This efficient one-pot transformation has been virtually ignored following its initial disclosure in 1984,[26] mainly because its success remained limited to certain substrates. We have reported preliminary results in this area.[27]

Results and discussion

Crucially, in relation to this proposed sequence, (±)-*exo*-2-trimethylsilyl-3*a*,4,7,7*a*-tetrahydro-4,7-methanoinden-1-one **12** is readily available in high yield and on multi-gram scale *via* an intermolecular Pauson–Khand reaction between trimethylsilylacetylene **13** and norbornadiene either under our microwave conditions,[28] or traditional thermal conditions.[29] Traces of the corresponding *endo*-diastereomer were detected in small amounts but this impurity may be removed following column chromatography, or recrystallisation from hexane (Scheme 1).

Pleasingly compound **12** readily participated in conjugate addition reactions on treatment with either organocuprate reagents or with Grignard reagents in the presence of copper(I) salts. These conjugate adducts could be isolated and characterised on protonation (see for example Scheme 3) but we were, however, delighted to find that the resultant intermediate enolate efficiently participated in a one-pot Peterson olefination reaction with a variety of structurally diverse aldehydes.¶ Table 1 summarises the one-pot conjugate addition–Peterson olefination reactions performed. Initial experiments focused on the addition of Gilman's cuprate to **12** in ether (Entry 1), or THF. This reaction was found to proceed to completion between −78 °C and −5 °C. The reaction mixture was then re-cooled to −78 °C and benzaldehyde was added. On warming, the formation of a more polar, UV active spot was detected which on isolation proved to be the hoped for exocyclic dienone **14a**. One geometric isomer and one diastereomer were detected and the structure of this solid compound **14a** was

¶ Classical Peterson olefination reactions may be performed following initial addition of LDA to the conjugate adduct followed by benzaldehyde. However, in our hands the yields for this two-step process were considerably lower than the reported, *in situ*, method.



Scheme 1 Proposed three-step sequence for the construction of cross-conjugated cyclopentenones.

Table 1 The one-pot conjugate addition–Peterson olefination reaction of *exo*-**12**

Entry	RM[a]	R′	Adduct	Yield[b]	*E* : *Z*[c]	Entry	RM[a]	R′	Adduct	Yield[b]	*E* : *Z*[c]
1	Me_2CuLi	Ph	**14a**	93%	>95 : 5	14	Me_2CuLi	*i*-Pr	**14l**	61%	65 : 35
2	MeMgBr	Ph	**14a**	86%	75 : 25	15	MeMgBr	*i*-Pr	**14l**	83%	30 : 70
3	*n*-Bu_2CuLi	Ph	**14b**	91%	>95 : 5	16	*n*-Bu_2CuLi	*n*-Hex	**14m**	82%	>95 : 5
4	*n*-Oct_2CuLi	Ph	**14c**	84%	>95 : 5	17	*n*-BuMgCl	*n*-Hex	**14m**	69%	30 : 70
5	Me_2CuLi	4-$O_2NC_6H_4$	**14d**	92%	>95 : 5	18	*i*-PrMgCl	Ph	**14n**	81%	60 : 40
6	Me_2CuLi	4-$MeOC_6H_4$	**14e**	45%	>95 : 5	19	VinylMgBr	Ph	**14o**	94%	95 : 5
7	Me_2CuLi	2-Furyl	**14f**	94%	>95 : 5	20	VinylMgBr	*i*-Pr	**14p**	88%	50 : 50
8	Me_2CuLi	2-Pyridyl	**14g**	45%	>95 : 5	21	*n*-Oct_2CuLi	$MeO_2C(CH_2)_5$	**14q**	81%	>95 : 5
9	Me_2CuLi	*N*-Me-3-indole	**14h**	13%	>95 : 5	22	*n*-OctMgBr	$MeO_2C(CH_2)_5$	**14q**	57%	35 : 65
10	Me_2CuLi	*N*-Ts-3-indole	**14i**	83%	>95 : 5	23	Me_2CuLi	*t*-Bu	**14r**	—	—
11	Me_2CuLi	*E*-PhCH=CH	**14j**	68%	>95 : 5	24	Me_2CuLi	PhCOMe	**14s**	—	—
12	Me_2CuLi	*E*-$MeCH_2CH$=CH	**14k**	88%	90 : 10	25	Me_2CuLi	$(CH_2)_5CO$	**14t**	—	—
13	MeMgBr	*E*-$MeCH_2CH$=CH	**14k**	93%	75 : 25						

[a] Conditions: 2 eq. RLi, 1 eq. CuI, Et_2O; or: 1.5 eq. RMgBr–Cl, 10 mol% CuI, Et_2O (for further details see Experimental section). [b] Yield following purification by flash column chromatography. [c] Ratio determined by ^{1}H-NMR spectroscopy of crude adducts **14**.

unambiguously confirmed by X-ray diffraction (Fig. 3).[30] This indicated that the formation of an *E*-alkene had occurred and that the initial conjugate addition had taken place on the less sterically encumbered, lower face. Based on isolated yields we found that the use of ether as a solvent for this process was preferable and further investigations focused on its use. Addition of a solution of **12** in ether to a mixture of methylmagnesium bromide in the presence of 10 mol% copper(I) iodide again resulted in smooth conjugate addition between −78 °C and −5 °C (Entry 2). The intermediate enolate was re-cooled to −78 °C and benzaldehyde was added. In terms of conversion the reaction proceeded equally effectively under these conditions, however, in this instance inspection of the crude ^{1}H-NMR spectrum indicated the presence of two compounds in a ratio of 75 : 25. The minor compound was separable and proved to be the corresponding *Z*-adduct **14a**. Alternative alkyl organocuprate reagents proceeded in a similar fashion with benzaldehyde (Entries 3 and 4); in each case only the *E*-alkenyl isomer was detected. The use of alternative aromatic and heteroaromatic aldehydes was successfully investigated in conjunction with Me_2CuLi (Entries 5–10) and again only one geometrical isomer was detected for the newly formed double bond. Based on the yields encountered it appears that electron rich and Lewis basic aldehydes (*i.e.* Entries 6, 8 and 9) do not participate as effectively as their more reactive, electron poorer counterparts (Entry 5 and 10). The process described also proceeded efficiently with α,β-unsaturated aldehydes (Entries 11, 12 and 13), thereby providing a strategy for the installation of the exocyclic dienone unit present in natural products **4**, **6** and **7** (Fig. 1). The 1,4-addition of isopropylmagnesium chloride, and vinylmagnesium bromide proceeded smoothly using catalytic CuI (10 mol%) and in both cases the corresponding magnesium enolate reacted efficiently with benzaldehyde, affording enones **14n** and **14o** as separable mixtures of *E*- and *Z*-stereoisomers (Entries 18 and 19).

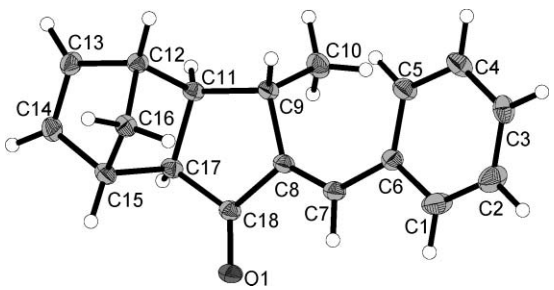


Fig. 3 X-Ray crystal structure of adduct **14a** (Ortep representation).

At this stage it was of interest to ascertain whether aldehydes possessing α-protons would participate in the process, or whether intermediate **17** might prove to be incompatible with such, potentially acidic, reaction partners. This concern proved to be unfounded and freshly distilled isobutyraldehyde gave good yields of the corresponding adducts **14l** using either the Gilman cuprate, or MeMgBr (Entries 14 and 15). Interestingly, the stereochemical integrity of the double bond formed was much less well defined in these instances and significant amounts of the readily separable *Z*-stereoisomers were formed. As before (Entries 2) this lack of stereoselectivity was most marked when the organomagnesium reagent was employed. Finally, this reaction sequence described was then applied to a rapid synthesis of (±)-TEI-9826 **15q**, an analogue of PGA_2 **2** which has been evaluated *in vivo* as a potential anticancer agent.[31] Thus, addition of either $(n\text{-Oct})_2CuLi$, or *n*-OctMgBr (10 mol% CuI) to **12**, followed by addition of methyl 7-oxoheptanoate[32] afforded the exocyclic enone **14q** in good yield (Entries 21 and 22). This latter reaction indicated that additional carbonyl functionality in the aldehyde Peterson olefination partner is tolerated under the reaction conditions. The use of pivaldehyde, acetophenone and cyclohexanone (Entries 23–25) only afforded the corresponding conjugate adduct and none of the hoped-for product of Peterson olefination. Based on these failures it appears that steric effects, in addition to the electronic reactivity of the carbonyl species, play an important role in this process (see also Scheme 5).

The *retro*-Diels–Alder reactions of the norbornadiene adducts *E*-**14a–14q** were performed in dichloromethane at 40 °C using $MeAlCl_2$ and an excess of maleic anhydride as a cyclopentadiene trap (Table 2).[25,33] Generally, this method provided good yields of the corresponding cross-conjugated cyclopentenones *E*-**15a–15q** with only minimal alkylidene isomerisation. Notable exceptions were compounds containing basic azo-functionality (Entries 8 and 9); in these examples none of the cyclopentenone products **15h** and **15i** were detected. It was also of interest that, following

Table 2 The preparation of cross-conjugated prostanoid mimics **15** by *retro*-Diels–Alder cycloaddition

Entry[a]	R	R′		Yield[b]	*E* : *Z*[c]	Entry	R	R′		Yield[b]	*E* : *Z*[c]
1	Me	Ph	*E*-**15a**	84%	>95 : 5	12	Me	*E*-$MeCH_2CH$=CH	*E*-**15k**	33%[g]	90 : 10
2	Me	Ph	*Z*-**15a**	64%[d]	>95 : 5	13	Me	*E*-$MeCH_2CH$=CH	*E*-**15k**	92%[h]	>95 : 5
3	*n*-Bu	Ph	*E*-**15b**	83%	>95 : 5	14	Me	*i*-Pr	*E*-**15l**	82%	90 : 10
4	*n*-Oct	Ph	*E*-**15c**	76%	>95 : 5	15	Me	*i*-Pr	Z-**15l**	67%[i]	90 : 10
5	Me	4-$O_2NC_6H_4$	*E*-**15d**	85%	>95 : 5	16	*n*-Bu	*n*-Hex	*E*-**15m**	84%	>95 : 5
6	Me	4-$MeOC_6H_4$	*E*-**15e**	68%	>95 : 5	17	*n*-Bu	*n*-Hex	Z-**15m**	33%[j]	65 : 35
7	Me	2-Furyl	*E*-**15f**	64%	>95 : 5	18	*i*-Pr	Ph	*E*-**15n**	87%	>95 : 5
8	Me	2-Pyridyl	*E*-**15g**	NR[e]	—	19	Vinyl	Ph	*E*-**15o**	73%	>95 : 5
9	Me	*N*-Me-3-indole	*E*-**15h**	NR[e]	—	20	Vinyl	*i*-Pr	*E*-**15p**	73%	90 : 10
10	Me	*N*-Ts-3-indole	*E*-**15i**	28%[f]	75 : 25	21	*n*-Oct	$MeO_2C(CH_2)_5$	*E*-**15q**	86%	80 : 20
11	Me	*E*-PhCH=CH	*E*-**15j**	78%	90 : 10						

[a] Conditions unless otherwise stated: 1–1.5 eq. $MeAlCl_2$, 5–10 eq. maleic anhydride, DCM, 40 °C (for further details see Experimental section). [b] Yield following purification by flash column chromatography. [c] Ratio by ^{1}H-NMR spectroscopy. [d] 84% based on recovered *E*-**14a**. [e] NR = no reaction. [f] 1 eq. $MeAlCl_2$, 5 eq. *N*-methyl maleimide, DCM, μ-wave, 70 °C, 25 min, 85%. [g] 83% based on recovered **14k**. [h] 1.5 eq. $MeAlCl_2$, 15 eq. maleic anhydride, DCM, μ-wave, 120 °C, 70 sec. [i] 89% based on recovered *E*-**14l**. [j] 95% based on recovered *E*-**14m**.

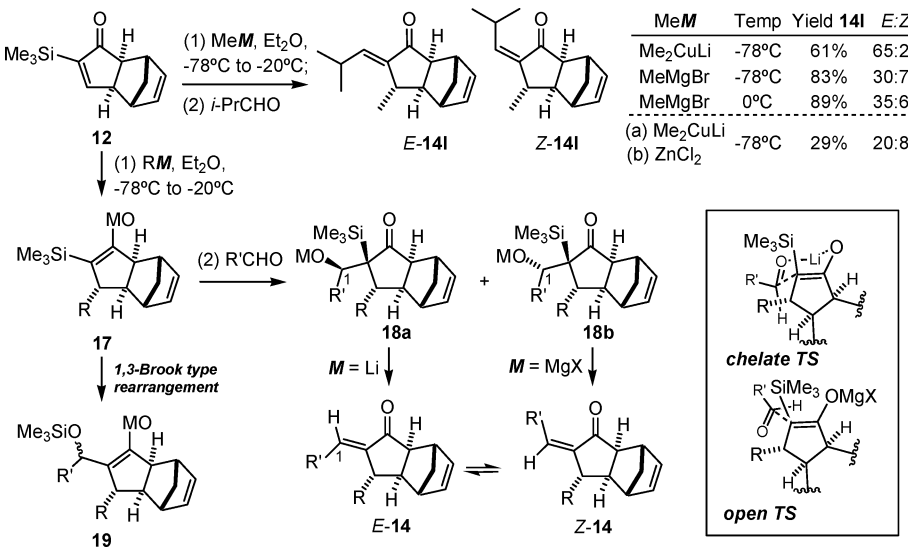
employment of this Lewis acid based methodology, the purified *Z*-exocyclic enones **14a**, **14l** and **14m** (Entries 2, 15 and 17) underwent significant alkene isomerisation, affording predominantly the *E*-cross-conjugated cyclopentenone products **15a**, **15l** and **15m**. For example, treatment of *Z*-**14l** gave **15l** in 67% yield (*E* : *Z*, 90 : 10) and 22% of isomerised starting material, *E*-**14l**. The functionalised adduct **14q** was smoothly converted to the target dienone **15q** in 86% yield.

In certain instances it proved advantageous to use alternative reaction conditions. For example, the use of *N*-methyl maleimide in conjunction with microwave heating gave *E*-**15i** in 85% yield, whereas under standard conductive heating the isolated yield was significantly lower (28%). The use of the alternative dienophile in this case facilitated product purification (Entry 10). Microwave irradiation for relatively short periods was also found to be useful in the conversion of *E*,*E*-**14k** into the corresponding cross-conjugated trienone *E*-**15k**, where both improved product yields and reduced alkylidene isomerisation was observed (Entries 12 and 13).

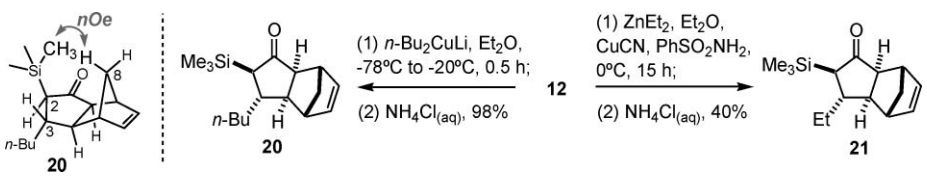
In summary, the one-pot conjugate addition–Peterson olefination reaction was employed in order to efficiently install both the 2-alkylidene and 3-alkyl side-chains present in cross-conjugated cyclopentenone natural products. The stereochemistry of the 2-alkylidene side-chain depends on the type of organometallic reagent employed in the conjugate addition reaction. Use of organocuprate reagents afforded high levels of *E*-selectivity, whereas copper-catalysed Grignard reagents gave significant amounts of the corresponding *Z*-isomer. In all examples the separation of geometrical alkylidene isomers proved possible by flash column chromatography.

It seems reasonable to speculate that the observation concerning the selective formation of *E*-Peterson olefination products with organocuprate reagents *versus* the formation of *Z*-adducts (albeit with variable selectivity) with Grignard reagents is due to a change in counterion in the intermediate **17** (*i.e.* Li → MgBr)[34] and that the identity of this enolate influences the path of the subsequent Peterson reaction. Another observation concerning the stereoselectivity was that the preponderance for *Z*-alkylidene formation increases corresponding to the size of the aldehyde. For this reason the one-pot conjugate addition–Peterson olefination process using isobutyraldehyde was further investigated. Using the Gilman cuprate to form **17** and subsequent addition of isobutyraldehyde at −78 °C afforded the adduct **14l** as a separable mixture of *E*- and *Z*-isomers (*E* : *Z* ; 65 : 25 determined by ^{1}H-NMR spectroscopy of the crude reaction mixture). The corresponding reaction with methylmagnesium bromide and a catalytic amount of copper(I) iodide preferentially formed *Z*-**14l** (*E* : *Z*; 30 : 70), which seemed to be relatively independent of the temperature (*i.e.* −78 °C to 0 °C) at which the aldehyde was added. Following addition of Gilman's cuprate to **12** the intermediate **17** (M = Li) was treated with 2 equiv. of $ZnCl_2$. Subsequent addition of isobutyraldehyde, at −78 °C, afforded **14l** in low yield (29%) but predominantly as *Z*-**14l** (*E* : *Z*; 20 : 80). This serves to highlight, again, that the counter ion plays a pivotal role in the stereochemical outcome of the Peterson olefination process (Scheme 2).

The initial carbon–carbon bond forming reaction could dictate the stereochemical outcome dependant on the identity of M.[35] We feel that this initial bond formation is likely to occur on the *Si*-face of **17** (for the diastereoselective protonation of **17** see Scheme 3, compound **20**); from this point the initial diastereomeric



Scheme 2 Mechanistic considerations in the conjugate addition–Peterson olefination reaction.



Scheme 3 Organocuprate and zinc conjugate addition reactions of **12**.

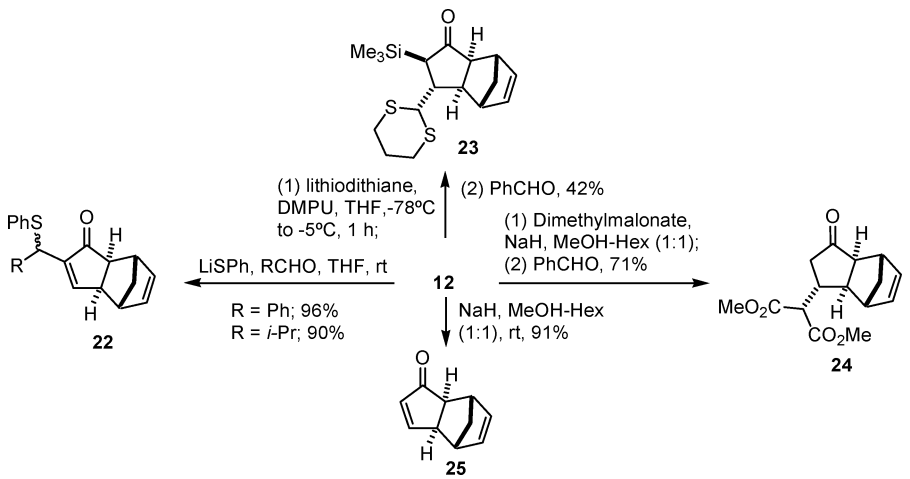
adducts **18** and **19** would then generate the corresponding products of Peterson olefination *via* a concerted silyloxy-elimination type pathway. Although this seems to be a plausible explanation and chelate (Zimmerman-Traxler–type) and open transition states can be postulated, the situation is somewhat clouded by the possibility that the initial diastereomeric adducts may undergo an initial Brook-type rearrangement, enabling bond rotation prior to elimination: it is also possible that the adducts may undergo post-Peterson isomerisation to some extent.

At this stage we became interested in applying this one-pot procedure for the preparation of more complex molecules. Therefore, the use of organozinc reagents was considered since it is well-documented that such species not only efficiently participate in conjugate addition reactions but that they are also able to carry functionality (such as carboxylic acid esters) not compatible with organolithium and magnesium reagents.[36] Initial investigations were conducted to determine whether **12** underwent conjugate addition with diethylzinc under standard conditions (Scheme 3).[36] Whereas cyclopentenone **12** readily undergoes conjugate addition under standard organocuprate conditions the analogous organozinc reaction was sluggish under several literature conditions and yields of only 10–40% of adduct **21** were obtained.[36] Optimum yields of **21** were achieved using Noyori's sulfonamide promoted conditions,[37] however, due to the low conversion of **12** into **21** and the use of additional additives we felt that the use of organozinc species was not attractive in terms of our one-pot Peterson approach. The stereochemistry of the newly formed α-keto centre was probed using NOE experiments. Irradiation of the methyl silicon substituent gave an enhancement to one of the diastereotopic methylene bridging protons thereby indicating that protonation of the enolate **17** occurs on the *Si* face.

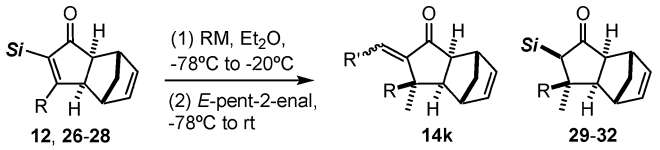
The use of alternative nucleophilic species as reaction partners in the conjugate addition–Peterson olefination reaction with the same enone **12** were investigated. The results of these studies are summarised in Scheme 4. It was found that a THF solution of PhSLi and benzaldehyde, or isobutyraldehyde generated an uncharacterised diastereomeric mixture of **22** (60 : 40) in 96% and 90% yields respectively. The formation of this adduct appears to result from an initial conjugate addition–Peterson olefination process followed by nucleophilic attack at the exocyclic double bond and elimination. Optimum yields for this process were achieved following a one-pot reaction protocol in which all the reagents were added simultaneously (Scheme 4).

It has been shown that lithiodithiane, in the presence of a polar aprotic additive such as HMPA or DMPU,[38] undergoes 1,4-conjugate addition to various enones. In our hands, although we could successfully generate adduct **23**, resulting from 1,4-conjugate addition and protonation, attempts to affect *in situ* Peterson olefination were unsuccessful. The use of malonate anions were also studied and again, although under standard conditions[39] the conjugate addition was successful, we were unable to link this process to the Peterson olefination in order to prepare adducts with a functional handle for further elaboration. It seems likely that under these conditions the intermediate enolate (of the type **17**) is formed reversibly and then undergoes protonation, which in turn facilitates the protodesilylation process, thereby affording **24**. Interestingly, under similar reaction conditions, in the absence of dimethylmalonate, **12** underwent efficient desilylation, a process we feel is likely to proceed *via* reversible methoxide conjugate addition.

At this stage all our experience of conducting the one-pot conjugate addition–Peterson olefination reaction had been using the same compound, namely *exo*-2-trimethylsilyl-3*a*,4,7,7*a*-tetrahydro-4,7-methanoinden-1-one **12**. Consequently, it was of interest to investigate whether alternative α-silicon bearing α,β-unsaturated carbonyl compounds would also participate in this tandem reaction. Therefore, compounds **26** and **27** possessing different silicon substituents, were prepared using an intermolecular PKR (Scheme 5). Compound **28**, in which a methyl substituent is present in the β-position was also prepared and these alternative cyclopentenone adducts were subjected to the reaction conditions described in Table 1. Whereas, compound **12** efficiently generated **14k**, the product of methyl conjugate addition and Peterson olefination with *E*-pent-2-enal (Entries 1 and 2), substrate **26** gave solely the conjugate adduct **30** with both organocuprate and Grignard reagents (Entries 3 and 4). We attributed the recalcitrance of the intermediate enolate to participate in the Peterson olefination reaction on the basis of the increased steric bulk of the triisopropylsilyl unit. Use of the less-bulky *tert*-butyldimethylsilyl group (Entry 5) led to a



Scheme 4 Attempted conjugate addition–Peterson olefination using alternative nucleophilic reagents.



12, **26-28** **14k** **29-32**

exo-**12**: ***Si*** = $SiMe_3$, R = H;
exo-**26**: ***Si*** = $Si(i\text{-}Pr)_3$, R = H;
exo-**27**: ***Si*** = $SiMe_2t$-Bu, R = H;
exo-**28**: ***Si*** = $SiMe_3$, R = Me

29: ***Si*** = $SiMe_3$, R = H;
30: ***Si*** = $Si(i\text{-}Pr)_3$, R = H;
31: ***Si*** = $SiMe_2t$-Bu, R = H;
32: ***Si*** = $SiMe_3$, R = Me

Entry	Substrate	Conditions	**14k**[a]	**29-32**[a]
1	**12**	(a) Me_2CuLi; (b) *E*-pent-2-enal	88% (*E*:*Z*; 9:1)	-
2	**12**	(a) MeMgBr, 10 mol% CuI; (b) *E*-pent-2-enal	93% (*E*:*Z*; 3:1)	-
3	**26**	(a) Me_2CuLi; (b) *E*-pent-2-enal	-	98%
4	**26**	(a) MeMgBr, 10 mol% CuI; (b) *E*-pent-2-enal	-	97%
5	**27**	(a) MeMgBr, 10 mol% CuI; (b) *E*-pent-2-enal	41% (*E*:*Z*; 1:1)	38%
6	**28**	(a) Me_2CuLi, Et_2O, TMSCl (2 eq.); (b) NH_4Cl(aq)	n/a	44%

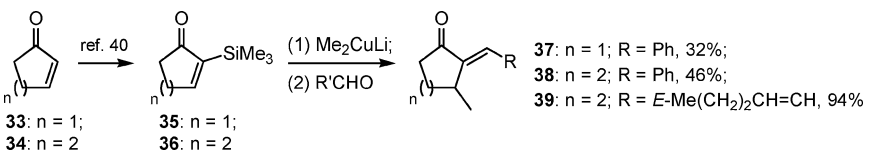
[a]Yield following purification by flash column chromatography; [b]Ratio determined by ^{1}H-NMR spectroscopy

Scheme 5 Attempted conjugate addition–Peterson olefination using different PK adducts.

mixture of the conjugate adduct **31** (30%) and the Peterson product **14k** (41%) suggesting again that steric factors play a significant role in the Peterson olefination reaction of this series of compounds. We found that substrate **28** was particularly reluctant to undergo conjugate addition under standard conditions, indeed this compound only underwent conjugate addition in the presence of TMSCl whereupon **32** was isolated in 44% yield following silyl enol ether cleavage. Based on the stereoselective formation of **20**, we assume that the formation of **30** to **32** generated the diastereomer resulting from protonation on the *Si* face of the enolate although this was not fully investigated.

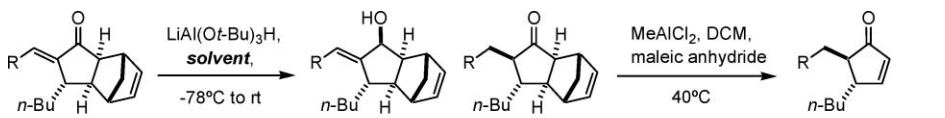
Alternative substrates do, however, effectively participate in the process (Scheme 6). Monocyclic trimethylsilanes **35** and **36** were prepared in three steps according to a four-step literature procedure[40] and under the standard conditions, indicated in Table 1, cyclopentenone **35** and cyclohexenone **36** afforded the *trans*-enones **37**, **38** and **39** stereoselectively albeit in variable, unoptimised yields (32–94%).

The chemoselective alkylidene reduction of the products of conjugate addition–Peterson olefination was investigated since on reduction followed by *retro*-Diels–Alder cycloaddition, 4,5-dialkyl substituted cyclopentenones of the type present in PGA_2 **2** and J_2 **3** would be accessed—such species would be of potential interest in terms of biological comparison with their cross-conjugated analogues. It has been reported that lithium tri-*tert*-butoxyaluminium hydride preferentially participates in the 1,4-selective reduction of α,β-unsaturated ketones resembling **14**.[24b] Therefore, we investigated whether we could utilise this reagent for the preparation of dialkyl-substituted cyclopentenones of the type **42**. It was found that the use of THF as opposed to Et_2O was crucial in order to obtain reasonable 1,4-reduction selectivity in the formation of **41b** and **41m**. However, significant amounts of the corresponding (separable) 1,2-reduced products **40b** and **40m** were still obtained (Scheme 7). The stereochemistry of the newly formed stereogenic centre was probed using NOE experiments; irradiation of the benzylic protons enhanced one of



33: n = 1; **34**: n = 2 **35**: n = 1; **36**: n = 2

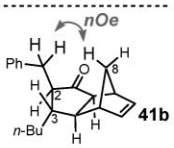
Scheme 6 The conjugate addition–Peterson reaction with cyclopent-2-enone **35** and cyclohex-2-enone **36**.



14b, **14m** **40b**, **40m** **41b**, **41m** **42b**: R = Ph; 97%; **42m**: R = *n*-Hex; 80%

	R	*solvent*	**40** (%)	**41** (%)
14b	Ph	Et_2O	68[a]	24
14b	Ph	THF	30[a]	64
14m	*n*-Hex	THF	20[b]	80

[a]Yield following purification by flash column chromatography; [b]Ratio determined by ^{1}H-NMR



Scheme 7 The conjugate reduction of exocyclic Peterson olefination adducts **14b** and **14m**.

the diastereotopic bridging methylene protons (see also Scheme 3). Subsequent *retro*-Diels–Alder cycloaddition, under the conditions described (Table 2), afforded the corresponding cyclopentenones **42b** and **42m** in good yield.

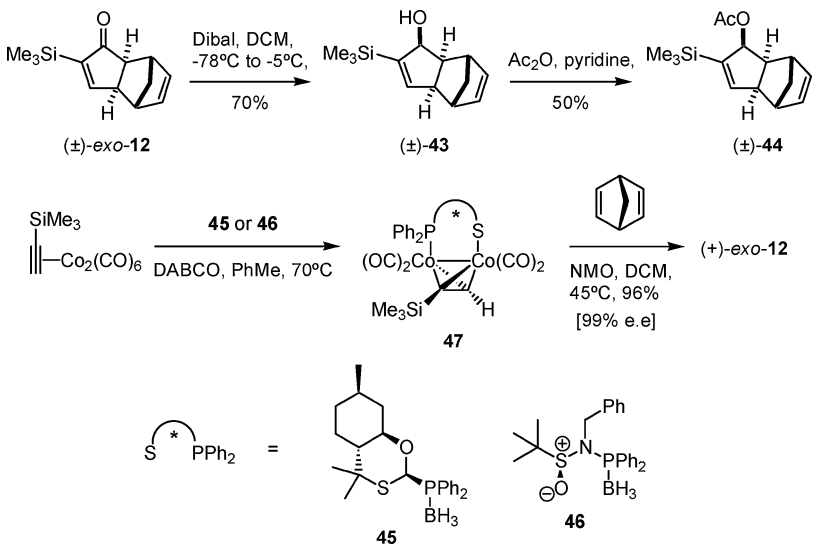
Due to the rigid conformation of *exo*-**12**, the diastereoselectivity of the conjugate addition reaction (and, for that matter, protonation of the intermediate enolate) is high. Consequently, if enantiomerically enriched forms of this compound were available, the preparation of either enantiomer of cross-conjugated compounds **15a–q** could be envisaged using the chemistry described. There are several reasons why a stereoselective synthesis of the types of compound illustrated in Fig. 1 is of interest. Firstly, from a biological perspective a comparison of the activities of racemic with enantioenriched materials is important. From a chemical perspective the configurational stability, or otherwise, of the doubly allylic stereogenic centre is also of interest. Finally, the question of stereogenicity and stereostability in this class of compound is of interest more generally since, although the prostanoids are synthesised following an enzymatically controlled pathway, the isoprostanes are formed in racemic form *via* the non-stereoselective oxidation of unsaturated fatty acids. The stereochemistry of the plant congeners is currently not completely known. Studies have shown that 12-oxophytodienoic acid **5** is formed in optically active form *via* the jasmonic acid allene oxide synthase–cyclase pathway. However, despite the structural similarities, it has been proposed that compound **6** is not formed following this pathway but is formed *via* the plant variant of the isoprostane pathway and is therefore, racemic. Following the original natural product isolation an optical rotation of +20 for the isolated $dPPJ_1$-I methyl ester **6** was reported by Bohlmann and co-workers.[8] Consequently, we felt that it was of interest to investigate the synthesis of such compounds in non-racemic form.

To this end the enzymatic kinetic resolution of racemic allylic alcohol **43** and acetate **44** was investigated. This approach is attractive from the perspective of an investigation into the biological properties of this compound class since, in principle, both enantiomers of **15** may be accessed. However, under standard conditions[41] no conversion of either compound could be achieved (Scheme 8). This failure was attributed to steric congestion around the reactive centre; therefore, alternative approaches were explored.

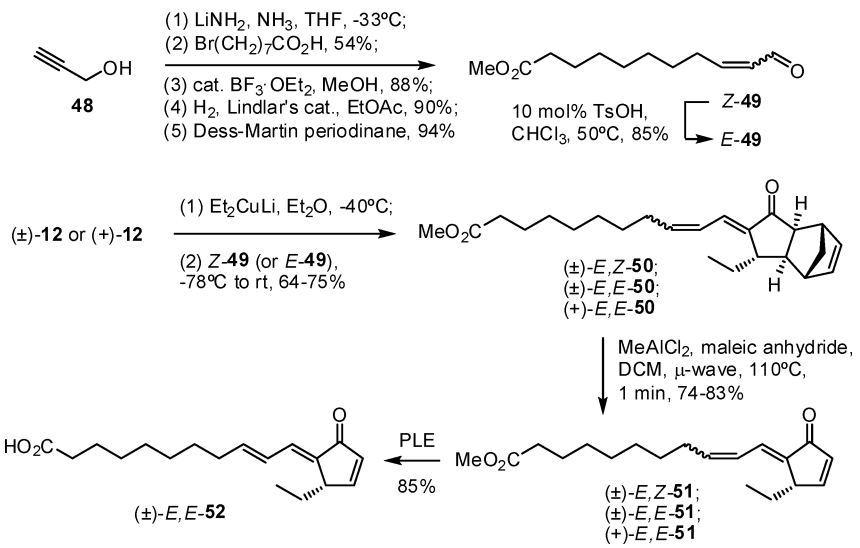
Recently we have reported several P,S chiral ligands for the asymmetric intermolecular Pauson–Khand reaction. The chiral-pool derived enantiopure ligand PuPHOS (**45**) and the PNSO ligand **46** both provided excellent results in the cyclisation with norbornadiene.[42] In the case of **46** both enantiomers are readily available in a multigram scale since they are prepared from the commercially available *tert*-butylsulfinamide. Ligand **46** can be stored either as its borane complex or as a borane-free ligand (Scheme 8). Release of the borane protection group *in situ* with DABCO and reaction of either **45** or **46** with the acetylene-hexacarbonyl dicobalt complex afforded a biased mixture of diastereomeric complexes (3 : 1 for **45**, 12 : 1 for **46**) from which the major complex **47** can be isolated by crystallisation.

The subsequent Pauson–Khand cyclisation from **47** enabled the preparation of the desired enantiomer of **12**. Thus, starting from the crystalline complex **47** the oxidative Pauson–Khand reaction with norbornadiene afforded (+)-**12** in high yield and 96–97% ee.[42] Recrystallisation of this material from hexane gave (+)-**12** in 99% ee. In our case, subsequent synthetic studies focused on the use of this enantiomer since conjugate addition–Peterson olefination would generate compounds possessing the *S*-configuration present in the naturally occurring cross-conjugated cyclopentenones (see Fig. 1).

Part of the argument in favour of the non-enzymatic phytoprostane pathway is that regioisomeric compounds **51** are formed in addition to compounds exhibiting the type of structure exemplified by **5** and **6**.[9] We employed a similar approach used in the preparation of TEI-9826 **14q** (Table 1, Entry 21) for the synthesis of ethyl phytoprostane **51** as the methyl ester (Scheme 9). Thus, both geometrical isomers of aldehyde **49** were prepared stereoselectively from 8-bromooctanoic acid and propargyl alcohol **48** using a known route.[43] Although it was found that *Z*-**49** readily underwent isomerisation both on prolonged storage in $CDCl_3$ and on silica gel during chromatographic purification, use of the crude



Scheme 8 Studies aimed towards the preparation of enantioenriched *exo*-**12**.



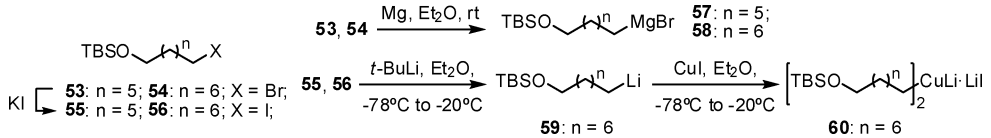
Scheme 9 Preparation of phytoprostanes **51**.

Z-aldehyde directly in the conjugate addition–Peterson olefination using (±)-**12**, gave the adduct **50** in good yield and stereoselectivity (*E*,*Z* > 95%). Proton NMR spectroscopy confirmed retention of the *Z*-alkene (*J*, 10.5 Hz). Finally, *retro*-Diels–Alder reaction gave the phytoprostane natural product *E*,*Z*-**51** (methyl ester) as the 9-*cis*-geometrical isomer. It was found that the use of short reaction periods and microwave irradiation was the key to minimise isomerisation of the alkylidene bond formed following the Peterson reaction. An identical synthetic approach using *E*-**49** gave the corresponding 9-*E* stereoisomer (*E*,*E*-**51**). Following the optimisation of this sequence in the racemic series an identical approach was performed using (+)-**12** and *E*-**49**. In this manner (+)-*E*,*E*-**51** was obtained in 56% overall yield for the two steps. Analysis by chiral HPLC indicated that this material had an enantiomeric excess of >99% thereby demonstrating that no epimerisation of the doubly allylic, single stereogenic centre had occurred during the *retro*-Diels–Alder reaction and purification. Conversion of *E*,*E*-**51** to the corresponding carboxylic acid *E*,*E*-**52** was efficiently achieved using hog liver esterase.[44]

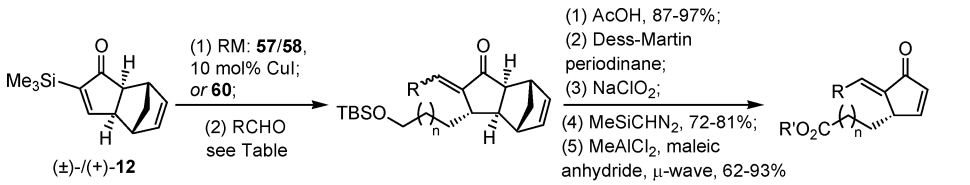
Next we investigated the preparation of phytoprostane **6**, and its double bond stereoisomers employing analogous chemistry to that reported by us previously for the synthesis of $\Delta^{12,14}$-15-deoxy-PGJ_1 **61**.[45] Appropriately functionalised organometallic species were prepared as illustrated in Scheme 10.

When the Grignard reagent **58** was employed in the tandem sequence, compound **62** was isolated (following Peterson olefination with *E*-pent-2-enal) in 84% yield with an *E* : *Z* ratio of 65 : 35 for the newly formed double bond (Scheme 11, Entry 2). In contrast, use of corresponding cuprate **60** gave enone **62** in good yield as essentially only the *E*-stereoisomer (*E* : *Z*; >95 : 5). As previously observed the geometrical isomers of **62** were separable *via* flash column chromatography. A standard deprotection–oxidation sequence was then employed to furnish the carboxylic acid in good overall yields for the three-step sequence. Finally, unmasking of the cyclopentenone group following an extremely rapid Lewis-acid mediated *retro*-Diels–Alder reaction performed under microwave irradiation gave (±)-**6** in good yield. Alternatively, methylation followed by the microwave-mediated *retro*-Diels–Alder process afforded the methyl ester (±)-**65** (39% overall). Saponification of (±)-**65** proceeded smoothly using hog liver esterase affording carboxylic acid **6**.

An identical sequence was employed using cuprate **60** and (+)-**12** in order to access enantioenriched enone (+)-**65**. All the intermediates on this sequence demonstrated strongly dextrorotary optical rotations and chiral HPLC analysis of the product (+)-**65** (Chiralpak AS) indicated an enantiomeric excess of 94%, again demonstrating that epimerisation of the doubly allylic single asymmetric centre did not occur to any significant extent. The dextrorotary reading obtained for **65** {$[\alpha]_D$ +144 (c = 1.0, $CHCl_3$)} compares in sign with the literature value {$[\alpha]_D$ +20 (c = 1.0, $CHCl_3$)} recorded during the natural product isolation;[8] however, the significant difference in magnitude suggests either epimerisation during extraction from the natural source, or that in nature, **6** is formed non-stereoselectively *via* the phytoprostane pathway. Several geometric isomers of **6** have been synthesised previously in racemic form by both the Bohlmann and Liu groups[8,46] and our synthetic compound corresponds with reported literature values in terms of spectroscopic data.



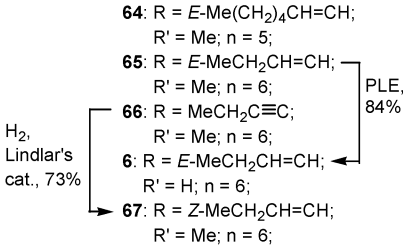
Scheme 10 Preparation of silyl ether protected organometallic reagents.



61: n = 5; R = *E*-Me$(CH_2)_4$CH=CH;
62: n = 6; R = *E*-MeCH_2CH=CH;
63: n = 6; R = MeCH_2C≡C

Entry	RM	n	R	Yield[a]	*E*:*Z*[b]
1[c]	**57**	5	*E*-Me$(CH_2)_4$CH=CH	**61**: 53%	25:75
2	**58**	6	*E*-MeCH_2CH=CH	**62**: 84%	65:35
3	**60**	6	*E*-MeCH_2CH=CH	**62**: 72%	>95:5
4[d]	**60**	6	*E*-MeCH_2CH=CH	(+)-**62**: 78%[e]	>95:5
5	**60**	6	MeCH_2C≡C	**63**: 75%	>95:5

[a]Yield following purification by flash column chromatography; [b]Ratio determined by ^{1}H-NMR spectroscopy; [c]See reference 47: combined yield of *Z*-**61** and *E*-**61** following separation of primary alcohols; [d]Performed using (+)-**12**; [e]$[\alpha]_D$ +355 (*c* 1.0, $CHCl_3$)



Scheme 11 Use of the conjugate addition–Peterson olefination reaction in the preparation of cross-conjugated cyclopentenones possessing oxidised alkyl substituents.

Activation of PPAR-γ

The cluster of so-called metabolic diseases, including type 2 diabetes hypertension and obesity represent a major global health concern. For example, it is currently estimated that approximately 5% of the world's population suffers from type 2 diabetes and this value appears to be on the increase and consequently has received widespread media coverage.[17,47] All appear to be closely linked to problems associated with our consumption and ability to process fatty acids. Notably inflammation is a characteristic additional problem associated with many disease states including diabetes. Therefore, a dual acting compound capable of inhibiting the development of inflammation *via* the inhibition of NFκB and promotion of lipid metabolism and insulin sensitivity *via* the activation of PPAR-γ could be a useful combination. The thiazolidindione (TZD) class of drugs for the treatment of the symptoms of type 2 diabetes [such as rosiglitazone **66** (Avandia, GSK)] are currently widely prescribed to patients suffering from the symptoms of this disease. These compounds improve the patient prognosis by increasing the sensitivity of cells towards insulin, possibly due to the release of a hormone called adiponectin, indirectly by binding to and activating PPAR-γ.

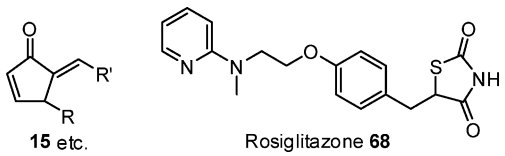
Due to the structural similarity of our synthetic compounds to the putative natural PPAR-γ ligand, $\Delta^{12,14}$-15-deoxy-PGJ_2 **4**, we investigated whether our synthetic cross-conjugated compounds possessed the ability to activate PPAR-γ. In order to achieve this a cell-based PPAR-γ assay was employed based on the Gal4-luciferase reporter gene.[48] Synthetic compounds at different doses were added to confluent human embryonic kidney cells (HEK293T) transfected with murine PPAR-γ and the luciferase vector. Activation of PPAR-γ was then determined based on luminescence. Dose response curves were constructed and the concentration at which 50% of the maximal activation (EC_{50}) was calculated. The level of PPAR-γ activation was also determined and was reported as a fold activation *versus* the baseline level of activation (Table 3). Additionally, our levels of activation were compared with controls, including $\Delta^{12,14}$-15-deoxy-PGJ_2 **4** (Entry 15) and rosiglitazone **68** (Entry 16).

Simple cross-conjugated compounds possessing either benzylidene, or isopropylidene R′ and methyl, or *n*-butyl side-chains (Entries 1–3) did not significantly alter residual PPAR-γ levels. However, increasing the lengths of both side chains did lead to compounds that activated this transcription factor. For example, **15m** (R′ = hexylidene and R = *n*-butyl) proved to be reasonably effective in terms of PPAR-γ activation. This effect was observed particularly for the *E*-stereoisomer (Entry 4); *Z*-**15m** proved to be a significantly less effective activator (Entry 5). Similarly, compound **42m**, in which the exocyclic enone has undergone reduction (see Scheme 7), also displayed diminished activation as compared to its cross-conjugated analogue *E*-**15m** (Entry 6). It was subsequently of interest to gauge whether the presence of an oxidised side chain led to increased activity, particularly since the fatty acid derived natural products possess this type of group (Fig. 1). Thus, *E*-**15q** (TEI-9826) was studied and although this did increase the levels of PPAR-γ activation the additional functional group in the R′ side-chain was found not to improve activation in comparison to *E*-**15m** (Entry 7). The synthetic phytoprostane natural products were then evaluated. Thus, it was found that both methyl ester *E*-**65** and carboxylic acid *E*-**6** did indeed activate PPAR-γ, in the case of the methyl ester did this slightly more effectively, possibly due to better cell permeation (Entries 8 and 9). Although the levels of activation were higher than *E*-**15m** and *E*-**15q** the EC_{50} value was not vastly improved. As before the corresponding *Z*-alkylidene, *Z*-**65** proved to be a much less effective agonist compared to its *E*-isomer (Entry 10).[49] Evaluation of (+)-**65** (ee 94%) indicated that the presence of the 9-*S* stereogenic centre did not improve activation compared to its racemic counterpart (Entry 11). The phytoprostane isomer **51** possessing a drastically different orientation of the R and R′ side-chains proved to be a poor PPAR-γ activator (Entry 12). Finally, our synthetic prostanoids *E*-$\Delta^{12,14}$-15-deoxy-PGJ_1 **64** (Entry 13) and *Z*-$\Delta^{12,14}$-15-deoxy-PGJ_1 **64** (Entry 14) were evaluated and these compounds both proved to be the most effective synthetic PPAR-γ activators, particularly, again,

Table 3 Activation of PPAR-γ by selected cross-conjugated $\Delta^{12,14}$-15-deoxy-PGJ_2 mimics and phytoprostanes

Entry	Compound	R	R′	PPAR-γ	EC_{50}[a](SEM)[b]	Fold activation[c]
1	*E*-**15a**	Me	Ph	ND	—	—
2	*E*-**15l**	Me	*i*-Pr	ND	—	—
3	*E*-**15b**	*n*-Bu	Ph	ND	—	—
4	*E*-**15m**	*n*-Bu	*n*-Hex	2.0 μM	(0.09 μM)	4.5
5	*Z*-**15m**	*n*-Bu	*n*-Hex	7.0 μM	(2.5 μM)	5.5
6	**42m**	*n*-Bu	*n*-Hex	10.0 μM	(4.0 μM)	3.5
7	*E*-**15q**	*n*-Oct	$MeO_2C(CH_2)_5$	2.0 μM	(0.7 μM)	3.0
8	*E*-**65**	$(CH_2)_7CO_2Me$	*E*-CH=CHCH$_2$Me	1.6 μM	(0.09 μM)	5.0
9	*E*-**6**	$(CH_2)_7CO_2H$	*E*-CH=CHCH$_2$Me	2.2 μM	(0.2 μM)	4.0
10	*Z*-**65**	$(CH_2)_7CO_2Me$	*E*-CH=CHCH$_2$Me	4.1 μM	(1.2 μM)	4.0
11	(+)-*E*-**65**	$(CH_2)_7CO_2Me$	*E*-CH=CHCH$_2$Me	2.4 μM	(0.3 μM)	5.5
12	*E*-**51**	Et	*E*-CH=CH$(CH_2)_7CO_2Me$	4.5 μM	(2.2 μM)	2.0
13	*E*-**64**	$(CH_2)_6CO_2Me$	*E*-CH=CH$(CH_2)_4$Me	0.5 μM	(0.07 μM)	6.0
14	*Z*-**64**	$(CH_2)_6CO_2Me$	*E*-CH=CH$(CH_2)_4$Me	1.2 μM	(0.11 μM)	3.0
15	**4**	R = *Z*-$CH_2CHCH(CH_2)_3CO_2H$; R′ = *E*-CH=CH$(CH_2)_4$Me		0.8 μM	(0.07 μM)	8.0
16	**68**	Rosiglitazone		1.4 μM	(0.05 μM)	40

[a] Based on an average of three experiments, each run in triplicate. Values calculated using PRISM software. [b] Standard error of the mean value. [c] Maximal value *versus* the control run containing only the vehicle.



15 etc. Rosiglitazone **68**

the *E*-stereoisomer. The levels of PPAR-γ activation displayed by *E*-**64** mimic rather closely the putative ligand $\Delta^{12,14}$-15-deoxy-PGJ_2 **4** (Entry 15). Rosiglitazone **68** is a much more potent PPAR-γ ligand than any of these prostanoids and prostanoid mimics (Entry 16).‖ However, several side-effects have been reported for the TZD drug class, particularly related to patients' weight gain and odema.[50] These side-effects have been linked to the high level of PPAR-γ activation, indicating that in the future less potent PPAR-γ compounds may have improved side-effect profiles.[51]

Conclusion

In conclusion, we have developed an efficient and novel method for the synthesis of cross-conjugated cyclopentadienones in two high yielding steps. Significantly the conjugate addition reaction proceeds with very high diastereoselectivity; the corresponding enantioenriched Pauson–Khand adducts have been employed to generate enantioenriched substrates. Furthermore, many of our synthetic compounds mimic the behaviour of **4**, the benchmark PPAR-γ activating fatty acid. In terms of the likely biological mechanism by which these compounds elicit these agonistic effects, it has been shown that a sulfahydryl, cysteine residue resides in the PPAR-γ–TZD binding pocket (Cys285)[52] and one can speculate that this residue forms a conjugate adduct with the electrophilic, endocyclic alkene.[2a] In terms of a related biological precedent for this type of protein modification, a link can be made with the well-appreciated prenylation of cysteinyl containing proteins.[53]

‖ The EC_{50} value of 1.4 μM is somewhat misleading since **68** begins to activate at a comparatively lower concentration and maintains and increases activation at doses above 10 μM reaching approximately a 40-fold activation over the control.

Experimental section

General procedure for the conjugate addition–Peterson olefination reactions

3-Methyl-2-[1-phenylmeth-(*E*)-ylidene]-2,3,3*a*,4,7,7*a*-hexahydro-4,7-methano-inden-1-one, *E*-14a. At −78 °C under nitrogen, a slurry of CuI (509 mg, 2.67 mmol, 1.2 eq.) in Et_2O (25 cm^3) was treated dropwise with a 1.6 M solution of MeLi in hexanes (3.36 cm^3, 5.37 mmol, 2.4 eq.). The reaction was warmed to −10 °C over a period of 2 h. This solution was cooled to −20 °C before a cooled (−20 °C) solution of the enone *exo*-**12** (485 mg, 2.23 mmol, 1 eq.) in Et_2O (25 cm^3) was added in a dropwise fashion. The flask containing *exo*-**12** was washed with Et_2O (5 cm^3) and this was also transferred to the reaction mixture. Stirring was continued for 1.5 h during which time the temperature rose to −10 °C. Upon cooling to −78 °C, benzaldehyde (0.35 cm^3, 3.44 mmol, 1.5 eq.) was added. The reaction was stirred for 3 h and warmed from −78 °C to 10 °C. A saturated solution of NH_4Cl (25 cm^3) was added and the resultant aqueous phase was further extracted with Et_2O (3 × 25 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed *in vacuo.* The crude product was then purified by flash column chromatography (Hex–Et_2O; 19 : 1) affording *E*-**14a** as a colourless solid (520 mg, 93%). Recrystallisation from *n*-hexane gave crystals of *E*-**14a** suitable for X-ray crystallography. Mp 82 °C (Hex); R_f 0.15 (Hex–Et_2O; 19 : 1); (Found C, 85.95; H, 7.42%, $C_{18}H_{18}O$ requires C, 86.36; H, 7.25%); ν_{max}/cm^{-1} 2934, 1694, 1609, 1494, 1448, 1332, 1236, 1183; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 7.0 Hz, CH_3), 1.28 (1H, dt, *J* 1.5, 9.5 Hz, CH_2), 1.36 (1H, d, *J* 9.5 Hz, CH_2), 1.93 (1H, d, *J* 7.5 Hz, CH), 2.48 (1H, d, *J* 7.5 Hz, CH), 2.86 (1H, s, CH), 3.12 (1H, s, CH), 3.19 (1H, q, *J* 7.0 Hz, CH), 6.18–6.26 (2H, m, CH), 7.28 (1H, d, *J* 2.0 Hz, CH), 7.34–7.44

(3H, m, ArH), 7.57 (2H, d, *J* 7.5 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.2, 38.9, 43.2, 48.5, 49.2, 49.5, 53.3, 128.8, 129.4, 130.7, 133.4, 135.9, 137.6, 139.0, 145.1, 209.0; *m/z* (EI) 250 (M^+, 25%), 183 (100%), 156 (50%), 141 (50%), 128 (40%), 115 (70%), 91 (50%), 66 (90%).

General procedure for the retro-Diels–Alder reactions: synthesis of adducts 15a to 15q

4-Methyl-5-[1-phenylmeth-(*E*)-ylidene]cyclopent-2-enone, 15a. Under nitrogen, a solution of *E*-**14a** (250 mg, 1.0 mmol, 1.0 eq.) and maleic anhydride (490 mg, 5.0 mmol, 5.0 eq.) in DCM (10 cm^3) was treated with a 1.0 M solution of $MeAlCl_2$ in hexane (1.1 cm^3, 1.1 mmol, 1.1 eq.). This mixture was heated to reflux for 6 h. On cooling, silica (*ca.* 2.5 g) was added and the solvent was removed under reduced pressure. Flash column chromatography (Hex–EtOAc; 3 : 1) gave the *title compound E*-**15a** (138 mg, 75%) as a colourless solid. Mp 64–66 °C; R_f 0.25 (Hex–EtOAc; 3 : 1); (Found C, 84.66; H, 6.60%, $C_{13}H_{12}O$ requires C, 84.78; H, 6.57%); ν_{max}/cm^{-1} 3077, 2983, 2944, 2886, 2340, 1680, 1623, 1580, 1446, 1380; δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 7.0 Hz, CH_3), 3.84–4.00 (1H, m, CH), 6.40 (1H, dd, *J* 1.75, 5.75 Hz, CH), 7.39–7.44 (4H, ArH), 7.54 (2H, d, *J* 7.0 Hz, ArH), 7.60 (1H, ddd, *J* 1.0, 2.5, 5.75 Hz, CH); δ_C (100 MHz, $CDCl_3$) 16.3, 38.8, 128.7, 129.3, 130.6, 131.7, 133.6, 134.8, 138.3, 163.9, 197.4; *m/z* (CI) 202 (NH_4^+, 20%), 185 (MH^+, 100%); Found 185.09654, $C_{13}H_{13}O$ requires 185.09665 (–0.6 ppm).

Acknowledgements

We thank the Ministry of Science and Technology and NIBGE, Pakistan for a Ph.D. scholarship awarded to M. I., the Irish research council for Science Engineering and Technology (IRCSET) for a postgraduate scholarship awarded to P. D. and the Science Foundation Ireland (SFI) for financial support. Financial support from Spanish MEC (CTQ2005-623) is also gratefully acknowledged. The pFA plasmids, containing the ligand binding domains of the PPAR proteins, were kindly provided by F. Gregoire (Metabolex Inc., Hayward CA, USA).

References

1 (*a*) For recent review articles on the chemistry and biology of cyclopentenone prostanoids see: M. Negishi and H. Katoh, *Prostaglandins & other Lipid Mediators*, 2002, **68–69**, 611; (*b*) D. S. Straus and C. K. Glass, *Med. Res. Rev.*, 2001, **21**, 185; (*c*) S. M. Roberts, M. G. Santoro and E. S. Sickle, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1735.
2 (*a*) M. Suzuki, M. Mori, T. Niwa, R. Hirata, K. Furuta, T. Ishikawa and R. Noyori, *J. Am. Chem. Soc.*, 1997, **119**, 2376; (*b*) M. Renedo, J. Gayarre, C. A. García-Domínguez, A. Pérez-Rodríguez, A. Prieto, F. J. Cañada, J. M. Rojas and D. Pérez-Sala, *Biochemistry*, 2007, **46**, 6607; (*c*) J. L. Oliva, D. Pérez-Sala, A. Castrillo, N. Martínez, F. J. Cañada, L. Boscá and J. M. Rojas, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 4772; (*d*) A.-L. Levonen, A. Landar, A. Ramachandran, E. K. Ceaser, D. A. Dickinson, G. Zanoni, J. D. Morrow and V. M. Darley-Usmar, *Biochem. J.*, 2004, **378**, 373.
3 (*a*) For general references see: C. D. Funk, *Science*, 2001, **294**, 1871; (*b*) R. Noyori and M. Suzuki, *Science*, 1993, **259**, 44; (*c*) P. W. Collins and S. W. Djuric, *Chem. Rev.*, 1993, **93**, 1533; (*d*) R. Noyori and M. Suzuki, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 847; (*e*) S. Das, S. Chandrasekhar, J. S. Yadav and R. Grée, *Chem. Rev.*, 2007, **107**, 3286.
4 F. A. Fitzpatrick and M. A. Wynalda, *J. Biol. Chem.*, 1983, **258**, 11713.
5 (*a*) J. D. Morrow, J. A. Awad, H. J. Boss, I. A. Blair and L. J. Roberts, *Proc. Natl. Acad. Sci. USA*, 1992, **89**, 10721; (*b*) Y. Chen, J. D. Morrow and L. J. Roberts, *J. Biol. Chem.*, 1999, **274**, 10863; (*c*) for a recent review see: U. Jahn, J.-M. Galano and T. Durand, *Angew. Chem. Int. Ed.*, 2008, **47**, 5894.
6 (*a*) J. L. Quiles, G. Barja, M. Battino, J. Mataix and V. Solfrizzi, *Nutrition Rev.*, 2006, **64**, S31; (*b*) M. H. Horani, M. J. Haas and A. D. Mooradian, *Nutrition*, 2006, **22**, 123; (*c*) G. Liu, D. M. Bibus, A. M. Bode, W.-Y. Ma, R. T. Holman and Z. Dong, *Proc. Natl. Acad. Sci. USA*, 2001, **98**, 7510; (*d*) Y. Wan, A. Saghatelian, L. W. Chong, C.-L. Zhang, B. F. Cravatt and R. M. Evans, *Genes & Dev.*, 2007, **21**, 1895; (*e*) M. Toborek, Y. W. Lee, R. Garrido, S. Kaiser and B. Hennig, *Am. J. Clin. Nutr.*, 2002, **75**, 119.
7 (*a*) M. H. Beale and J. L. Ward, *Nat. Prod. Rep.*, 1998, 533; (*b*) E. J. Corey and S. P. T. Matsuda, *Tetrahedron Lett.*, 1987, **28**, 4247.
8 (*a*) F. Bohlmann, R. K. Gupta, R. M. King and H. Robinson, *Phytochem.*, 1981, **20**, 1417; (*b*) F. Bohlmann, N. Borhtakur, R. M. King and Robinson, *Phytochem.*, 1982, **21**, 125; (*c*) F. Bohlmann, P. Singh, J. Jakupovic, R. M. King and H. Robinson, *Phytochem.*, 1982, **21**, 371.
9 (*a*) M. Krischke, C. Loeffler and M. J. Mueller, *Phytochem.*, 2003, **62**, 351; (*b*) I. Thoma, M. Krischke, C. Loeffler and M. J. Mueller, *Chem. Phys. Lipids*, 2004, **128**, 135.
10 (*a*) H. Kikuchi, Y. Tsukitani, K. Iguchi and Y. Yamada, *Tetrahedron Lett.*, 1983, **24**, 1549; (*b*) H. Nagaoka, K. Iguchi, T. Miyakoshi, N. Yamada and Y. Yamada, *Tetrahedron Lett.*, 1986, **27**, 223.
11 (*a*) M. E. Jung, J. A. Berliner, D. Angst, D. Yue, L. Koroniak, A. D. Watson and R. Li, *Org. Lett.*, 2005, **7**, 3933; (*b*) H. P. Acharya and Y. Kobayashi, *Tetrahedron Lett.*, 2005, **46**, 8435; (*c*) G. Subbanagounder, J. W. Wong, H. Lee, K. F. Faull, E. Miller, J. L. Witztum and J. A. Berliner, *J. Biol. Chem.*, 2002, **277**, 7271.
12 H. Singh, R. Sen, D. Baltimore and P. A. Sharp, *Nature*, 1986, **319**, 154.
13 A. Hoffmann and D. Baltimore, *Immunological Rev.*, 2006, **210**, 171.
14 (*a*) A. Rossi, P. Kapahi, G. Natoli, T. Takahashi, Y. Chen, M. Karin and M. G. Santoro, *Nature*, 2000, **403**, 103; (*b*) 15-deoxy-$\Delta^{12,14}$-PGJ_2 has also been shown to affect NF-κB/DNA binding through covalent modification of the p50 subunit: E. Cernuda-Morollon, E. Pineda-Molina, F. J. Canada and D. Pérez-Sala, *J. Biol. Chem.*, 2001, **276**, 35530; (*c*) D. S. Straus, G. Pascual, M. Li, J. S. Welch, M. Ricote, C. H. Sengchanthalangsy, L. L. Ghosh and C. K. Glass, *Proc. Natl. Acad. Sci. USA*, 2000, **97**, 4844.
15 (*a*) H. R. Saibil, *Curr. Opin. Struc. Bio.*, 2008, **18**, 35; (*b*) M. G. Santoro, *Trends Microbiol.*, 1997, **5**, 276.
16 R. M. Evans, *Science*, 1988, **240**, 889.
17 (*a*) T. M. Willson, P. J. Brown, D. D. Sternbach and B. R. Henke, *J. Med. Chem.*, 2000, **43**, 527; (*b*) L. A. Sorbera, L. Leeson, L. Martin and J. Castaner, *Drugs Future*, 2001, **26**, 354; (*c*) A. B. Jones, *Med. Res. Rev.*, 2001, **21**, 540; (*d*) S. A. Kliewer and T. M. Willson, *Curr. Opin. Genet. Dev.*, 1998, **8**, 576; (*e*) T. M. Willson and W. Wahli, *Curr. Opin. Chem. Biol.*, 1997, **1**, 235; (*f*) B. Staels and J. Auwerx, *Curr. Pharm. Des.*, 1997, **3**, 1; (*g*) B. M. Spiegelman, *Diabetes*, 1998, **47**, 507; (*h*) K. Schoonjans, G. Martin, B. Staels and J. Auwerx, *Curr. Opin. Lipidol.*, 1997, **8**, 159; (*i*) B. R. Henke, *J. Med. Chem.*, 2004, **47**, 4118.
18 (*a*) B. M. Forman, P. Tontonoz, J. Chen, R. P. Brun, B. M. Spiegelman and R. M. Evans, *Cell*, 1995, **83**, 803; (*b*) S. A. Kliewer, J. M. Lenhard, T. M. Willson, I. Patel, D. C. Morris and J. M. Lehman, *Cell*, 1995, **83**, 813.
19 (*a*) W. S. Powell, *J. Clin. Invest.*, 2003, **112**, 828; (*b*) L. C. Bell-Parikh, T. Ide, J. A. Lawson, P. McNamara, M. Reilly and G. A. FitzGerald, *J. Clin. Invest.*, 2003, **112**, 945.
20 (*a*) M. Suzuki, T. Kiho, K. Tomokiyo, K. Furuta, S. Fukushima, Y. Takeuchi, M. Nakanishi and R. Noyori, *J. Med. Chem.*, 1998, **41**, 3084; (*b*) B. Cox, L. J. Murphey, W. E. Zackert, R. Chinery, R. Graves-Deal, O. Boutaud, J. A. Oates, R. J. Coffey and J. D. Morrow, *Biochim. Biophys. Acta*, 2002, **1584**, 37; (*c*) I. Hubatsch, M. Ridderstrom and B. Mannervik, *Biochem. J.*, 1998, **330**, 175; (*d*) I. Hubatsch, B. Mannervik, L. Gao, L. J. Roberts, Y. Chen and J. D. Morrow, *Chem. Res. Toxicol.*, 2002, **15**, 1114.
21 A. M. O'Hara and F. Shanahan, *EMBO Reports*, 2006, **7**, 688.
22 (*a*) C. Loeffler, S. Berger, A. Guy, T. Durand, G. Bringmann, M. Dreyer, U. V. Rad, J. Durner and M. J. Mueller, *Plant Physiol.*, 2005, **137**, 328; (*b*) E. E. Farmer and C. Davoine, *Curr. Opin. Plant Biol.*, 2007, **10**, 380; (*c*) S. Mueller, B. Hilbert, K. Dueckershoff, T. Roitsch, M. Krischke, M. J. Mueller and S. Berger, *Plant Cell*, 2008, **20**, 768; (*d*) M. Iqbal, P. Evans, A. Lledó, X. Verdaguer, M. A. Pericàs, A. Riera, C. Loeffler, A. K. Sinha and M. J. Mueller, *ChemBioChem*, 2005, **6**, 276.

23 (*a*) For representative recent syntheses of this class of compound see: H. Tanaka, T. Hasegawa, N. Kita, H. Nakahara, T. Shibata, S. Oe, M. Ojika, K. Uchida and T. Takahashi, *Chem. Asian J.*, 2006, **1**, 669; (*b*) C. Kuhn, E. Roulland, J.-C. Madelmont, C. Monneret and J.-C. Florent, *Org. Biomol. Chem.*, 2004, 2028; (*c*) M. Schelwies, P. Dübon and G. Helmchen, *Angew. Chem. Int. Ed.*, 2006, **45**, 2466; (*d*) H. P. Acharya and Y. Kobayashi, *Tetrahedron*, 2006, **62**, 3329; (*e*) G. Zanoni, A. Porta and G. Vidari, *J. Org. Chem.*, 2002, **67**, 4346; (*f*) J. F. Bickley, V. Jadhav, S. M. Roberts, M. G. Santoro, A. Steiner and P. W. Sutton, *Synlett*, 2003, 1170; (*g*) K. M. Brummond, P. C. Sill and H. F. Chen, *Org. Lett.*, 2004, **6**, 149.

24 (*a*) G. Stork, G. L. Nelson, F. Rouessac and O. Gringgore, *J. Am. Chem. Soc.*, 1971, **93**, 3091; (*b*) J.-B. Wiel and F. Rouessac, *J. Chem. Soc. Chem. Commun.*, 1976, 446.

25 A. J. H. Klunder, J. Zhu and B. Zwanenburg, *Chem. Rev.*, 1999, **99**, 1163.

26 (*a*) O. Tsuge, S. Kanemasa and Y. Ninomiya, *Chem. Lett.*, 1984, 1993; (*b*) J. Taneka, S. Kanemasa, Y. Ninomya and O. Tsuge, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 466; (*c*) J. Tanaka, H. Kobayashi, S. Kanemasa and O. Tsuge, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 1193.

27 M. Iqbal and P. Evans, *Tetrahedron Lett.*, 2003, **44**, 5741.

28 M. Iqbal, N. Vyse, J. Dauvergne and P. Evans, *Tetrahedron Lett.*, 2002, **43**, 7859.

29 For a recent review see: J. B. Urgoiti, L. Añorbe, L. P. Serrano, G. Domínguez and J. P. Castells, *Chem. Soc. Rev.*, 2004, **33**, 32.

30 Crystal structural data for compound **14a**: $C_{18}H_{18}O$ $M = 250.32$; orthorhombic, *Pbcn*; $a = 8.8975(5)$ Å, $b = 12.1847(7)$ Å, $c = 24.8677(4)$ Å; $U = 2696.6(3)$ Å^3; $T = 150$ K; $Z = 8$; 15692 reflections measured, 3200 unique ($R_{int} = 0.0192$). The final wR^2 was 0.1339 (all data). CCDC reference number 219462.

31 (*a*) H. Sasaki, S. Niimi, M. Akiyama, T. Tanaka, A. Hazato, S. Kurozumi, S. Fukushima and M. Fukushima, *Cancer Res.*, 1999, **59**, 3919; (*b*) F. Shoji, T. Yoshikazu, K. Shuichi, Y. Shoichi, U. Kenji, S. Satoshi, S. Masaaki, F. Kyoji, N. Ryoji, S. Hiroshi, K. Yoshihiro, K. Tsunekazu, Y. Takao, S. Junichi, K. Michio, H. Atsuo, K. Seiji and F. Masanori, *Anti Cancer Drugs*, 2001, **12**, 221.

32 M. Suzuki, T. Kawagishi, A. Yanagisawa and T. Suzuki, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1299.

33 P. A. Grieco and N. Abood, *J. Chem. Soc. Chem. Commun.*, 1990, 410.

34 (*a*) B. H. Lipshutz, D. H. Aue and B. James, *Tetrahedron Lett.*, 1996, **37**, 8471; (*b*) S. Woodward, *Chem. Soc. Rev.*, 2000, **29**, 393.

35 (*a*) L. F. van Staden, D. Gravestock and D. J. Ager, *Chem. Soc. Rev.*, 2002, **31**, 195; (*b*) R. K. Boeckman, Jr. and R. L. Chinn, *Tetrahedron Lett.*, 1985, **26**, 5005; (*c*) M. B. Gillies, J. E. Tonder, D. Tanner and R.-O. Norrby, *J. Org. Chem.*, 2002, **67**, 7378.

36 P. Knochel and R. D. Singer, *Chem Rev.*, 1993, **93**, 2117.

37 M. Kitamura, T. Miki, K. Nakano and R. Noyori, *Bull. Chem. Soc. Jpn.*, 2000, **73**, 999.

38 W. H. Sikarski and G. J. Reich, *J. Am. Chem. Soc.*, 2001, **123**, 6527.

39 S. Reddy, H. Krishna, C. Kazuhiro, S. Yongmao and K. D. Moeller, *Tetrahedron*, 2001, **57**, 5183.

40 C. Shih, E. L. Fritzen and J. S. Swenton, *J. Org. Chem.*, 1980, **45**, 4462.

41 M. Ohno and M. Otsuka, *Org. React.*, 1989, **37**, 1.

42 (*a*) J. Solà, M. Revés, A. Riera and X. Verdaguer, *Angew. Chem. Int. Ed.*, 2007, **46**, 5020; (*b*) X. Verdaguer, A. Moyano, M. A. Pericàs, A. Riera, M. Angel Maestro and J. Mahía, *J. Am. Chem. Soc.*, 2000, **122**, 10242; (*c*) X. Verdaguer, A. Lledó, C. López-Mosquera, M. Angel Maestro, M. A. Pericàs and A. Riera, *J. Org. Chem.*, 2004, **69**, 8053.

43 For the synthesis of **49** see: D. Ranganathan, S. Ranganathan and M. M. Mehrotra, *Tetrahedron*, 1980, **36**, 1869.

44 M. Suzuki, A. Yanagisawa and R. Noyori, *J. Am. Chem. Soc.*, 1988, **110**, 4718.

45 M. Iqbal, Y. Li and P. Evans, *Tetrahedron*, 2004, **60**, 2531.

46 (*a*) G. Krüge, C. Hard and F. Bohlmann, *Tetrahedron Lett.*, 1985, **26**, 6027; (*b*) Z.-Y. Liu and X.-J. Chu, *Tetrahedron Lett.*, 1993, **34**, 3885; (*c*) Z.-Y. Liu, H. Dong and X.-Y. Chu, *Tetrahedron*, 1994, **50**, 12337.

47 G. Williams and J. C. Pickup, *Handbook of Diabetes*, 3rd edn, Blackwell Publishing Ltd., Oxford, 2004.

48 T. Allen, F. Zhang, S. A. Moodie, L. E. Clemens, A. Smith, F. Gregoire, A. Bell, G. E. O. Muscat and T. A. Gustafson, *Diabetes*, 2006, **55**, 2523.

49 For a report suggesting that Z^{12}-$\Delta^{12,14}$-15 deoxy-PGJ$_2$ **4** more effectively activates PPAR-γ see: K. M. Maxey, E. Hessler, J. MacDonald and L. Hitchingham, *Prostaglandins & other Lipid Med.*, 2000, **62**, 15.

50 H. Zhang, A. Zhang, D. E. Kohan, R. D. Nelson, F. J. Gonzalez and T. Yang, *Proc. Natl. Acad. Sci. USA*, 2005, **102**, 9406.

51 Y. Li, Z. Wang, N. Furukawa, P. Escaron, J. Weiszmann, G. Lee, M. Lindstrom, J. Liu, X. Liu, H. Xu, O. Plotnikova, V. Prasad, N. Walker, R. M. Learned and L.-J. Chen, *J. Biol. Chem.*, 2008, **283**, 9168.

52 R. T. Nolte, G. B. Wisely, S. Westin, J. E. Cobb, M. H. Lambert, R. Kurokawa, M. G. Rosenfeld, T. M. Willson, C. K. Glass and M. V. Milburn, *Nature*, 1998, **395**, 137.

53 For a review on protein prenylation see: F. L. Zhang and P. J. Casey, *Ann. Rev. Biochem.*, 1996, **65**, 241.