Novel synthetic strategies for the preparation of prostacyclin and prostaglandin analogues – off the beaten track†

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The recent increase in activity in the fields of neuroscience and life sciences has been mirrored by the design and synthesis of novel chemically and metabolically stable prostaglandin and prostacyclin analogues. Consequently, convenient and practical access to these important classes of compounds is greatly coveted. Various strategies for the preparation of prostacyclin, prostaglandin and isoprostane analogues are discussed, with particular focus on novel approaches developed in our own laboratories.

Introduction

Prostacyclin and its stable analogues

Prostacyclin (PGI_2) **1**,[1,2] has shown diverse biological activity ranging from being a potent vasodilator and inhibitor of blood platelet aggregation to playing an important role not only in the peripheral organs, but also in the central nervous system (CNS).[3] Unfortunately, any clinical application of prostacyclin has been hampered by the chemical and metabolic instability of its vinyl ether moiety to hydrolysis ($t_{1/2}$ = 5 min at pH 7.4).[2,4]

Prostacyclin and selected stable analogues

Nevertheless, **1** has stimulated interest from researchers spanning medicine, biology and chemistry which has ultimately led towards the design and development of hundreds of analogues with the aim of chemical and metabolical stability combined with physiological activity (Fig. 1, **2–9**).[5] In addition to the chemical and metabolical stability of **1**, many groups have been interested in altering the biological specificity of prostacyclin itself – to reduce its vasodilator potency while still maintaining its platelet inhibitory potency.[5d] This search has led to the development of a number of stable and biologically active analogues: carbacyclin (**2**),[6] isocarbacyclin (**6**),[7] 3-oxaisocarbacyclin (**7**),[8] iloprost (**3**),[9] 3-oxa-iloprost (**4**),[10] and cicaprost (**5**),[11] to highlight some of the most recent promising candidates. The importance of these prostacyclin analogues is further exemplified by the discovery by Takechi *et al*., of a novel IP_2 sub-type of the prostacyclin (PGI_2) receptor,[3] one exhibiting different properties compared with those of the known prostacyclin receptor. Isocarbacyclin (**6**),[7] which is a potent agonist for the known prostacyclin receptor, also possesses high affinity for the novel sub-type. Further investigation led to the design of CNS-specific PGI_2 ligands 15-deoxy-TIC (**8**),[12] and 15*R*-TIC (**9**),[13] – which exhibit neuronal survival-promoting activity.[14] Moreover these ligands have been implemented to successfully visualize the specific location of the IP_2 receptor for both *in vitro* and *in vivo*[15] systems by autoradiography of rat brain slices and positron emission tomography (PET),[15,16] of a living rhesus monkey.[17] CNS specific PGI_2 ligands 15-deoxy-TIC (**8**), and 15*R*-TIC (**9**) both have exhibited an inhibitory effect on apoptosis of neuronal cells induced by high oxygen (50%) atmosphere.[18]

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† Dedicated to Professor Werner Skuballa on the occasion of his 65th birthday.

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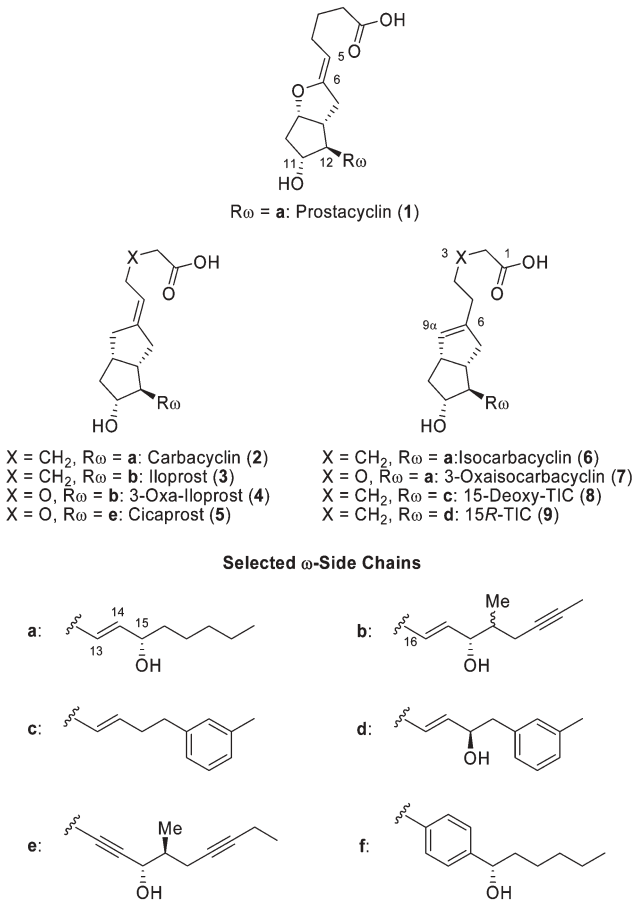


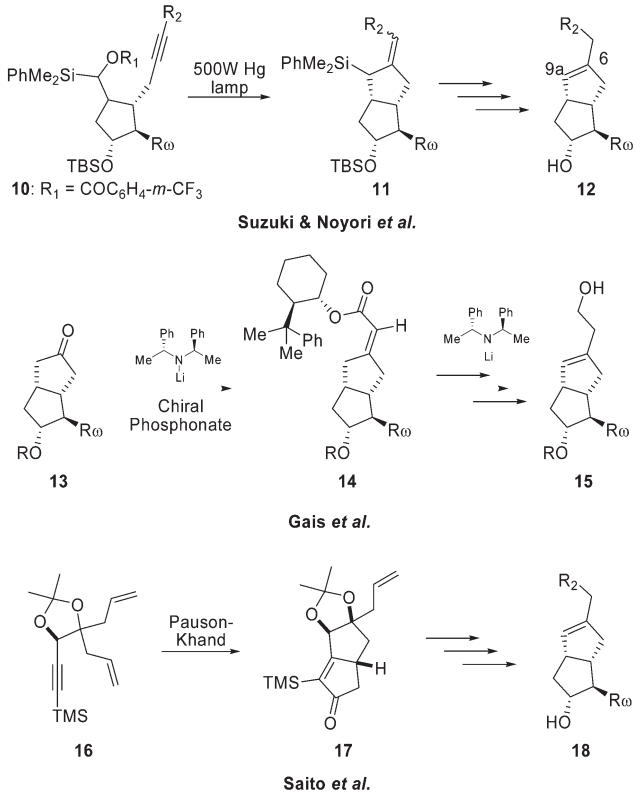
Fig. 1 Prostacyclin and selected biologically active analogues.

Introduction of the C6–C9α endocyclic double bond and introduction of the α-side chain for isocarbacyclin analogues

The important biologically activity of prostacyclin analogues, combined with the academic challenge of their syntheses: regioselectivity of the C6–C9α[19] endocyclic double bond and α-side chain introduction for isocarbacyclin analogues; and more generally, how to introduce stereoselectively the C15 hydroxyl functionality of the ω-side chain, has been responsible for the vast number of groups undertaking new and innovative syntheses.[5c,6–15] The focus of our research has been to develop various strategies which would allow the flexible synthesis of prostacyclin analogues, not only with respect to the regioselectivity of the C6–C9α endocyclic double bond and α-side chain introduction, but more generally, the stereocontrolled introduction of the C15 hydroxyl functionality of the ω-side chain.

Selected literature synthesis for C6–C9α endocyclic double bond and α-side chain introduction

Introduction of the troublesome C6–C9α endocyclic double bond has inspired many research groups to make valuable contributions to its solution.[7,8,20–23] For instance, Noyori and Suzuki's 5-*exo*-*dig* radical cyclisation to construct the bicyclic system followed by protodesilylation to generate the C6–C9α endocyclic double bond (**10** → **12**);[7b] the asymmetric HWE olefination approach of Gais which has been used to access several analogues (**13** → **15**),[21] and the Pauson–Khand approach of Saito (**16** → **18**),[22] the most recent example of this strategy, which has also been used by numerous research groups in analogous syntheses (Scheme 1).[23]



Scheme 1 Selected literature approaches for C6–C9α endocyclic double bond and α-side chain introduction.

Generation of the C6–C9α endocyclic double bond *via* regiospecific deprotonation under substrate control

Our approach for generation of the C6–C9α endocyclic double bond hinges upon the "desymmetrisation" of bicyclic ketone **19**. Previous work has been carried out on the desymmetrisation of such bicyclic systems, all, to the best of our knowledge, have employed the use of a chiral base.[21] In stark contrast to this, we wanted to take advantage of a cost efficient synthesis, available on gram scale, where regiospecific deprotonation would be effected under substrate control and not by the use of an expensive chiral base (Fig. 2).

Tricyclic methyl ester **20**, readily available in kg-quantities,[24] was converted to the C11-TBS ether. Reduction of the methyl ester delivered **21**. Cleavage of the ketal group of **21** followed by tritylation of the primary alcohol delivered orthogonally protected bicyclic ketone **19** (Scheme 2).

Single crystals of bicyclic ketone **19**, suitable for X-ray diffraction studies, were obtained by slow diffusion of hexane into a corresponding chloroform solution (Scheme 2). Inspection of the crystal structure for bicyclic ketone **19** clearly revealed that the bulky trityl protecting group would exhibit a strong shielding effect at the C7 position. This

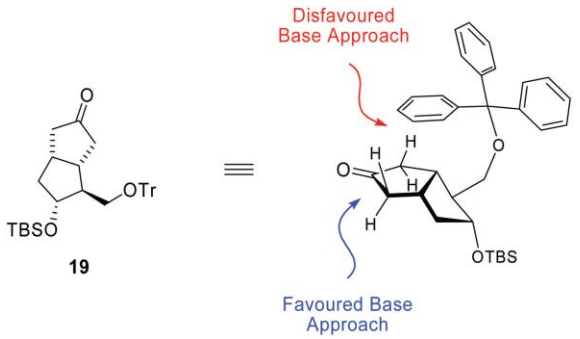
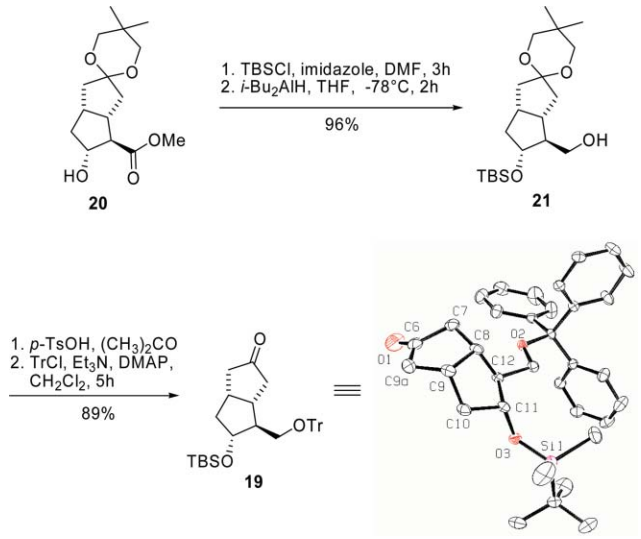


Fig. 2 Bicyclic ketone **19** revealing the less hindered face for regiospecific deprotonation.

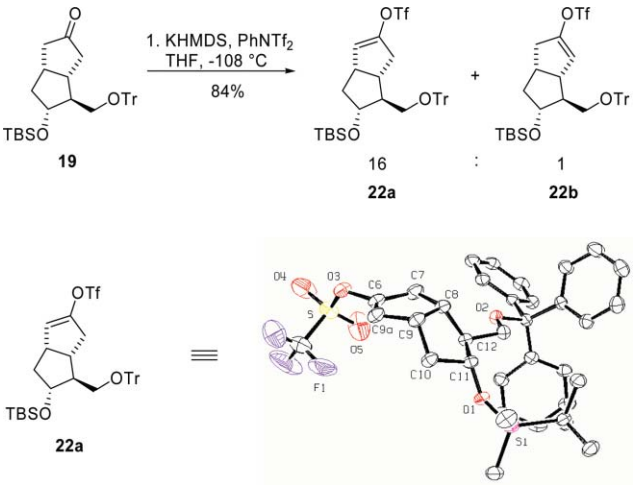


Scheme 2 Synthesis of bicyclic ketone **19** and ORTEP[25] representation of the crystal structure of **19**.

shielding effect, combined with the roof-shaped structure of bicyclic ketone **19** would inhibit the approach of a suitable base from the side of C7 and leave the C9α side open for deprotonation (Scheme 2). In fact, **19**, after treatment with KHMDS (2 equiv.) at −108 °C, in THF, and trapping of the enolate by the addition of $PhNTf_2$ provided enol triflates **22a** and **22b**, in a ratio of 16 : 1 (Scheme 3). Recrystallisation of the resultant mixture of triflates **22a/b** yielded needles suitable for X-ray diffraction. The obtained crystal structure for **22a**, in combination with 2D NMR studies unequivocally confirmed the regiochemistry to be that of the desired compound (Scheme 3).

α-Side chain installation *via* palladium catalysed sp^2–sp^3 Kumada–Tamao cross-coupling

For the introduction of the α-side chain, a Kumada–Tamao type cross coupling was used. Enol triflate **22a**,[26] was treated with Grignard reagent **23**, (1.1 equiv.)[27] in the presence of $Pd(PPh_3)_4$ (2 mol%) and LiCl,[28] to give a 2 : 1 mixture of desired cross coupled product **25** and its β-hydride elimination product **24**, respectively. In sharp contrast to this 2 : 1 product mixture, enol triflate **22a** and Grignard reagent **23**, when



Scheme 3 Regiospecific deprotonation of bicyclic ketone **19** and ORTEP projection of triflate **22a**. Selected bond lengths: C6–C9α 1.32 Å, C6–C7 1.49 Å.

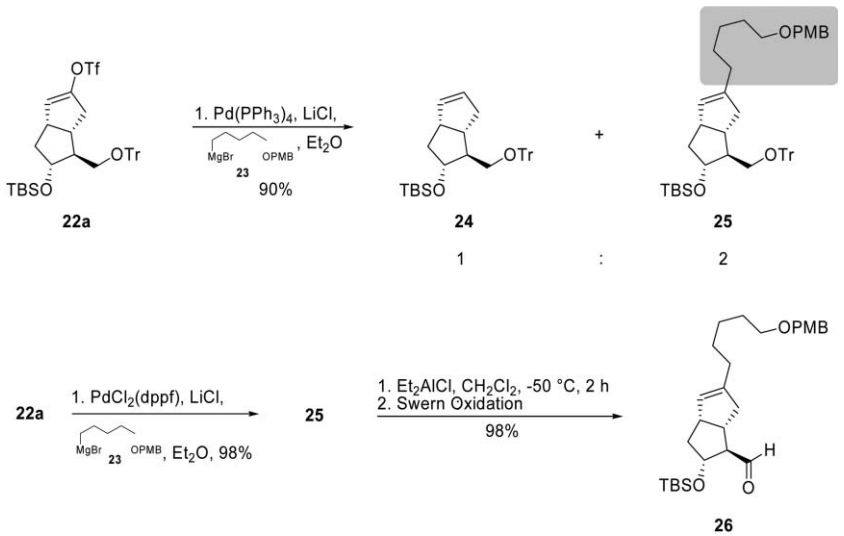
treated with a palladium catalyst with a bidentate ligand: $PdCl_2$(dppf) (2 mol%), cross coupled product **25** was obtained as the sole product in 98% yield (Scheme 4). Chemoselective deprotection of the trityl group proved to be tricky under standard conditions,[29] resulting either in global deprotection or a 2 : 1 mixture of the desired primary alcohol and the diol resulting from additional TBS deprotection, respectively. After intensive investigation, clean deprotection of trityl ether **25** was effected with Et_2AlCl at −50 °C. Swern oxidation of the resulting primary alcohol delivered aldehyde **26** (98% yield over two steps).[30] This introduction of the α-side chain for isocarbacyclin analogues, seems flexible enough, as the only requirement is the use of a stable Grignard derivative in the Kumada–Tamao coupling. Next, we turned our attention towards the flexible introduction of the ω-side chain.

Introduction of ω-side chain for isocarbacyclin analogues

In addition to the biological activity of isocarbacyclin analogues being very dependant on the stability of the bicyclic core and α-side chain, the ω-side chain also plays an important role, reflected by the diversity and number of ω-side chains which have been reported in recent years (Fig. 1). Many of these ω-side chains have been incorporated into both isocarbacyclin and carbacyclin skeleton analogues, as well as other modified bicyclic systems. A notable example of such a modification is iloprost (**3**), developed by Skuballa and Vorbrüggen at Schering AG,[9] where it is commercially available under the names Ilomedin® and Ventavis® for the treatment of peripheral arterial occlusive disease, severe thrombo-angiitis obliterans, and Raynaud's disease;[31] and pulmonary arterial hypertension (PAH),[32] respectively.

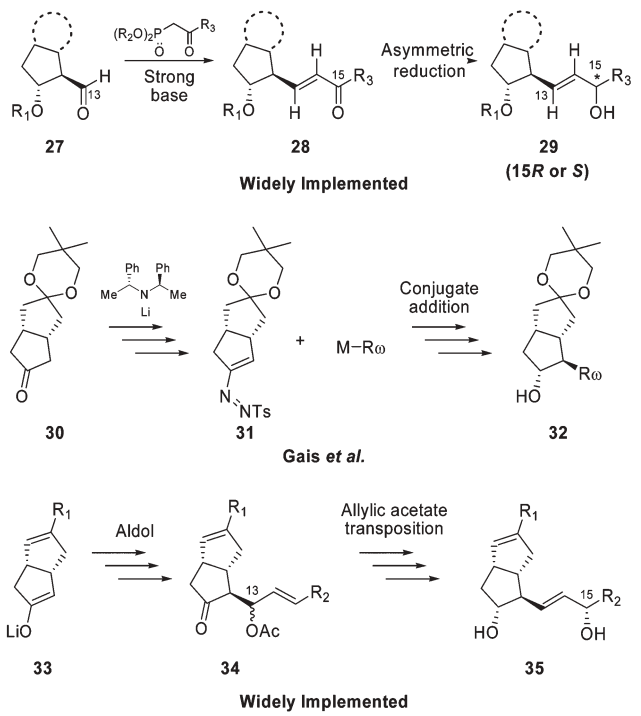
Selected literature synthesis for ω-side chain introduction

Typically, the ω-side chain for isocarbacyclin and carbacyclin analogues has been introduced *via* an (*E*)-selective HWE olefination reaction (C13–C14),[11c,33] followed by



Scheme 4 Kumada–Tamao Pd-catalysed sp^2–sp^3 cross-coupling reaction.

diastereoselective reduction of the C15 carbonyl functionality under reagent control (**27** → **29**) (Scheme 5).[34] This being said, there have been a number of alternative approaches worthy of mention: Gais' conjugate addition–azoalkene strategy (**30** → **32**), which has been successfully applied on numerous occasions.[21,35] On the other hand, Pd(II)-catalysed allylic acetate transposition (**33** → **35**), originally developed for prostaglandin synthesis, has also found considerable application for prostacyclin analogues by several groups.[20i,21a,36] Unfortunately, although this [3,3]-sigmatropic rearrangement facilitates complete transfer of chirality from the C13 to the C15 position, initial aldol selectivity for the C13 position is poor. As a result, we set out to develop a strategy which would not only be reliable and reproducible but also be robust enough to allow various fully functionalised ω-side chains to be introduced from a common synthetic intermediate, with only a minimum of synthetic transformations.

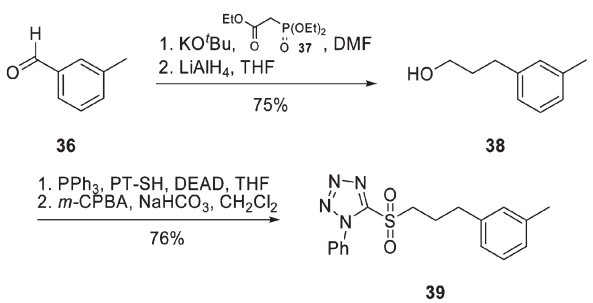


Scheme 5 Selected literature approaches for ω-side chain introduction.

Introduction of ω-side chain *via* Julia–Kocieński olefination strategy for 15-deoxy-TIC

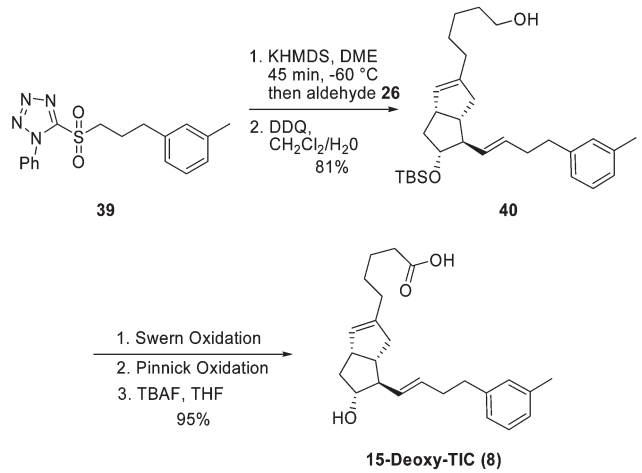
In our first approach to 15-deoxy-TIC (**8**) we used a Julia–Kocieński olefination. Required ω-side chain sulfone **39** was thus prepared from commercially available *m*-tolyl aldehyde **36**. HWE olefination reaction with triethyl phosphonocacetate **37** provided the corresponding α,β-unsaturated ethyl ester. Reduction of both the ester moiety and double bond gave alcohol **38** in good yield. Finally, required phenyl tetrazole sulfone **39** was obtained by Mitsunobu reaction of alcohol **38** with 1-phenyl-5-mercaptotetrazole (PT-SH) followed by oxidation with *m*-CPBA (57% yield over four steps) (Scheme 6).

Despite the fact that a similar aldehyde to **26** (*vide supra*) has been documented to be unstable towards strongly basic conditions,[12] we assumed that this referred to the Barbier variation of the Julia–Kocieński olefination reaction, and as such, a pre-metallated sulfone species should not therefore present a problem. The dropwise addition of bicyclic aldehyde **26** to a solution of pre-metallated phenyl tetrazole sulfone **39**



Scheme 6 Sulfone **39** for Julia–Kocieński olefination.

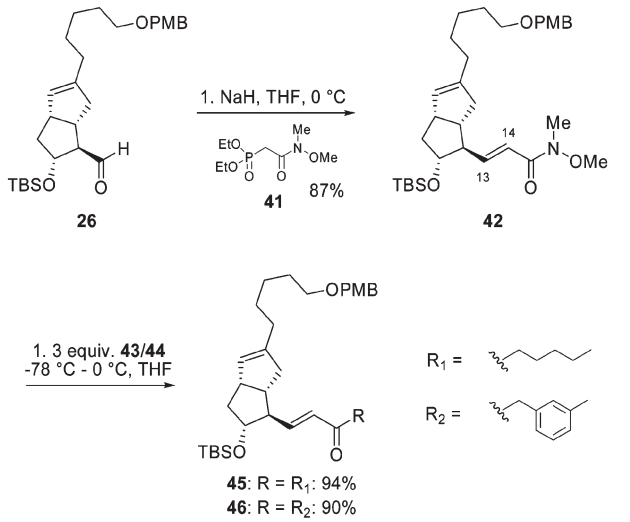
(KHMDS at −60 °C for 45 min) yielded the 15-deoxy-TIC carbon skeleton with the selective formation of the desired C13–C14 (*E*)-double bond. NMR analysis showed no visible traces of its (*Z*)-geometric isomer or epimerization at the C12 position (Scheme 7). Deprotection of the PMB ether with DDQ delivered primary alcohol **40**. Swern and Pinnick oxidations of primary alcohol **40** gave its corresponding carboxylic acid. Deprotection of the C11 TBS ether was effected by the addition of TBAF, to give 15-deoxy-TIC (**8**), although a reaction time of up to 4 days was required.[30] Spectral comparison of our synthetic material with data provided by Professor Masaaki Suzuki matched perfectly.[37]



Scheme 7 Completion of 15-deoxy-TIC (**8**).

Introduction of ω-side chain for isocarbacyclin analogues *via* Grignard reagent addition strategy

Although implementation of the Julia–Kocieński olefination reaction for the 15-deoxy-TIC (**8**) ω-side chain proved synthetically useful, it was limited to substrates which did not contain a C15 hydroxyl group. Although one might suspect, that under basic conditions, a protected C15 hydroxyl functionality would act as a good leaving group and be eliminated in an E1cB type mechanism, we only observed re-isolation of starting materials. We then turned our attention towards a strategy where a Grignard reagent would be added to a suitable α,β-unsaturated Weinreb amide for the introduction of the ω-side chain (Scheme 8). Treatment of aldehyde **26** with Weinreb amide phosphonate **41** provided α,β-unsaturated Weinreb amide **42**, with exclusive (*E*)-selectivity (C13–C14) and in excellent yield. Slow addition of either *n*-pentyl

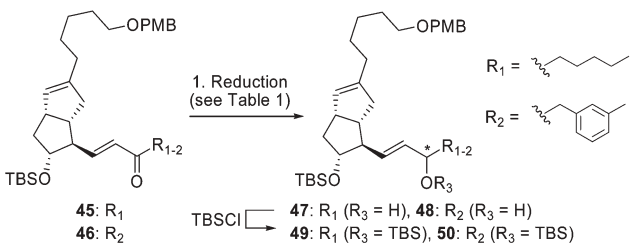


Scheme 8 Grignard reagent addition strategy.

magnesium bromide **43** (3 equiv.), or (3-methylbenzyl)magnesium bromide **44** (3 equiv.) delivered their corresponding isocarbacyclin and 15*R*-TIC skeletons **45** and **46**, respectively (Scheme 8).

Reduction of ω-side chain enone moieties under reagent control

Enones **45** and **46** were both subjected to CBS and BINAL-H reduction reactions, which resulted in modest to excellent diastereoselectivities (Scheme 9, Table 1), and was subsequently followed by protection to give TBS protected allylic alcohols **49** and **50**.



Scheme 9 Diastereoselective reduction of enone systems. TBS protections of **47** and **48**, 96–100 and 96%, respectively.

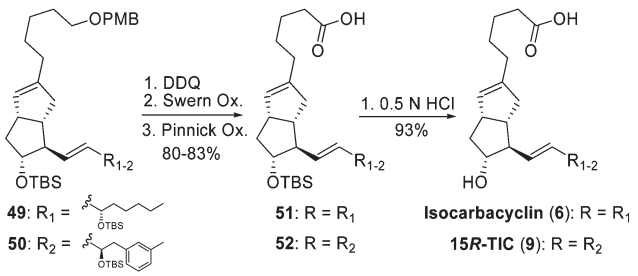
Reduction of enone **45** with (*R*)-Me-CBS gave the C15 (*S*)-allylic alcohol **47** with a *d.r.* of 9 : 1 (Table 1, entry 1). Changing to (*R*)-*n*-Bu-CBS, often documented to increase the diastereoselectivity, showed little effect on enone **45** resulting

Table 1 Diastereoselective reduction of enones **45** and **46**

Entry	Substrate	Reduction method	*d.r.*[a]	Product	C15 configuration	Yield[b] (%)
1	**45**	(*R*)-Me-CBS	9 : 1	**47**	*S*	96
2	**45**	(*R*)-*n*-Bu-CBS	10 : 1	**47**	*S*	92
3	**46**	(*S*)-Me-CBS	6 : 1	**48**	*R*	95
4	**46**	(*S*)-*n*-Bu-CBS	7 : 1	**48**	*R*	86
5	**45**	(*S*)-BINAL-H	>35 : 1	**47**	*S*	91
6	**46**	(*R*)-BINAL-H	8 : 1	**48**	*R*	90

[a] Assigned from ^{1}H NMR analysis. [b] Isolated yields.

in only a slight increase of *d.r.* (10 : 1) for the reduction (Table 1, entry 2). Enone **46**, however, when treated with (*S*)-Me-CBS or (*S*)-*n*-Bu-CBS resulted in allylic alcohol **48** with lower diastereoselectivities (6 : 1 and 7 : 1, respectively) (Table 1, entries 3 and 4). Reduction using Noyori's BINAL-H reagent was also carried out (Table 1, entries 5 and 6), although, without the aid of a stock solution, the resulting reactions proved only capricious, at best. However, with the aid of a stock solution of (*S*)-BINAL-H, the reduction of enone **45** proceeded smoothly (at −100 °C) to give allylic alcohol **47** with an impressive *d.r.* of over 35 : 1 (>94% d.e.). On the other hand, enone **46**, when treated with (*R*)-BINAL-H, also at −100 °C, delivered **48** with only a slightly improved *d.r.* of 8 : 1 compared to that obtained with the CBS reagents (*d.r.* 7 : 1). Enone systems of this type – prostacyclin (and prostaglandin) analogues – have been well documented to give in many cases a mismatched situation;[36b,38a] especially true for the reduction of enone systems resulting with the unnatural (*R*)-C15 configuration, as is the case for **48**. Allylic alcohols **47** and **48** were both protected as the TBS ethers to give **49** and **50** (Scheme 9).



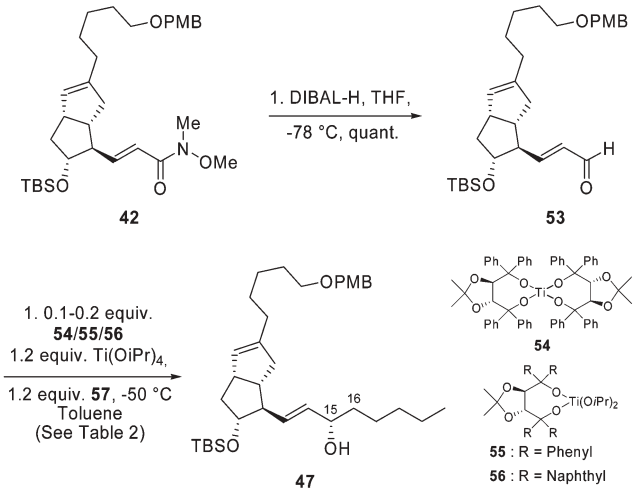
Scheme 10 Completion of isocarbacyclin (**6**) and 15*R*-TIC (**9**).

Isocarbacyclin and 15*R*-TIC carbon skeletons **49** and **50** were readily converted to their corresponding carboxylic acids, **51** and **52**, by means of *p*-methoxy-benzyl ether deprotection, followed by Swern and Pinnick oxidation reactions. Double TBS ether deprotection at C11 and C15 delivered isocarbacyclin (**6**) and 15*R*-TIC (**9**) without complication (Scheme 10).[38b,39]

Introduction of ω-side chain for isocarbacyclin analogues *via* Seebach's alkylation strategy

An alternative strategy for the incorporation of the ω-side chain takes advantage of Weinreb amide **42** (*vide supra*) which after reduction to α,β-unsaturated aldehyde **53**, can be subjected to Seebach's alkylation chemistry.[40] This would of course set both the C15–C16 bond and the C15 stereochemistry in one reaction, by the addition of a suitable dialkyl zinc reagent to α,β-unsaturated aldehyde **53**, catalysed by a Ti-TADDOL complex (Scheme 11).[41] Moreover, the capricious diastereoselective reduction of the enone moiety would no longer be necessary and would hopefully circumvent the need for difficult column chromatography or HPLC separation of the resultant mixture.

α,β-Unsaturated aldehyde **53** was obtained from the DIBAL-H reduction of Weinreb amide **42** at −78 °C.



Scheme 11 Isocarbacyclin skeleton *via* Seebach's alkylation chemistry.

Dipentyl zinc **57**, prepared from its parent Grignard reagent,[42] was added to aldehyde **53** in the presence of spirotitanate **54** to give its corresponding allylic alcohol **47** with excellent diastereoselective induction, *d.r.* of over 30 : 1 (Scheme 11, Table 2).[43]

Table 2 Seebach's diastereoselective alkylation

Entry	Substrate	Catalyst	*d.r.*[a]	Product	C15 configuration	Yield[b] (%)
1	**53**	**54**	>30 : 1	**47**	*S*	82
2	**53**	**55**	28 : 1	**47**	*S*	84
3	**53**	**56**	>30 : 1	**47**	*S*	81

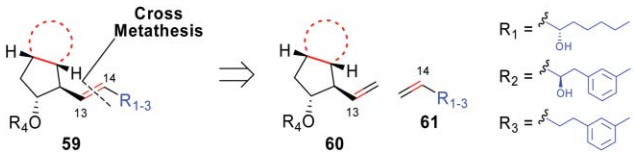
[a] Assigned from ^{1}H NMR analysis. [b] Isolated yields.

Documented to give increased selectivities, catalysts **55** and **56** were also investigated for the diastereoselective alkylation reaction (Table 2, entries 2 and 3 respectively). Unfortunately, in our case no increase in diastereoselectivity was observed. The resulting allylic alcohol **47** was subsequently protected with TBS to give protected isocarbacyclin skeleton **49**, as previously described (Scheme 9). An analogous strategy for 15*R*-TIC (**9**), using bis(3-methylbenzyl)zinc **58**,[42] was also investigated. Unfortunately, dibenzyl zinc **58** proved to be sluggish and unselective, compared to its alkyl analogue, presumably due to its π-conjugation.[40] Although the desired 1,2-addition of bis(3-methylbenzyl)zinc **58** was achieved, low yields were obtained with a *d.r.* of 5 : 1, comparable to that for reduction of enone **46**. The use of selected amino alcohols,[44] as a source of catalytic asymmetric induction, was also investigated, however, the diastereoselectivities obtained for both the isocarbacyclin and 15*R*-TIC substrates were inferior to those previously mentioned.[45]

Introduction of ω-side chain *via* cross metathesis (CM) strategy

Reflecting on our own experiences regarding the substrate dependency of certain prostacyclin analogue enone systems, in particular the modest C15 *pro*-(*R*)-selectivity obtained in our preparation of 15*R*-TIC (**9**), we were prompted to seek an

alternative strategy for the introduction of the ω-side chain. Taking this under consideration, we proposed that an already fully functionalised ω-side chain could be coupled with its bicyclic counterpart at a late synthetic stage, again circumventing the need for a problematic diastereoselective reduction reaction.

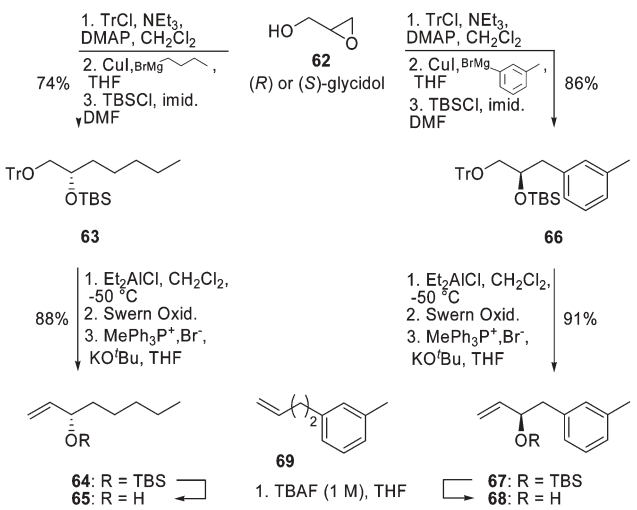


Scheme 12 General CM strategy.

We envisaged that ω-appendage **61**, with an enantiomerically pure C15 hydroxyl group, might be introduced *via* a cross metathesis (CM) reaction (Scheme 12).[46] Looking through the literature we were only able to find a few examples where a metathesis reaction had been applied to prostacyclin or prostaglandin analogue syntheses.[47,48] This CM approach, with appropriate selection of coupling partners, should not only provide high (*E*)-selectivities for the C13–C14 double bond,[46d] but additionally act as a general strategy for the preparation of isocarbacyclin, carbacyclin and prostaglandin analogues (Scheme 12).

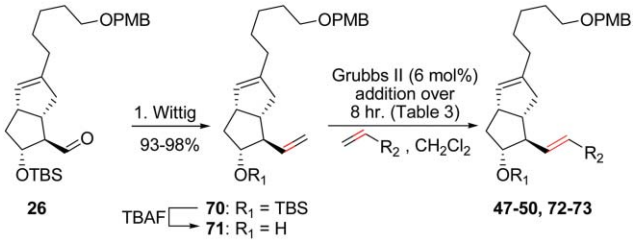
Synthesis of ω-side chain olefins for cross metathesis

The ω-side chains, olefins **64**, **65**, and **67–69**, required for prostacyclin analogues **2** and **6–9** were obtained from either (*R*)- or (*S*)-trityl protected glycidol. Regioselective oxirane ring opening, achieved by the addition of a suitable cuprate reagents, yielded protected diols **63** and **66**. Trityl ether deprotection, Swern oxidation followed by Wittig reaction provided allylic alcohols **64** and **67** in 66 and 80% yield over six steps, respectively (Scheme 13). Unprotected allylic alcohols **65** and **68** were obtained by treatment with TBAF. The 15-deoxy-TIC ω-side chain **69** was prepared in a two-step oxidation/Wittig sequence from a known primary alcohol.[49]



Scheme 13 ω-Side chain olefins for CM strategy.

Application of CM strategy to isocarbacyclin analogues

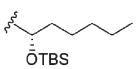
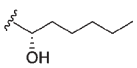
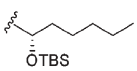
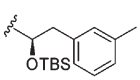
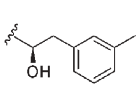
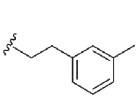


Scheme 14 CM Strategy for isocarbyclin analogues.

Bicyclic aldehyde **26** was subjected to a Wittig methylenation to give olefin **70**. C11 TBS-deprotection also provided olefin **71**. Scheme 14 and Table 3 outline the results obtained from various CM reactions between bicyclic olefins **70** and **71** and ω-side chain olefins **64**, **65** and **67–69** in the presence of Grubbs 2nd generation catalyst.[50] Various metathesis catalysts were investigated for this CM reaction: Grubbs 1st generation catalyst did not prove reactive enough and the Hoveyda–Grubbs 2nd generation catalyst,[51] proved to be too reactive, resulting in percentages of bicyclic olefin dimerization. All reaction entries for the CM reaction between **70**/**71** and ω-side chain olefins demonstrated high (*E*)-selectivities, with modest to excellent yields, where some are notably better than others.

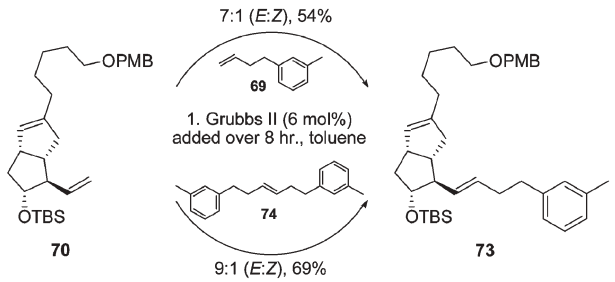
Variation of the bicyclic component, a free C11 hydroxyl moiety, did not have a significant effect on the outcome of the CM reaction with regards to either yield or *E* : *Z* selectivity (Table 3, entry 3). Conversely, a free hydroxyl functionality at

Table 3 Isocarbacyclin analogue cross metathesis (yields not optimized)[a]

Entry	Bicyclic olefin	R_1	ω-Side chain olefin R_2[b]	Product	*E* : *Z*	Yield[c] (%)
1	**70**	TBS		**49**	15 : 1	82
2[d]	**70**	TBS		**47**	12 : 1	61[d]
3[e]	**71**	H		**72**	13 : 1	74
4	**70**	TBS		**50**	19 : 1	90
5	**70**	TBS		**48**	16 : 1	66[d]
6[d]	**70**	TBS		**73**	7 : 1	54

[a] Reactions carried out in CH_2Cl_2 at 40 °C. [b] 2 equiv. of ω-side chain used where up to 0.5 equiv. recovered. [c] Isolated yields. [d] 30–35% homodimerized ω-side chain recovered. [e] Toluene was used as solvent at 80 °C.

the C15 allylic position did not greatly affect the E : Z selectivity, although yields were slightly diminished as a result of unwanted homodimerization of ω-side chains (Table 3, entries 2 and 5 *c.f.* entries 1 and 4). For the CM reaction of bicyclic olefin **70** with ω-side chain **69** to proceed, a change of reaction solvent from CH_2Cl_2 to toluene, and an increased reaction temperature of 80 °C was necessary, where the slightly lower E : Z selectivity obtained (7 : 1) can be attributed to the absence of the C15 stabilizing hydroxyl group (Table 3, entry 6).[52]



Scheme 15 Cross metathesis of ω-side chain **71** *vs.* secondary metathesis with symmetrical alkene **74**.

Furthermore, it was observed that unlike with entries 1–5 (Table 3) ω-side chain **69** (entry 6) first underwent homodimerization to give symmetrical alkene **74**, allowing bicyclic olefin **70** time to also undergo homodimerization, ultimately decreasing the yield (54%). Upon treatment, however, of bicyclic olefin **70** with symmetrical olefin **74** directly (as opposed to ω-side chain **69**), 15-deoxy-TIC skeleton **73** was achieved with an increase in both E : Z selectivity and yield (E : Z 9 : 1, 69%) (Scheme 15), which constitutes a formal synthesis of 15-deoxy-TIC (**8**).[30] It may be noted that the C13–C14 double bond in **73** has been installed with complete (*E*)-selectivity *via* our earlier Julia–Kocieński olefination work. CM products **49** and **50** were both readily converted to their prostacyclin analogues, isocarbacyclin (**6**) and 15*R*-TIC (**9**) without complication (*vide supra*).[39] C13–C14 (*Z*)-double bond geometric isomer could be removed by HPLC separation. However, after carrying the mixture through four more synthetic steps after the CM reaction no (*Z*)-double bond geometric isomers could be detected. Thus, both our Julia–Kocieński olefination and CM reaction approaches can be used in a complementary fashion to introduce a wide selection of ω-side chain appendages.

Prostaglandins and isoprostanes

The prostaglandins (PGs),[53,54] have demonstrated a wide range of potent pharmacological properties over the years.[55] Their intriguing structures have sparked the imagination of the organic chemist, striving for a more efficient, convergent, and naturally, where possible, more elegant synthesis; reflected by the scores of PG syntheses over the years:[5c,38a,56] $PGF_{2\alpha}$ (**75**),[57] PGJ_2 (**76**)[58] and travoprost (**77**).[59]

In addition to prostaglandins which incorporate a *trans*-configuration for the α-and ω-side chains, the relatively recent discovery of epimeric PGs has been reported: isoprostanes and neuroprostanes (**78**, **80** and **81**) containing a *cis*-configuration for both the α-and ω-side chains (Fig. 3).[60] Characteristic examples are 8- and 12-*epi*-$PGF_{2\alpha}$ (**78** and **80**), of which **78** has been isolated and shown to be a potent renal and pulmonary vasoconstrictor.[60] 12-*epi*-$PGF_{2\alpha}$ (**80**), however, has not been found in nature, so far, though it should also be formed *via* a free radical cascade. Isoprostanes are generated in racemic form, which is consistent with a non-enzymatic pathway.

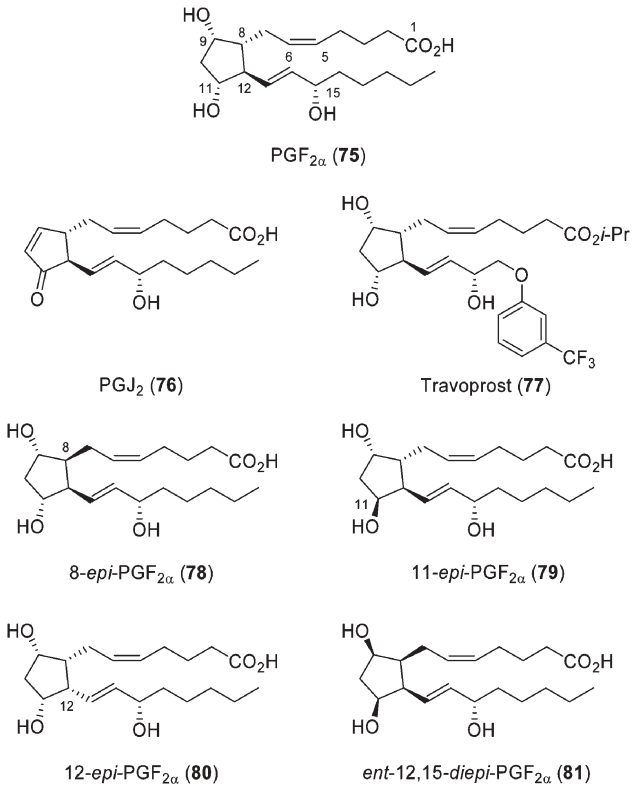
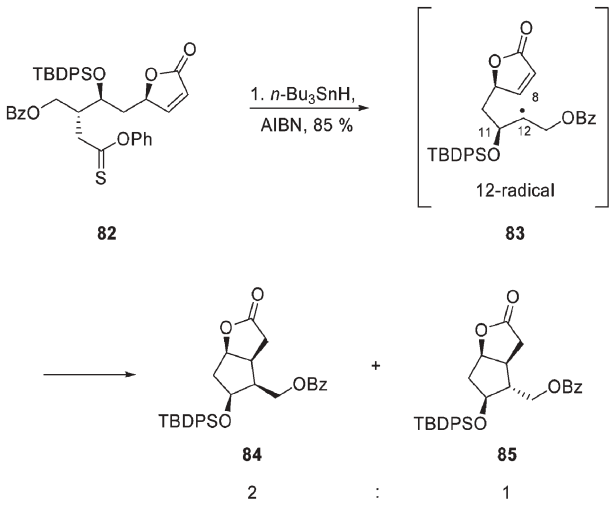


Fig. 3 Prostaglandins $F_{2\alpha}$ (**75**) and J_2 (**76**), travoprost (**77**) and isoprostanes 8-*epi*-$F_{2\alpha}$ (**78**), 11-*epi*-$F_{2\alpha}$ (**79**), 12-*epi*-$F_{2\alpha}$ (**80**) and *ent*-12,15-*diepi*-$F_{2\alpha}$ (**81**).

Application of a C8–C12-free radical cyclisation strategy for isoprostane analogues

As several syntheses of "natural" 12-*epi*-$PGF_{2\alpha}$ (**80**) have already been reported,[33f,61] we turned out attentions to its unnatural isomer *ent*-12,15-*diepi*-$PGF_{2\alpha}$ (**81**), as both compounds would be desirable for biological evaluation. We proposed that the required all *cis*-configuration could be achieved *via* the stereocontrolled biomimetic free radical C8–C12-cyclization reaction (Scheme 16). There is ample literature precedence for isoprostane syntheses *via* such a radical process, in particular from the Rokach group.[62] In all cases, however, diastereomeric mixtures were obtained.[63] Some time ago we studied the free radical annulation of a C12-radical to a butenolide acceptor (Scheme 16). Treatment of thiocarbonate **82**, with tributyl tin hydride, furnished Corey lactone derivatives **84** and **85** in 85% yield and 2 : 1 diastereomeric ratio.[64] The annulation to the butenolide exclusively generates



Scheme 16 C8–C12-free radical isoprostane cyclisation strategy.

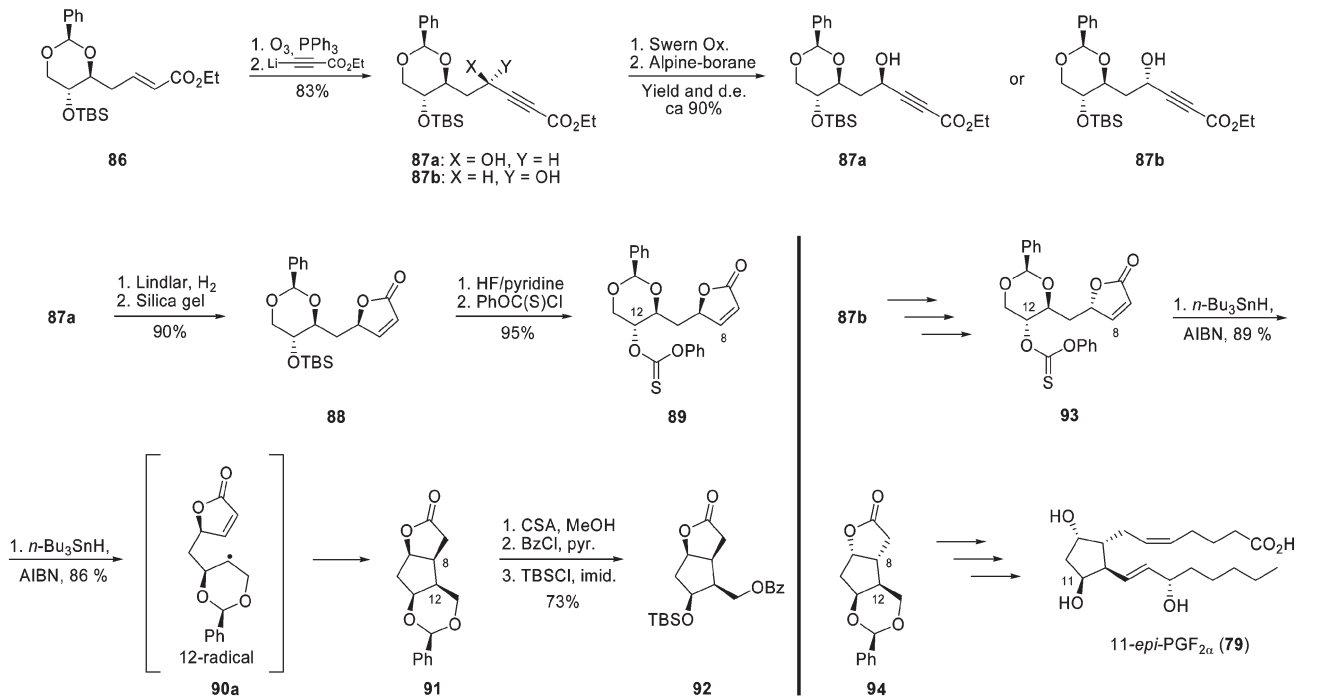
the *cis*-fused system, however, the C12-radical, as in all the cases reported so far,[62] lacks facial selectivity, due to rapid rotation around the C11–C12-axis. To inhibit such a rotation, the incorporation of the C11–C12 bond into a cyclic template appeared appropriate, following precedent by Rajan Babu.[65]

Thus, in our synthesis of **81**, known benzylidene acetal **86**[66] was transformed into an epimeric mixture of the acetylides **87a/b**. To rectify the configuration of the C4-carbinol, the mixture was oxidised to the ketone and subsequently reduced with Alpine-borane,[67] to give either **87a** or **87b** with high diastereocontrol (Scheme 17). Pure propargylic alcohol **87a** was hydrogenated and cyclised to give butenolide **88** which was converted into thiocarbonate **89** and then into free radical **90a**.[68] Twofold *cis*-annulation occurred to give *ent*-12-*epi*-Corey lactone derivative **91** as a single stereoisomer in high yield. By routine functional group manipulation, **91** was transformed into **92**, *i.e.* the enantiomer of Rokach's intermediate in his synthesis of 12-*epi*-$PGF_{2\alpha}$ (**80**).[61b] Analogously thiocarbonate **93**, obtained from **87b**, was converted into **94**, again as a single stereoisomer (Scheme 17), which may serve as an intermediate in a synthesis of 11-*epi*-$PGF_{2\alpha}$ (**79**).[69]

The transition states of the respective free radical cyclizations (**90a** and **90b**) may be rationalised in terms of the crystal structures of **91** and **94**, respectively (Fig. 4). These representations clearly depict the stereo-chemical course of the addition of an endocyclic cyclohexyl type radical, at C12, to the butenolide C7–C8 acceptor double bond. Both the *cis*-annulation to the six membered acetal and the *cis*-annulation to the butenolide guarantee the stereochemical outcome of the cyclisation.

Application of developed CM strategy to prostaglandin and carbacyclin analogues

Optimistic that we had a promising, reproducible approach towards the installation of enantiomerically pure C15 side-chains for isocarbacyclin analogues, we wished to establish its scope and limitations, in the form of our CM Strategy (*vide supra*) and if it could be applied to a broader spectrum of substrates: prostaglandin and carbacyclin analogues, namely $PGF_{2\alpha}$ (**75**), PGJ_2 (**76**) and carbacyclin (**2**), respectively. Corey lactone **95** was converted to olefin **96** *via* an oxidation/Wittig reaction sequence, with a modest yield of 66% (Scheme 18). Our preliminary results from the CM reaction of Corey lactone-derived olefin **96** with ω-side chain olefin **64** is outlined in Scheme 18 and Table 4. Unfortunately, CM



Scheme 17 Benzylidene acetal C8–C12-free radical cyclisations strategy leading to Corey lactone derivatives **85** and 11-*epi*-$PGF_{2\alpha}$ (**81**).

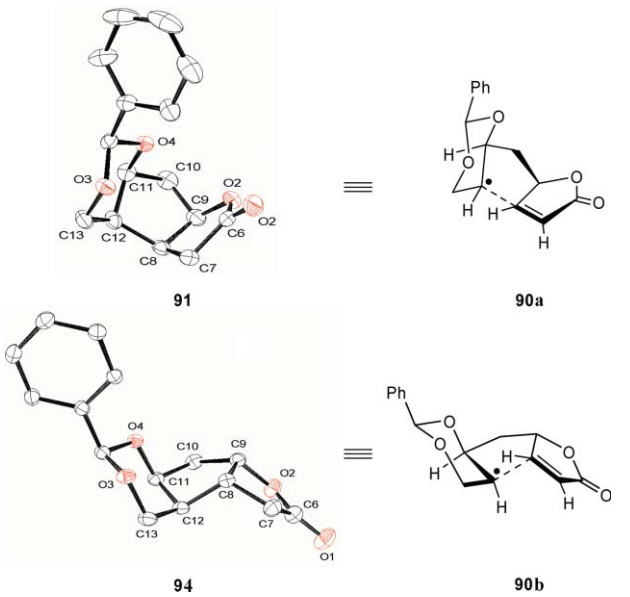
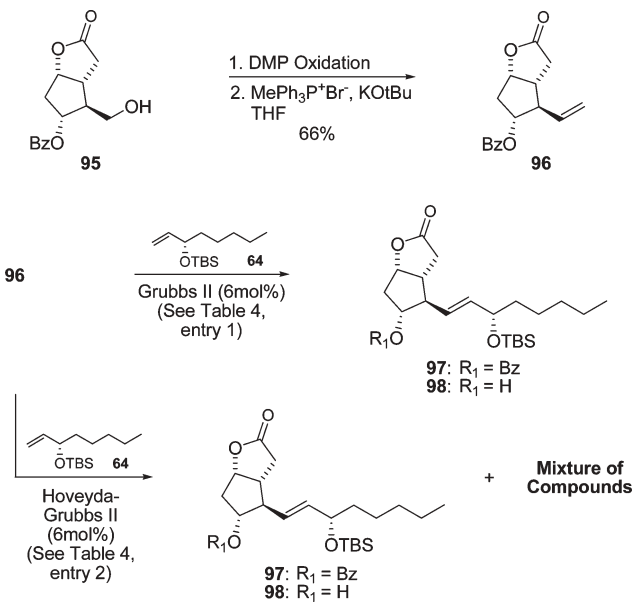


Fig. 4 Transition states (**90a** and **90b**) for the radical annulations as derived from the crystal structures of the cyclisation products **91** and **94**.



Scheme 18 Corey lactone for CM reaction.

Table 4 Prostaglandin analogue cross metathesis (yields not optimized)[a]

Entry	Bicyclic olefin	R_1	ω-Side chain olefin R_2[b]	Product	$E:Z$	Yield[c] (%)
1	**96**	Bz	OTBS	**97** **98**	7 : 1 6 : 1	40 25
2	**96**	Bz	OH	**97** **98**	7 : 1 6 : 1	25 15

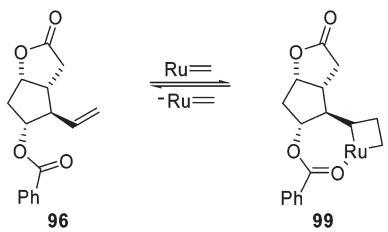
[a] Catalyst added over 8 h or 12 h in CH_2Cl_2 at 40 °C. [b] 2 equiv. of ω-side chain used where up to 0.5 equiv. was recovered. [c] Isolated yields.

reaction between bicyclic olefin **96** and allylic alcohol **64**, in the presence of Grubbs 2nd generation catalyst (Table 4, entry 1), delivered desired CM product **97** with only a modest $E:Z$ ratio of 7 : 1 (40% yield). Furthermore, deprotected benzoate CM product **98** was isolated, also with modest $E:Z$ ratio (6 : 1) in 25% yield. Similar results were obtained when using the Hoveyda–Grubbs 2nd generation catalyst (Table 4, entry 2).

Proposed influence of benzoate group on CM reaction

In spite of initial results for this CM reaction with isocarbacyclin analogues being very positive (*vide supra*), the benzoate protecting group at the homoallylic C11 position was unstable towards the CM reaction conditions and as such, proved unsuitable for our purposes.

In addition to this instability, the influence of protecting groups for allylic and homoallylic alcohols has been documented on metathesis reactions.[70] We postulated that the C11 homoallylic benzoate protecting group could coordinate with the initially formed metallacycle, leading to its deactivation (Scheme 19). This is supported by an analogous example, reported by Cossy and co-workers (albeit allylic, not homoallylic) where catalyst deactivation was observed, which could account for the observed low yields.[71] We therefore chose to investigate the effects of both a free hydroxyl functionality and silyl protecting group (TBS ether) at both the C11 homoallylic, and the C15 allylic positions on the CM reaction.[72]

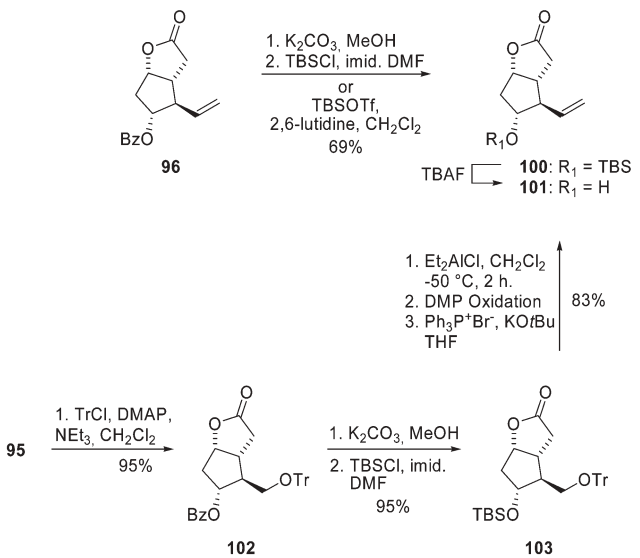


Scheme 19 Possible deactivation of catalyst by C11 benzoate group.

Alternative protecting group strategy for CM Corey lactone derivatives

A simple interconversion of the C11 benzoate to the corresponding TBS ether was imagined, although proved more difficult than first imagined. All efforts to protect the C11 position with TBS, either with TBSCl or TBSOTf only delivered disappointingly low yields of C11 TBS-protected secondary alcohol **100** (Scheme 20). As the Corey lactone C11 benzoate had proven problematic over several steps, it was decided that installation of the C11 TBS protecting group would be more efficient at an earlier stage of the sequence (Scheme 20).

Trityl ether protection of the primary alcohol of Corey lactone **95** provided **102**, subsequently followed by cleavage of the C11 benzoate with K_2CO_3, and re-protection as the TBS ether, to deliver **103** (Scheme 20). Trityl ether deprotection under Lewis acid conditions, followed by Dess–Martin oxidation and Wittig olefination reactions provided **100** in 75% yield over six steps, much improved compared to the previous 46% yield over four steps.



Scheme 20 Alternative C11 substituted Corey lactone derivatives **101/102** for CM reaction.

The results of X-ray diffraction studies of both benzoate **102** and TBS ether **103** as single crystals, obtained by slow diffusion of hexane into the corresponding chloroform solutions, are depicted in Fig. 5.

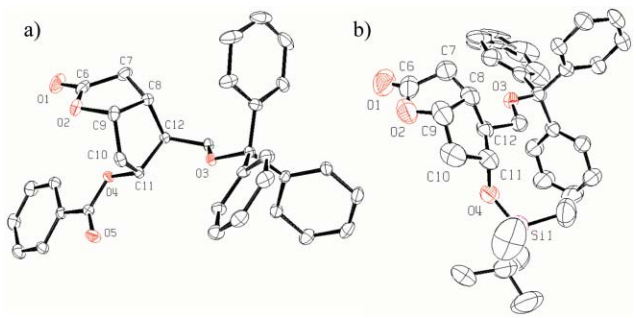
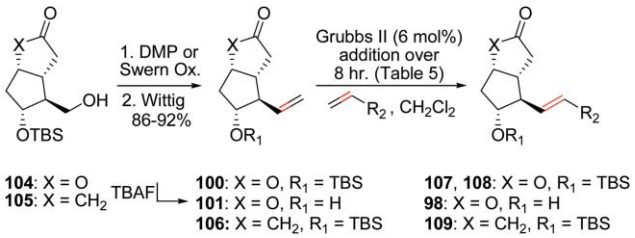


Fig. 5 ORTEP representations of (a) benzoate **102** and (b) TBS ether **103** (ellipsoids at 50% probability).

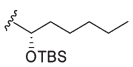
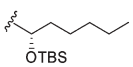
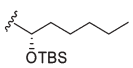
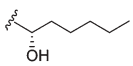
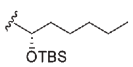
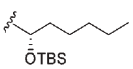
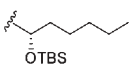
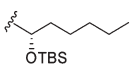
CM reactions, between Corey lactone derived bicyclic olefins **100/101**, (Table 5, entries 1–5), or carbacyclin core **106**‡ (Table 5, entries 6–8) with ω- side chain olefins **64** or **65**, demonstrated high E : Z selectivities (Scheme 21), although longer catalyst addition times were required to attain the same high E : Z selectivities as obtained for isocarbacyclin analogues (Scheme 14, Table 3) evident on comparison of Table 5, entries 1 and 6 (8 h catalyst addition) with entries 3 and 8 (12 h catalyst addition). Furthermore, re-exposure of products described in entries 1 and 6 to the Grubbs 2nd generation catalyst led to an equilibration of the C13–C14 double bond, presumably *via* a secondary metathesis reaction, resulting in (*E*)-double bond enrichment with a mild sacrifice in yield. It

‡ Carbacyclin bicycle **106** was also more successfully achieved by the oxidation of its known spiro ketal precursor (see ref. 30), followed by treatment with the methyl Wittig ylide and subsequent ketal cleavage, to give the desired product.



Scheme 21 Prostaglandin and carbacyclin CM strategy.

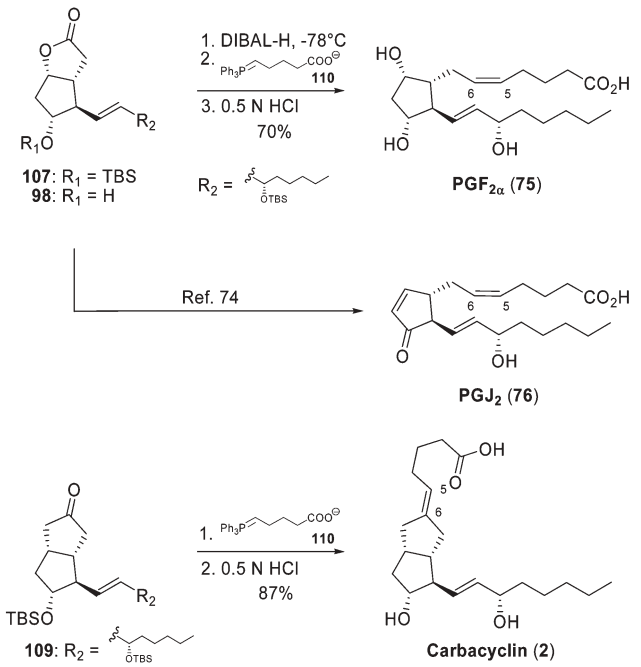
Table 5 Prostaglandin and carbacyclin analogue cross metathesis (yields not optimized)[a]

Entry	Bicyclic olefin	R_1	ω-Side chain olefin R_2[b]	Product	E : Z	Yield[c] (%)
1	**100**	TBS		**107**	6 : 1	76
2[d]	**100**	TBS		**107**	12 : 1	68
3[e]	**100**	TBS		**107**	17 : 1	84
4	**100**	TBS		**108**	12 : 1	60[f]
5	**101**	H		**98**	14 : 1	70
6	**106**	TBS		**109**	7 : 1	69
7[g]	**106**	TBS		**109**	10 : 1	65
8[e]	**106**	TBS		**109**	10 : 1	86

[a] Reactions carried out in CH_2Cl_2 at 40 °C. [b] 2 equiv. of ω-side chain used where up to 0.5 equiv. recovered. [c] Isolated yields. [d] Re-exposure of entry 1 to Grubbs 2nd generation catalyst for 12 h at 40 °C. [e] Catalyst added over 12 h at 40 °C. [f] 30% homodimerised ω-side chain recovered. [g] Re-exposure of entry 6 to Grubbs II for 12 h at 40 °C.

can be concluded, from the results in Tables 3, 4 and 5, that protection of the C15 hydroxyl group (in our case as the TBS ether) not only leads to higher (*E*)-selectivity, but also slows the rate of ω-side chain homodimerization, ultimately increasing the reaction yield (Table 3: entries 1 and 4; Table 5: entries 3 and 8). Furthermore, deprotection of either the C11 or C15 TBS protected alcohols did not have a significant effect where only a mild sacrifice in both yield and E : Z selectivity was observed. The observed drop in yields was attributed to the respective compound with either a free hydroxyl group at C11 or C15 undergoing more rapid homodimerisation.

Corey lactone derivative **107** was reduced with DIBAL-H to give its corresponding lactol, which after subsequent treatment with phosphonium ylide **110** gave the (*Z*)-double bond



Scheme 22 Completion of prostaglandins $F_{2\alpha}$ (**75**) and J_2 (**76**) and carbacyclin (**2**) syntheses.

(C5–C6) isomer as the only detectable product. Finally, TBS deprotection was effected by the treatment with 0.5 M HCl to gave $PGF_{2\alpha}$ (**75**) (Scheme 22).[72,73] Cross metathesis reaction product **98** also constitutes a formal of PGJ_2 (**76**).[74] CM product **109**, after treatment with phosphonium ylide **110** give a 4 : 1 mixture (separable by column chromatography) of the *E* : *Z exo* C5–C6 double bond. After chromatographic separation and deprotection of both C11 and C15 TBS protected alcohols, with 0.5 N HCl, carbacyclin (**2**) was obtained without complication.[75] C13–C14 (*Z*)-double bond geometric isomers were removed as previously described (Scheme 22).[52]

Conclusions

The problems posed by isocarbacyclin and prostaglandin analogue syntheses: the introduction of both the α- and ω-side chains in a stereocontrolled and convergent manner have received much attention and many ingenious solutions over the years, some of which have been mentioned here. Using our substrate controlled regiospecific deprotonation reaction to access to the troublesome C6–C9α endocyclic double bond, we have provided an alternative solution to its introduction. Furthermore, through an palladium catalysed sp^2–sp^3 Kumada–Tamao cross coupling reaction, the C5 α-side chain for isocarbacyclin (**6**), 15-deoxy-TIC (**8**) and 15*R*-TIC (**9**) could be introduced. This cross coupling strategy would potentially allow the introduction of a number of alternatively functionalised α-side chains for isocarbacyclin analogues. Regarding the introduction of the ω-side chain appendage, we have discussed several strategies developed in our laboratories for its introduction. Firstly, we investigated the use of the Julia–Kocieński olefination reaction, applied in the synthesis of 15-deoxy-TIC (**8**), but proved not to be compatible with dealing with an α-substituted sulfone. Several alkylation strategies were also investigated: addition of selected Grignard reagents to a bicyclic Weinreb amide core to give α,β-unsaturated enones and subsequently reduced under reagent control giving modest to excellent diastereoselectivities; and the use of Seebach's alkylation chemistry, also with excellent diastereoselectivity. Both strategies led to the successful syntheses of isocarbacyclin (**6**) and 15*R*-TIC (**9**). We also extensively investigated the use of the cross metathesis reaction for the introduction of the ω-side chain, of not only isocarbacyclin analogues but also carbacyclin and prostaglandin analogues. This cross metathesis strategy proved, by far, to be superior to its predecessors, allowing the introduction of enantiomerically pure C15 alcohols and circumventing the need for chiral reducing agents; ultimately leading to the syntheses of isocarbacyclin (**6**), 15*R*-TIC (**9**), carbacyclin (**2**), $PGF_{2\alpha}$ (**75**) and the formal syntheses of 15-deoxy-TIC (**8**) and PGJ_2 (**76**). In addition, a fully stereocontrolled C8–C12-free radical cyclisation strategy has been described for the isoprostane series and demonstrated its utility for the syntheses of 11-*epi*-$PGF_{2\alpha}$ (**79**) and *ent*-12,15-*diepi*-$PGF_{2\alpha}$ (**81**). These combined strategies constitute not only convergent, but practical access for building libraries of structurally interesting prostacyclin, prostaglandin and isoprostane analogues for the purpose of further biological appraisal.

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