RECENT APPROACHES TO THE TOTAL SYNTHESIS OF PHYTOPROSTANES, ISOPROSTANES AND NEUROPROSTANES AS IMPORTANT PRODUCTS OF LIPID OXIDATIVE STRESS AND BIOMARKERS OF DISEASE

EMANUELA JAHN[a], **THIERRY DURAND**[b], **JEAN-MARIE GALANO**[b], **and ULLRICH JAHN**[a]

[a] *Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo náměstí 2, 166 10 Prague, Czech Republic,* [b] *Institut des Biomolécules Max Mousseron (IBMM), UMR CNRS 5247 – Universités de Montpellier I et II, Faculté de Pharmacie, ENSCM, 15 Av. Charles Flahault, BP 14491, 34093 Montpellier cedex 05, France*
jahn@uochb.cas.cz

Keywords: lipids, oxidative stress, phytoprostanes, isoprostanes, neuroprostanes, total synthesis

---

Contents

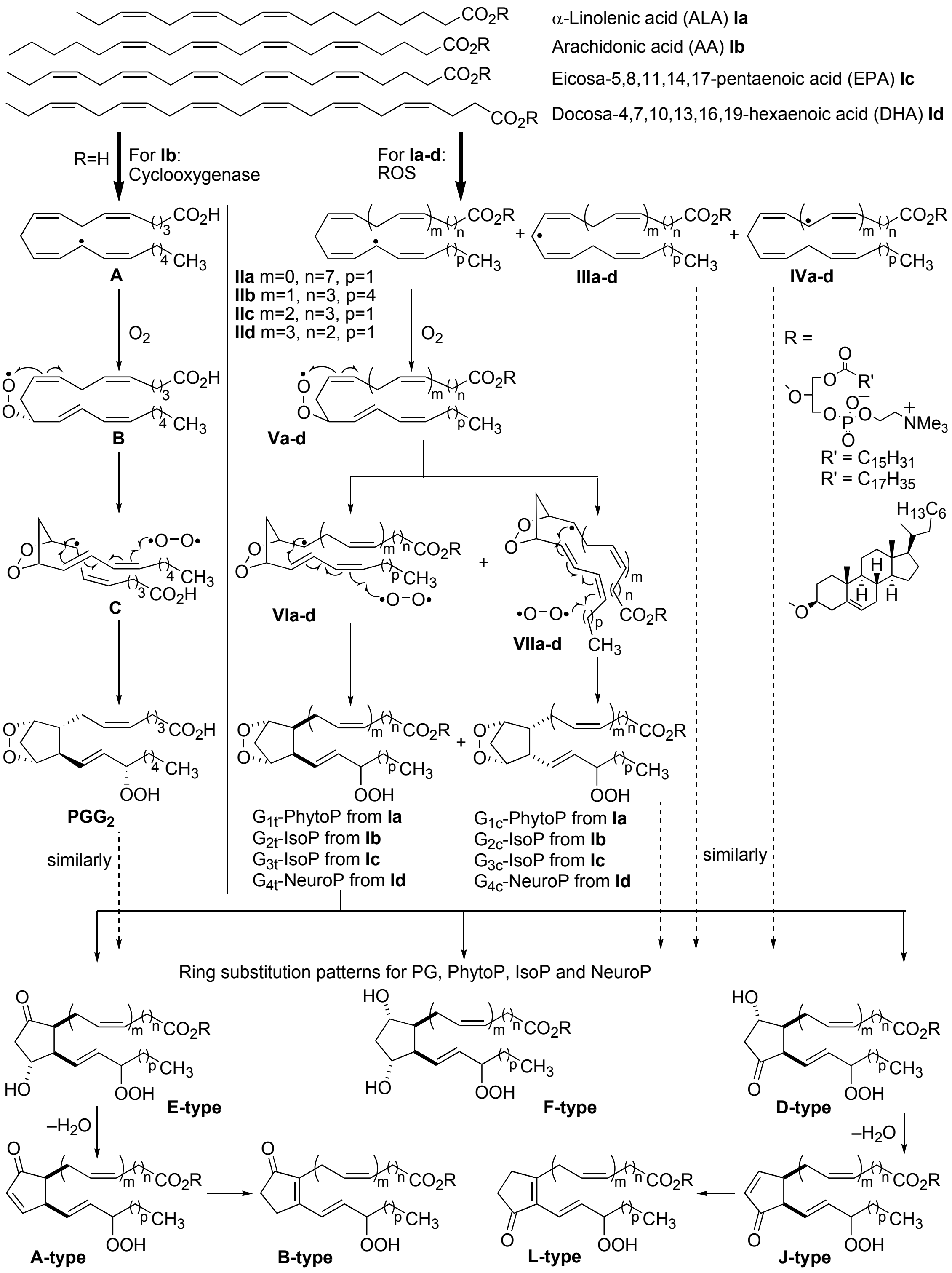
1. Introduction

All living organisms are subject to oxidative stress at major classes of primary metabolites, such as DNA, RNA, proteins, and lipids[1,2]. Especially lipid peroxidation is a very prominent process in plants and animals[3,4]. It occurs predominately at polyunsaturated fatty acid (PUFA) groups bound in the phospholipids of membranes (R = acyl(phosphoryl)glyceryl) or at PUFA cholesteryl esters (R = cholesteryl) in low-density lipid proteins (LDL) (Scheme 1). The extent of peroxidation is dependent on the degree of unsaturation in the corresponding PUFA unit; the more unsaturated, the more prone to autoxidation it is[5–7], increasing from α-linolenic acid (ALA) **Ia**, *via* arachidonic acid (AA) **Ib** and eicosapentaenoic acid (EPA) **Ic** to docosahexaenoic acid (DHA) **Id**. Other factors contributing to the extent of peroxidation are the concentration of oxygen in the tissue, the presence of reducing equivalents in the cell (vitamins C, E, and glutathione) and the presence of radical initiating species, especially reactive oxygen species, generated by mitochondrial leakage, electron transfer from transition metal compounds or radiation. Lipid peroxidation starts usually by hydrogen atom abstraction at a bisallylic position of the corresponding PUFA. Autoxidative hydrogen atom abstraction proceeds in contrast to the enzymatic formation of prostaglandins (PG)[8–11], where the hydrogen atom in 13-position of free AA **1b** is selectively abstracted by the cyclooxygenase enzyme to give radical **A**, with almost equal probability at all available bisallylic positions leading to radicals **IIa-d**, **IIIa-d** and **IVa-d**. Thus a much larger variety of reactive radicals are generated in parallel. The enzymatic PG and the autoxidative PhytoP, IsoP, and NeuroP formation proceed by the same elementary steps, namely coupling of the pentadienyl radical **A** or **IIa-d** with oxygen, radical 5-exo cyclization of the resulting peroxyl radical **B** or **Va-d** to an available olefinic unit in the PUFA chain, radical 5-exo cyclization of the carbon radical **C** or **VIa-d** and **VIIa-d** to the diene unit and coupling of the resulting allylic radical to oxygen giving either PGG_2 or the G-type PhytoP, IsoP or NeuroP derived from **Ia-d**[5,7,12].

The major difference between the enzymatic and autoxidative process consists of the stereoselectivity of the coupling of the initial radical with oxygen, which occurs for **A** with high enantioselectivity in the enzyme, but without for **IIa-d** on peroxidation, and in the diastereoselectivity of the cyclopentane forming step. Under autoxidative conditions a kinetically controlled cyclization of **Va-d** prevails with high selectivity, which leads to a *cis*-orientation of the side chains forming **VIa-d** and **VIIa-d**, whereas the cyclooxygenase enzyme forces the side chains of **C** in a *trans*-orientation for radical cyclization. As a consequence of these two factors PGs are single enantiomers with *trans*-configuration of the chains as shown for the first observable PGG_2, whereas PhytoP, IsoP and NeuroP occur in Nature as regioisomeric mixture of racemic isomers, however, with relative *cis*-configuration at the ring. Further processing of the G-type IsoP proceeds by reduction to the F-Type IsoP or reduction and Kornblum-DeLaMare rearrangement to the D- and E-type IsoP, from which A- and J-type IsoP result by dehydration. The latter can isomerize to the B- and L-type IsoP[13].

These differences have important consequences for the biological activity of these compounds. Whereas PGs act mostly as local hormones[8–11], PhytoP and IsoP have been shown to display wide-ranging biological activities. They were summarized recently in several reviews and the reader should consult them for further information[5,12,14,15]. Very recently discovered activities concern the vascular homeostasis, the modulatory role on excitatory neurotransmitter release, neuroprotection, and anti-arrhythmic properties. Moreover especially the F-type IsoP and PhytoP serve as important biomarkers for oxidative lipid stress in vivo, since they can be quantified easily by a number of mass-spectrometric or immunological techniques[16].

As a direct consequence of their formation, PhytoP,



Scheme 1. **The similar, but contrasting formation of prostaglandins and isoprostanes.** (Note that the ring substitution pattern is only shown for IsoP resulting from G_{xt}-metabolites. The same substitution patterns are also found in PG, and metabolites resulting from IIIa-d, IVa-d and G_{xc}-metabolites.)

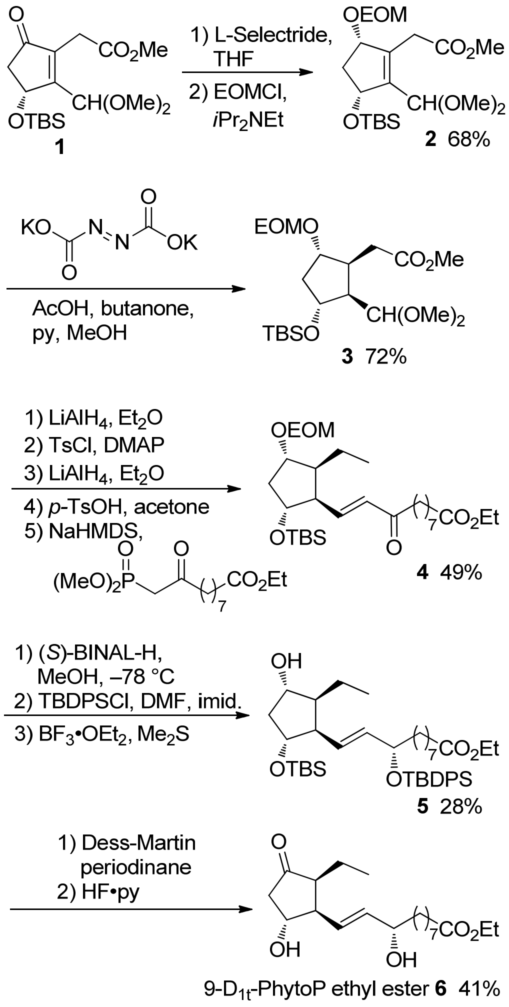
IsoP and NeuroP are regio- and diastereomeric mixtures, which are essentially impossible to separate. Therefore, it is impossible to use the natural material for biological investigations to draw meaningful conclusions. For this reason, the only way to investigate them is to rely on synthetic material. Only this will allow a deeper understanding of the biological properties of PhytoP, IsoP and NeuroP. We summarized the state of the art of the total syntheses of oxidatively formed lipid metabolites some time ago[5]. Since then a number of new synthetic approaches have been developed, which will be analyzed here to provide a complete picture of the opportunities known to date. The organization of the review is by metabolite class, PhytoP are treated first, followed by IsoP and NeuroP.

2. PhytoP Total Syntheses

Durand's Syntheses

In 2008, the Durand group fully implemented their previously developed furan-based strategy to B_1-PhytoPs[17,18] towards the more challenging synthesis of the ethyl ester of 9-D_{1t}-PhytoP[19] (called PPE type II[20] in the original paper[19]; for the nomenclature of oxidatively formed cyclic lipid metabolites, see[5,13]) (Scheme 2). 15-E_2-IsoP[19], resulting from arachidonic acid, and later 4-F_{3t}-NeuroP[21], derived from ω-6 docosapentaenoic acid (DPA), were similarly synthesized by this approach. Intermediate **1**, which is accessible in 6 steps in 13% yield[19], was reduced with L-Selectride with complete stereoselectivity followed by ethoxymethyl protection to give cyclopentene **2** with mandatory orthogonal protection of the two hydroxy groups for the synthesis of E- and D-PhytoP as well as IsoP. Hydrogenation of the hindered tetrasubstituted double bond using in situ generated diimine permitted access to the *trans*-*cis*-*trans*-substituted cyclopentane **3** with complete control.

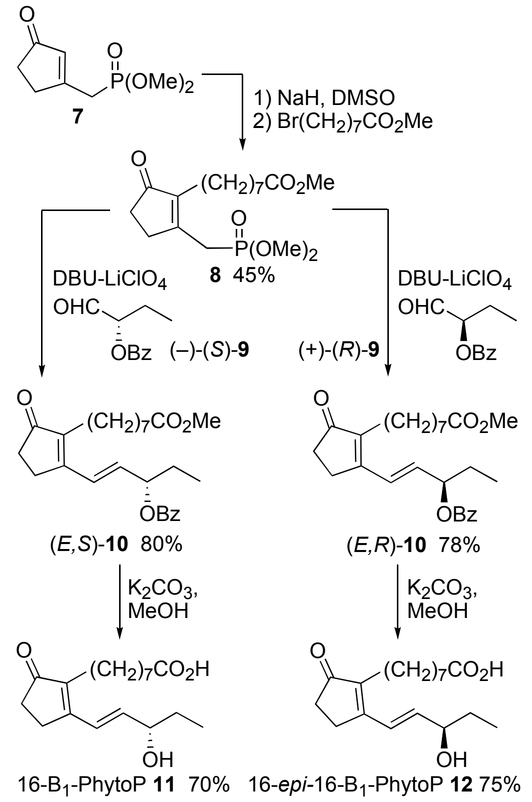
Introduction of the ethyl appendage of 9-D_{1t}-PhytoP was accomplished from **3** in three steps by $LiAlH_4$ reduction of the methyl ester, protection of the resulting hydroxyl group with TsCl and $LiAlH_4$ reduction of the tosylate group in 73% overall yield. Mild deprotection of the acetal group with *p*-TsOH in acetone, followed by a Horner-Wadsworth-Emmons (HWE) reaction with dimethyl [9-(ethoxycarbonyl)-2-oxononyl]phosphonate in the presence of NaHMDS afforded the *trans*-α,β-enone ester **4** in 70% yield after two steps. The diastereoselective reduction of the C15 keto group in **4** with the chiral reducing agent (*S*)-BINAL-H developed by Noyori et al.[22] gave the 15(*S*) derivative which was protected with TBDPSCl in 57% yield for these two steps. Selective deprotection of the EOM group with $BF_3 \cdot OEt_2$ and Me_2S was achieved in modest 49% yield, but provides the TBS ether **5**. Dess-Martin oxidation led quantitatively to the corresponding ketone, which was used without purification in the next step. Desilylation with the HF•pyridine complex gave the desired 9-D_{1t}-PhytoP ethyl ester **6** in an overall yield of 2.8% in 10 steps from **1**.



Scheme 2. **Durand's total synthesis of 9-D_{1t}-PhytoP ethyl ester**

Mikołajczyk's Syntheses

16-B_1-PhytoP, 9-B_1-PhytoP and their 16- and 9-epimers respectively are formed *via* nonenzymatic autoxidative processes in plants and exhibit biological activities in humans. A very short total synthesis of 16-B_1-PhytoP **11** and its 16-epimer **12** was published recently by Mikołajczyk et al. (Scheme 3)[23]. 3-[(Dimethoxyphosphoryl)methyl]cyclopent-2-enone **7** served as a starting material, which is available in three steps in ca. 55% yield from cyclopentenone[24]. Alkylation of the dienolate of **7** with 8-bromooctanoate allowed the introduction of the α-chain. The resulting product **8** was subjected to a Horner-Wadsworth-Emmons reaction with enantiopure α-benzoyloxybutanals **9** under mild basic conditions providing the full chain methyl esters (*E*,*S*)-**10** and (*E*,*R*)-**10**. Subsequent saponification furnished the enantiomeric 16-B_1-PhytoP **11** and 16-*epi*-16-B_1-PhytoP **12** in ca. 25% overall yield from **7**.



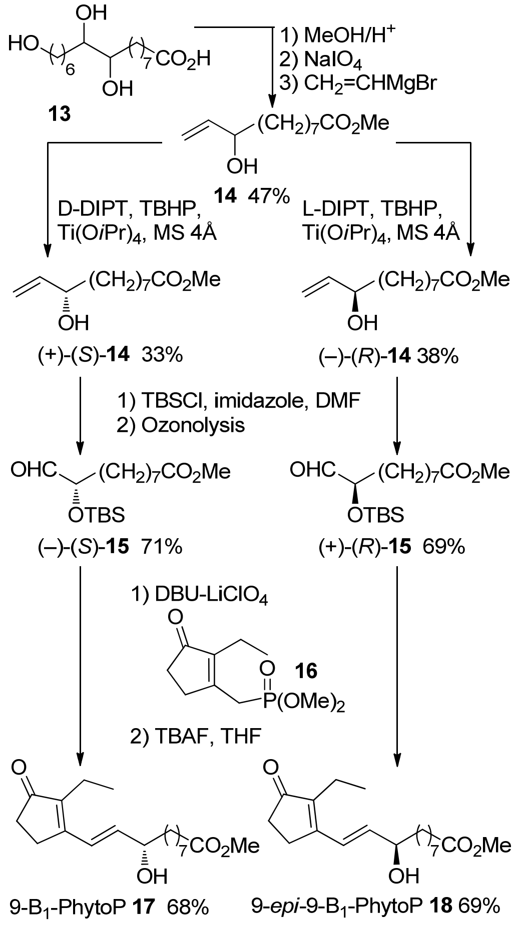
Scheme 3. **Mikołajczyk's synthesis of B$_1$-PhytoP**

The methyl esters of 9-B$_1$-PhytoP **17** and 9-*epi*-9-B$_1$-PhytoP **18** were also synthesized in eight linear steps from commercially available aleuritic acid **13** using a similar strategy (Scheme 4)[25]. It was converted to allylic alcohol **14** in three steps in 47% yield by esterification, oxidative cleavage with sodium metaperiodate and addition of vinyl magnesium bromide to the resulting aldehyde. Kinetic resolution gave allylic alcohols (+)-(*S*)-**14** and (–)-(*R*)-**14** (ref.[26]) by enantioselective Sharpless epoxidation of the undesired enantiomer of **14**. Subsequently (+)-(*S*)-**14** and (–)-(*R*)-**14** were protected and converted into aldehydes (–)-(*S*)-**15** and (+)-(*R*)-**15** by ozonolysis. Horner olefination with phosphorylmethyl cyclopentenone **16**, followed by desilylation provided 9-B$_1$-PhytoP **17** and 9-*epi*-9-B$_1$-PhytoP **18** in overall yields of 7.5% and 8.5%, respectively.

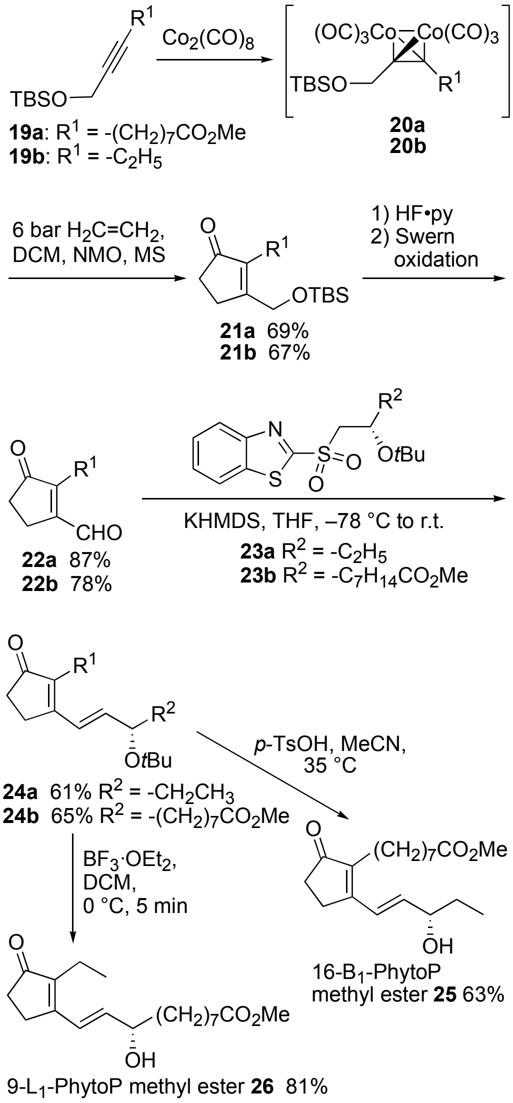
Riera's Synthesis

The Riera group highlighted the applicability of the Pauson-Khand reaction by completing total syntheses of enantiopure B$_1$- and L$_1$-PhytoP[27,28], which they applied previously in a synthesis of deoxy-J$_1$-PhytoPs[29]. Whereas the intramolecular Pauson-Khand reaction is famous to synthesize five-membered hydrocarbon cycles, the intermolecular version using internal alkynes has scarcely been used, probably because of the lower reactivity as well as the more difficult regioselectivity control.

They reasoned that the electronegativity of a silyloxymethyl group, although low, would be enough to control the regioselectivity (Scheme 5)[30]. Alkyne precursor **19a** was obtained by alkylation of propargyl alcohol with the corresponding ω-bromo acid, subsequent esterification and TBS protection in excellent yield, while **19b** was synthesized by silylation from commercially available 2-pentynol. Alkynes **19a,b** were treated with a stoichiometric amount of $Co_2(CO)_8$ to give, after filtration through alumina, the corresponding hexacarbonylcobalt complexes **20a,b**. They were used directly in the intermolecular PKR under 6 bar ethylene gas using anhydrous *N*-methylmorpholine *N*-oxide (NMO) as the promoter in the presence of molecular sieves. The corresponding cyclopentenones **21a**,**b** were obtained in satisfactory yields and with complete regioselectivity. Pauson-Khand adducts **21a**,**b** were transformed to aldehydes **22a**,**b** by a sequence of deprotection using the pyridine·HF complex and a Swern oxidation. Introduction of the side chain of the different PhytoPs was accomplished using the Julia-Kocienski ole-



Scheme 4. **The synthesis of 9-B$_1$-PhytoP**



Scheme 5. **Riera's synthesis of enone PhytoP *via* a Pauson-Khand strategy**

fination with sulfones **23a**,**b** giving exclusively the (*E*)-isomers **24a**,**b** in all cases, whereas (*E*/*Z*)-mixtures resulted under Barbier-type conditions with TBS-protected sulfones. Deprotection of the *tert*-butyl ethers in **24a**,**b** required much experimentation and using five equiv. of *p*-toluenesulfonic acid in acetonitrile gave the desired methyl ester of 16-B_1-PhytoP **25** in 63% yield after purification by chromatography. These conditions were not suitable for the deprotection of **24b**, however, the use of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 0 °C for a few minutes allowed the isolation of the methyl ester of 9-L_1-PhytoP **26** (ref.[13]) in a very good 81% yield.

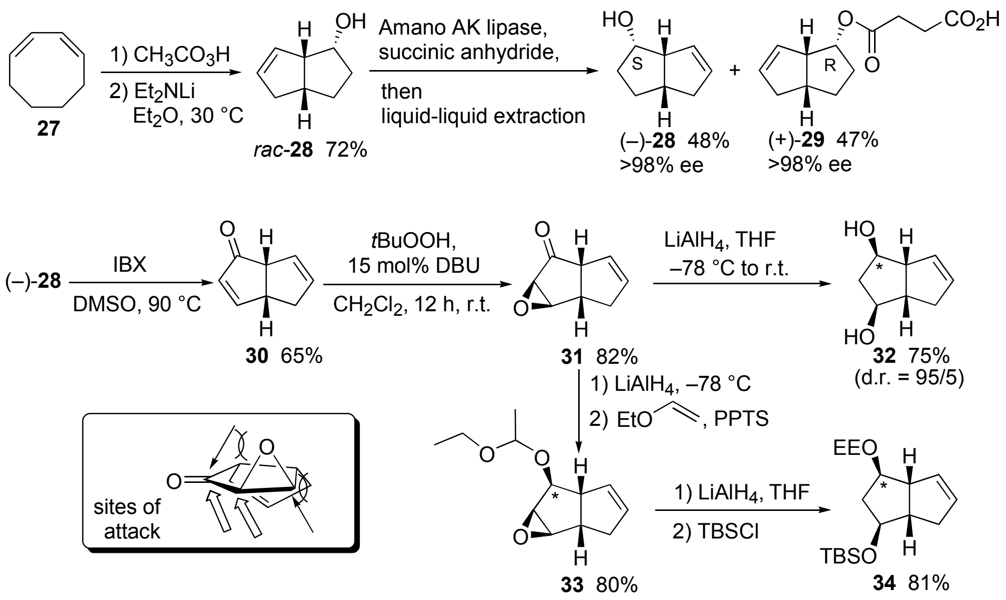
3. Total Syntheses of F_2- and F_3-IsoPs

The Galano-Durand Syntheses

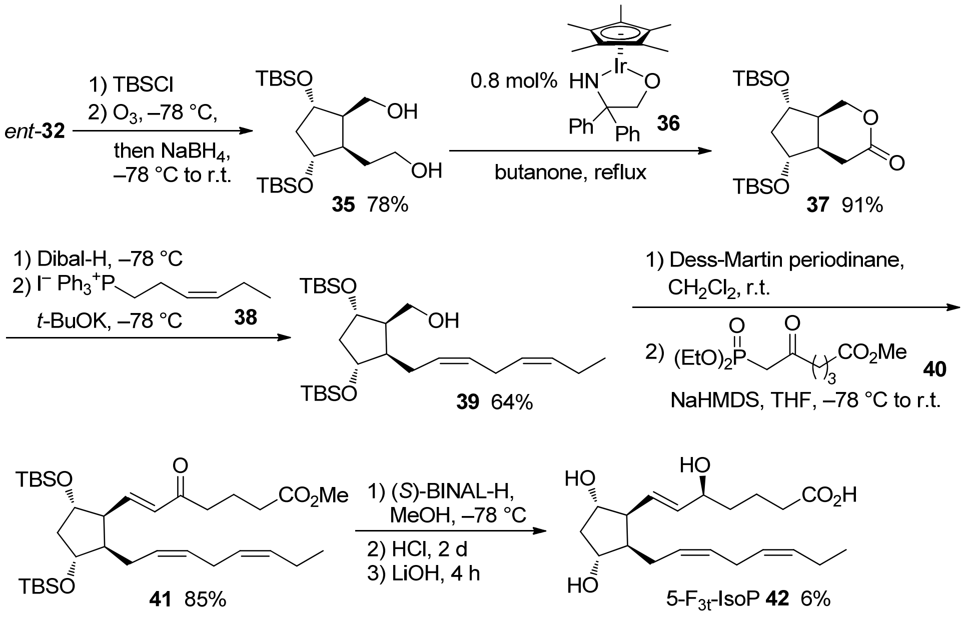
In 2008, the Durand group disclosed a novel strategy based on a completely different way of securing the desired *trans-cis-trans* stereochemistry of the cyclopentane ring (Scheme 6)[31]. They relied on the use of a bicyclo [3.3.0]octene skeleton, which served not only to lock the side-chain stereochemistry, but also solved the inherent problem of introducing *cis*-1,3-hydroxy groups on the cyclopentane ring system. Monoepoxidation of commercially available 1,3-cyclooctadiene **27** by peracetic acid followed by transannular C-H insertion of the lithium carbenoid generated by lithiation with Et_2NLi in Et_2O gave access to approx. 40 g of desired bicyclic alcohol **28**. Enzymatic resolution of 20 g of **28** using amano AK lipase and succinic anhydride as the acylating agent furnished both enantiomers by the means of a simple liquid-liquid extraction procedure. Compound (–)-**28** was then oxidized to the corresponding enone **30** with IBX in hot DMSO. Stereoselective epoxidation with *tert*-BuOOH and catalytic DBU proceeded as expected at the convex face yielding the keto epoxide **31**.

The stereoselective reduction of the ketone group was accomplished with $LiAlH_4$ at –78 °C. The trajectory of the attack was directed by the epoxide to the concave face furnishing *cis*-epoxy alcohol **33** after protection. The reductive ring opening of the epoxide proved also to be regioselective and occurred at the more accessible remote carbon from the ring fusion providing access to 1,3-diol **32** when allowing the temperature to rise slowly to room temperature. Remarkably, derivatives **32** or **33** are the first intermediates to be purified by silica gel chromatography and up to 4 g of **32** or 8 g of **34** can be prepared in one batch from 8 g of (–)-**28**. An interesting feature of this approach is the chemoselective ketone reduction of **31** in the presence of the epoxide allowing orthogonal protection leading to compound **34**, from which either the E- or the D-series of IsoPs can be approached.

This strategy was initially validated by providing 15-F_{2t}-IsoP and its 15-epimer (not shown)[31]. It proved more valuable to access 5-F_{3t}-IsoP (Scheme 7)[32]. Starting point was the enantiomer of **32** derived from (+)-**28**. Its exhaustive TBS protection and subsequent ozonolysis with reductive workup produced diol **35**, which was oxidized regioselectively to lactone **37** in 91% yield in a 98:2 ratio by using iridium catalyst **36** (ref.[33]). Dibal-H reduction to the corresponding lactol followed by introduction of the ω-chain by a Wittig reaction with phosphonium salt **38** and *t*-BuOK in THF gave dienylcyclopentane **39** in 64% yield. The α-chain was appended in 85% yield by a two-step sequence of Dess-Martin oxidation and a HWE reaction with β-ketophosphonate **40**. Diastereoselective reduction of the enone **41** using Noyori's (*S*)-BINAL-H reagent provided a mixture of the corresponding allylic alcohol and the 1,5-lactone (not shown) in a 1:1 ratio with good diastereomeric ratio for both (d.r. >95%). Deprotection of the



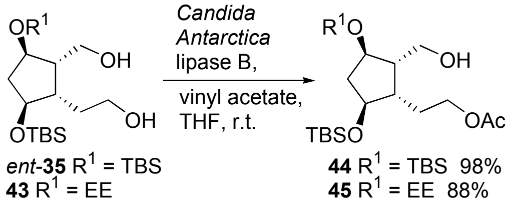
Scheme 6. **Access to bicyclo[3.3.0]octendiol intermediates on large scale**



Scheme 7. **Access to 5-F$_{3t}$-IsoP based on bicyclo[3.3.0]octendiol**

TBS groups under acidic conditions and subsequent basic hydrolysis of the methyl ester and lactone units gave 5-F$_{3t}$-IsoP **42** in poor 6% yield because the final steps were not optimized. 5-F$_{3t}$-IsoP can be obtained in a higher overall yield (*vide infra*), however, this synthesis permitted to clarify the absolute stereochemistry at C5 for the first time.

A drawback of the bicyclic approach became clear, when confronted with the introduction of more complex and sensitive side chains. The rather poor reactivity of the lactol derived from **37** did not permit to use complex skipped diene or diyne phosphonium salts for the introduction of the ω-chain in the Wittig reaction.



Scheme 8. **Regioselective lipase-catalyzed monoacetylation of unsymmetrical primary 1,5-diols**

In order to overcome this limitation, a novel methodology for the enzymatic monoprotection of unsymmetrical primary 1,5-diols using *Candida antarctica* lipase (CALB) was found, which proceeded with high selectivity and complete regiocontrol (Scheme 8)[34]. For example, monoacetate **44** obtained in 98% from diol *ent*-**35** served well to introduce complex side chains bearing skipped dienes or diynes (*vide infra*, Scheme 24). The orthogonally protected acetate intermediate **45** was similarly obtained from diol **43** and allowed access to the challenging first syntheses of 15-D_{2t}-IsoP **46** together with 15-*epi*-15-E_2-IsoP **47** (Figure 1)[35]. This methodology was also used in a synthesis of 17-F_{2t}-dihomo-IsoP **48** and *ent*-7-*epi*-7-F_{2t}-dihomo-IsoP **49** derived from adrenic acid (AdA)[32,36].

Helmchen's Synthesis

Helmchen et al. described a short diastereoselective synthesis of all-*cis*-Corey lactone and employed it for the total syntheses of *ent*-5-F_{2c}-IsoP and *ent*-5-*epi*-5-F_{2c}-IsoP (Scheme 9)[37]. A seven step sequence starting with a Diels-Alder reaction of chiral fumarate **50** and cyclopentadiene followed by an iodolactonization provided lactone **51**, which was transformed to enantiopure carboxylic acid **52** (ref.[38]) in 53% overall yield. *exo*-Chloronorbornane derivative **53** was prepared by selective cyclopropane ring opening of **52** by treatment with HCl, from which two pathways for the synthesis of bicyclic lactone **56** were explored. On path A lactone **54** was obtained by a Baeyer-Villiger oxidation of **53**, which was converted to **56** by a chemoselective reduction of the carboxylic acid *via* a mixed anhydride and translactonization. Alternatively, on route B the order of reduction and rearrangement was reversed. The mixed anhydride obtained from carboxylic acid **53** and ethyl chloroformate was chemoselectively reduced with zinc borohydride, giving alcohol **55** in 85% yield. Subsequent Baeyer-Villiger oxidation afforded lactone **56**. The secondary alcohol function was protected as a PMB-ether **57** by treatment with *p*-methoxybenzyl trichloroacetimidate in

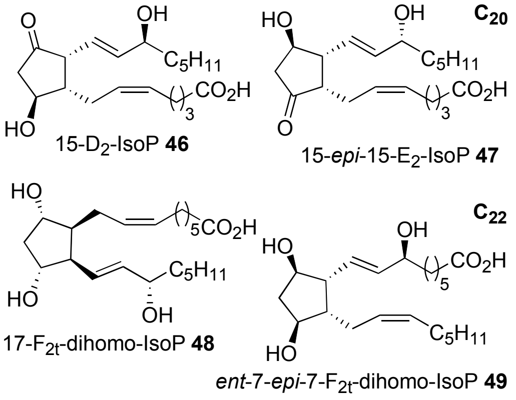
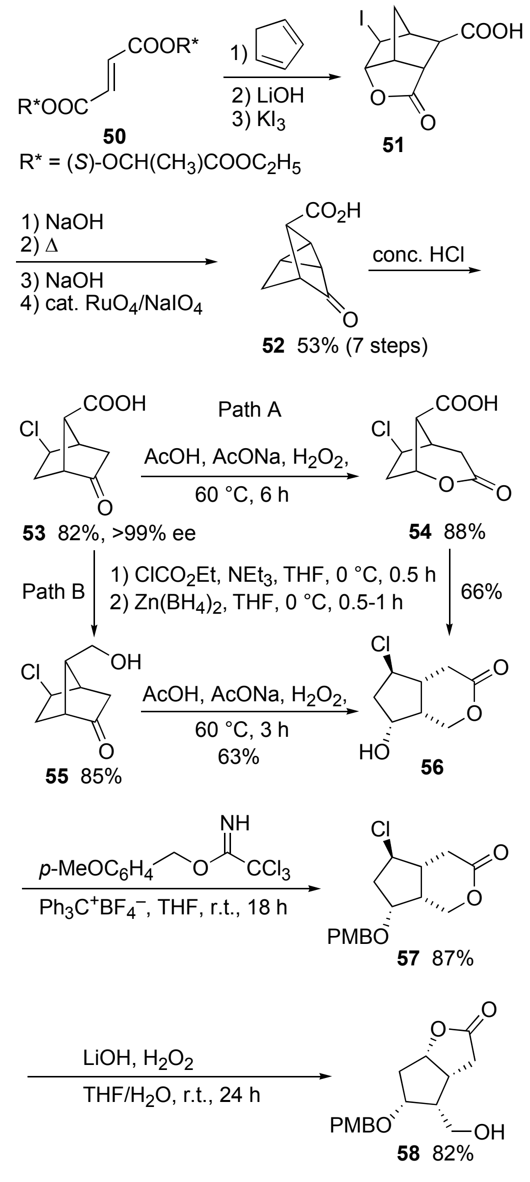


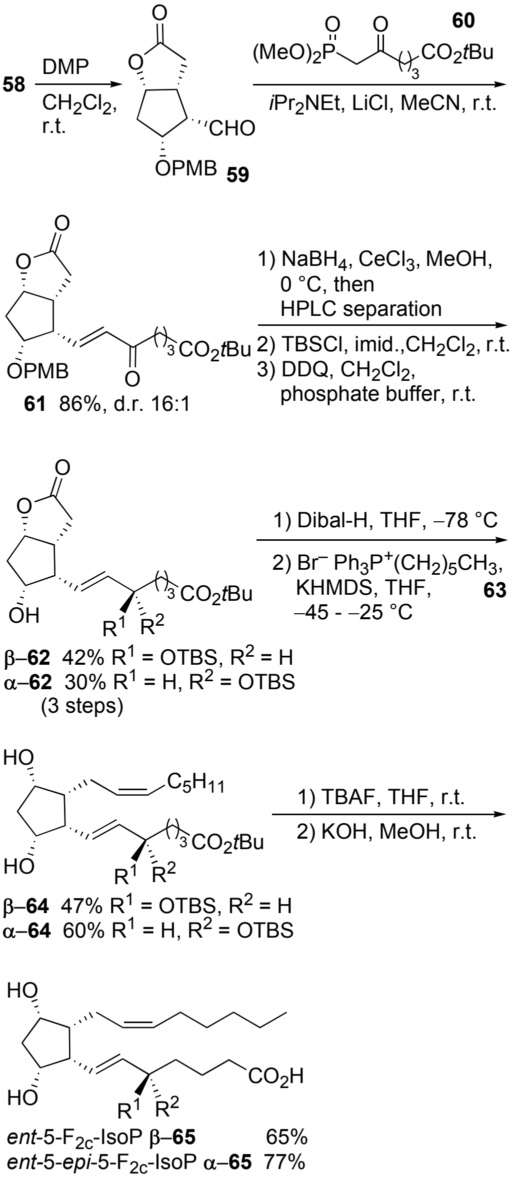
Fig. 1. **IsoPs obtained from Durand's bicyclo[3.3.0]octene precursors**



Scheme 9. **Helmchen's synthesis of all-*cis*-Corey lactone 58**

the presence of a catalytic amount of triphenylmethyl tetrafluoroborate. Lactone saponification and subsequent nucleophilic substitution yielded 82% of Corey lactone isomer **58** (ref.[39,40]).

Aldehyde **59** was prepared by a Dess-Martin oxidation of lactone **58** and submitted crude to a HWE olefination with β-keto phosphonate **60** using the Masamune-Roush protocol[41] providing lactone **61** in 86% yield and 16:1 *E/Z*-selectivity (Scheme 10). Luche reduction of **61** gave a mixture of diastereomeric alcohols, which were separated by preparative HPLC. Their esterification with (*S*)-or (*R*)-*O*-methylmandelic acids, respectively, and analysis of the ^{1}H NMR spectra of the resulting esters allowed

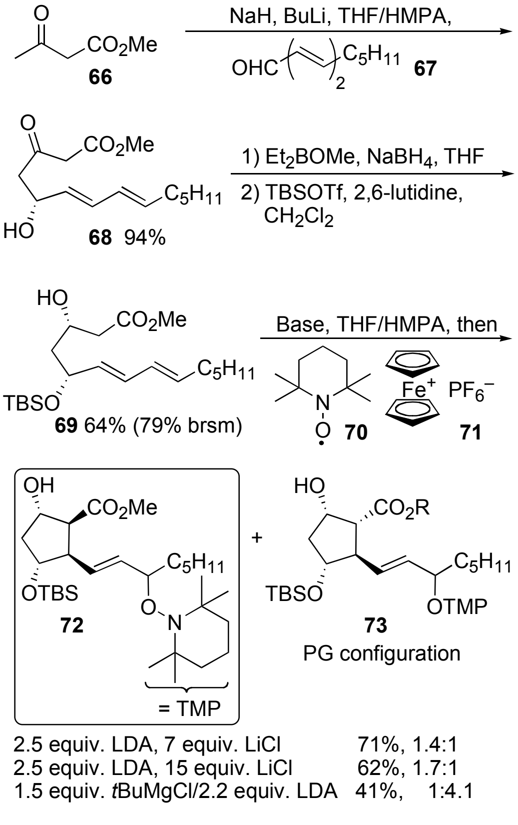


Scheme 10. **Total synthesis of *ent*-5-F$_{2c}$-IsoP and its 5-epimer**

the unambiguous assignment of the C5-configuration (not shown). The hydroxy group at C5 was protected as a TBS ether and the PMB group was oxidatively deprotected with DDQ affording diastereomers **β-62** and **α-62**. The introduction of the C14-C20 unit was accomplished in two steps consisting of mild reduction of the lactone to the lactol, and subsequent Wittig olefination with phosphonium salt **63**. Finally, the TBS-groups in **β-64** and **α-64** were deprotected and the ester units were saponified providing the diastereomeric *ent*-5-F$_{2c}$-IsoP **β-65** and *ent*-5-*epi*-5-F$_{2c}$-IsoP **α-65** after 12 linear steps in an overall yield of 4% for each from carboxylic acid **52**.

Jahn's Syntheses

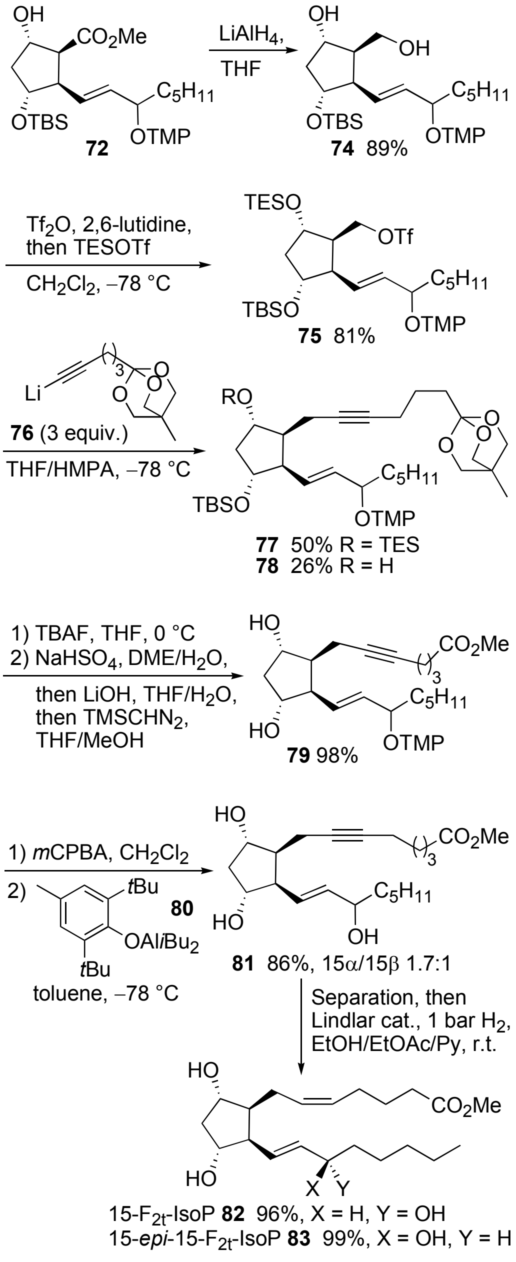
Jahn et al. reported a new strategy, comprising an oxidative radical anion cyclization/oxygenation methodology and the introduction of the α-chain by linking C6-C7 *via* an acetylide alkylation reaction[42]. The total syntheses started with a vinylogous aldol addition of methyl acetoacetate **66** and (*E*,*E*)-decadienal **67** (Scheme 11). The almost quantitatively isolated product **68** was *syn*-selectively reduced and the resulting diol was regioselectively protected giving cyclization substrate **69** in good yield. The dianion of **69** was generated under diverse deprotonation con-



Scheme 11. **Jahn's oxidative cyclization to cyclopentanecarboxylates**

ditions and submitted to tandem oxidative 5-exo cyclization/oxygenation triggered by single-electron oxidation by ferrocenium hexafluorophosphate **71** and subsequent oxygenation by TEMPO **70**. The cyclization was stereodivergent depending on the deprotonation conditions, giving a moderate excess of either cyclopentanecarboxylate **72** with IsoP configuration or **73** with PG configuration, which were separable by flash chromatography.

Methyl cyclopentanecarboxylate **72** was reduced with $LiAlH_4$ and the resulting diol **74** was converted to the triflate **75** by a one-pot *O*-triflation and TES protection (Scheme 12). The α-chain was appended subsequently by alkylation of an excess orthoester lithium acetylide **76** with **75**, affording the full C20 skeletons **77** and **78** in 76% combined yield. Methyl ester **79** was obtained almost quantitatively from this mixture by a sequence of deprotection of the silyl groups, hydrolysis of the orthoester, saponification and esterification. The tetramethylpiperidinyl group was subsequently oxidatively removed with *m*CPBA leading to a keto function in 15-position, which was reduced by Yamamoto's reagent **80** to a mixture of 15α/β-**81** in a 1.7:1 ratio. After separation by flash chromatography, a quantitative Lindlar hydrogenation in ethanol/ethyl acetate gave 15-F_{2t}-IsoP **82** and 15-*epi*-15-F_{2t}-IsoP **83**, respectively, in an overall yield of 14% over 12 steps for the sum of both diastereomers.

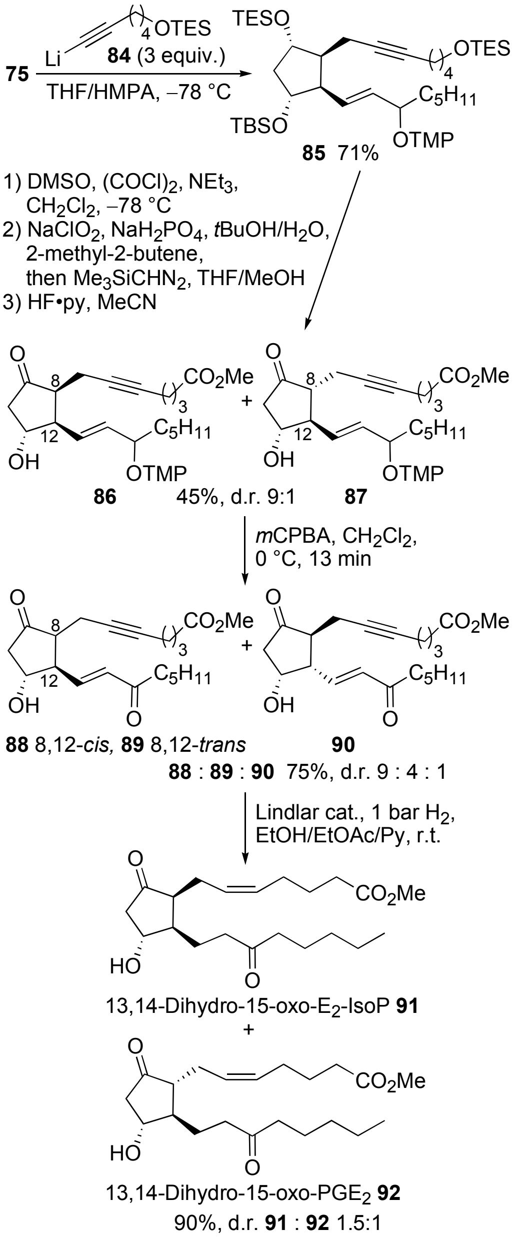


Scheme 12. **Completion of the total synthesis of 15-F_{2t}-IsoP and its 15-epimer**

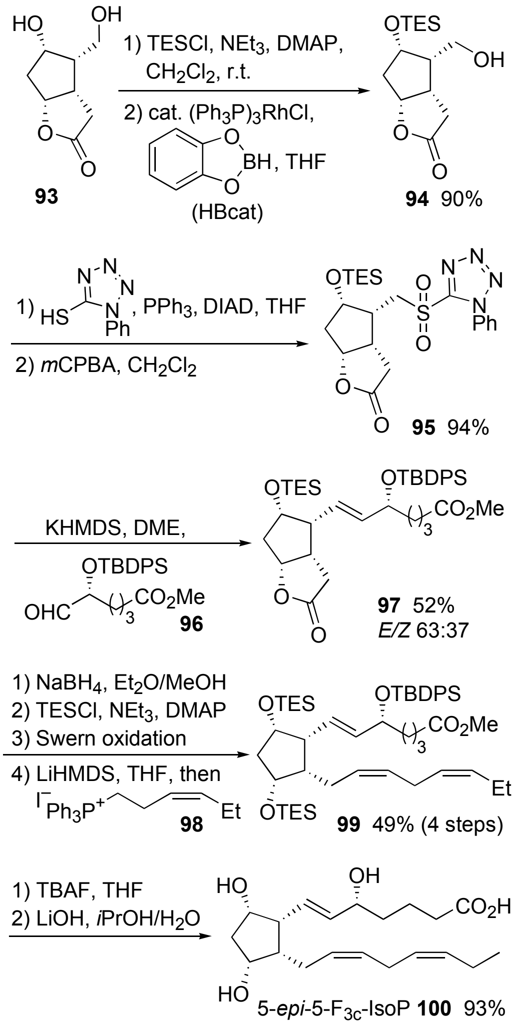
This methodology was adapted for the synthesis of potential metabolites of 15-E_2-IsoP, 13,14-dehydro-15-oxo-E_2-IsoP and 13,14-dehydro-15-oxo-PGE_2 (ref.[43]). Here, the α-chain was introduced in high yield by alkylation of lithium acetylide **84** with triflate **75** (Scheme 13). With the C20 precursor **85** in hand, the functional groups were adjusted as follows: both triethylsilyloxy groups were oxidized under Swern conditions to an intermediate keto aldehyde[44], which was subjected to a Pinnick oxidation to the corresponding keto acid and transformed into the methyl ester. Mild deprotection of the TBS group by the pyridine•HF complex gave cyclopentanone esters **86** and **87** with little epimerization at the very sensitive 8-position. Oxidative removal of the tetramethylpiperidinyl group with *m*CPBA afforded enones **88**, **89** and **90** in 75% yield in a 9:4:1 ratio. Considerable epimerization occurred at 8-position, and little also at the 12-position. The total synthesis of **91** and **92** was accomplished by Lindlar hydrogenation of the mixture of **88**–**90**, during which further epimerization at the 8-position occurred. Metabolites 13,14-dehydro-15-oxo-E_2-IsoP **91** and 13,14-dehydro-15-oxo-PGE_2 **92** were isolated in a 1.5:1 ratio. The synthesis revealed the high susceptibility of 15-E_2-IsoP derivatives towards epimerization under slightly acidic or basic conditions, suggesting a common pathway of 15-E_2-IsoP and PGE_2 metabolism. Metabolites **91** and **92** were obtained in 11 steps and 1.4% overall yield.

Rokach's Syntheses

In 2008, Rokach et al. complemented their impressive number of IsoP and NeuroP metabolites by synthesizing the major metabolites of EPA, 5-F_{3c}-IsoP and its C5 epimer[45]. They previously showed that 5-F_{3t}-IsoP is stable *in vivo* and does not significantly metabolize[46]. In this new report they showed that both epimers of the all-*cis*-series are the most abundant F_3-IsoP metabolites in urine. The synthesis of 5-*epi*-5-F_{3c}-IsoP started from their central precursor, the dihydroxy lactone **93** (Scheme 14)[47]. After exhaustive TES protection of the alcohol units, the primary TES ether was selectively deprotected to lactone **94** in excellent yield using their Rh-catalyzed catechol borane procedure[48]. Two further steps, namely a Mitsunobu-type substitution followed by an *S*-oxidation afforded the desired 1-phenyl-1*H*-tetrazol-5-yl sulfone **95** in 94% yield, which was coupled *via* the Kocienski-modified Julia olefination with enantiopure aldehyde **96**. Lactone **97** was obtained in 52% yield after separation of the initial 2:1 (*E/Z*)-mixture.



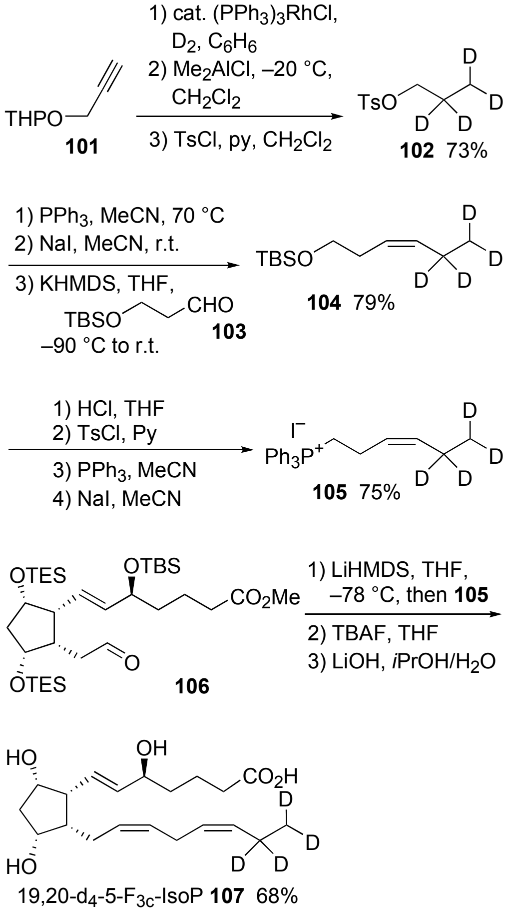
Scheme 13. **Synthesis of potential 15-E_2-IsoP metabolites**



Scheme 14. **Rokach's approach to 5-*epi*-5-F_{3c}-IsoP**

Compound **97** was subsequently transformed in four steps to the C20 derivative **99**. These included reduction of the lactone to the corresponding diol, bis-TES protection, a concomitant selective deprotection of the primary TES ether function and Swern oxidation. The obtained aldehyde was coupled with the (*Z*)-3-hexenyl Wittig reagent giving **99** in 49% yield. Complete deprotection of the silyl ethers with TBAF and saponification yielded 5-*epi*-5-F_{3c}-IsoP **100** in 93% yield over two steps. This total synthesis proceeded in 11 steps and 20% overall yield starting from **93**, which was obtained in gram quantity in 8 additional steps.

Recently, the group described a significant improvement[49] of a previous access[50] to tetradeuterated 5-F_{3c}-IsoP derivatives. It started from the propargyl tetrahydropyranyl ether **101** (Scheme 15), which was treated with deuterium gas in the presence of Wilkinson's catalyst to generate the tetradeuterated THP ether, from which the low-boiling volatile three-carbon alcohol was liberated on treatment with Me_2AlCl. The crude alcohol was treated with TsCl to generate the stable and high-boiling tosylate **102**. Treatment with triphenylphosphine in CH_3CN generated the



Scheme 15. **Rokach's improved synthesis of deuterated 5-F_{3c}-IsoP derivatives**

corresponding phosphonium tosylate. An anion exchange to the corresponding phosphonium iodide with NaI was necessary to obtain a better yield in the following Wittig reaction with aldehyde **103** (85% yield compared to 22–38% yield with the tosylate). (*Z*)-Olefinic deuterated silyl ether **104** was transformed to phosphonium iodide **105** *via* deprotection of TBS group, tosylation, reaction with triphenylphosphine and another anion exchange with NaI in 75% yield over 4 steps. The synthesis of 19,20-d_4-5-F_{3c}-IsoP **107** was achieved by coupling **105** and aldehyde **106**, which was obtained as described before (*cf.* Scheme 14), TBS deprotection and saponification.

Snapper's Synthesis

Snapper et al. developed a stereodivergent route to a library of all eight enantiomerically enriched 5-F_2-IsoPs **108** (Fig. 2)[51]. The approach is based on previous total syntheses of 15-F_{2t}-IsoP isomers[52–55].

The relative ring stereochemistry was set by *exo*- and *endo*-4-(*tert*-butyldimethylsilyloxy)bicyclo[3.2.0]hept-7-ene-2-ols *exo*-**109a** and *endo*-**109b** (Scheme 16). They were subjected individually to a ring-opening metathesis applying the Grubbs I catalyst **110** in the presence of ethylene. The resulting racemic divinylcyclopentane **111** and its all-*cis*-diastereomer (not shown) underwent cross-metatheses with enone **113** using the Hoveyda-Grubbs II catalyst **112** affording dienones **114** or **115** with the entire α-chain.

The secondary alcohol in (±)-**114** was temporarily protected as a TMS ether and the resulting enone was enantioselectively reduced by the (*R*)-CBS catalyst (*R*)-**116** in the presence of catechol borane, providing diastereomers (+)-**117a** and (+)-**117d**, which were separated by chromatography (Scheme 17). Employing the (*S*)-CBS catalyst (*S*)-**116**, diastereomers (–)-**117b** and (–)-**117c** were similarly prepared.

For the obtained diastereomers **117a-d** the secondary alcohol functions were protected as TBS ethers as exemplified for (+)-**117a** (Scheme 18). Hydroboration/oxidation of the terminal olefin afforded the primary alcohol, which was subjected to a one-pot oxidation/Wittig reaction with hexylphosphonium ylide. Global deprotection with TBAF and saponification yielded 5-F_{2t}-IsoP **108a** in 4.3% overall yield from bicyclo[3.2.0]heptene *exo*-**109a**. The 5-F_{2c}-IsoP precursor (±)-**115** was converted similarly, thus all eight 5-F_2-IsoPs **108a-h** were accessed in a stereodivergent manner from *exo*- or *endo*-**109** in 7–8 steps in overall yields of 4.3–13%.

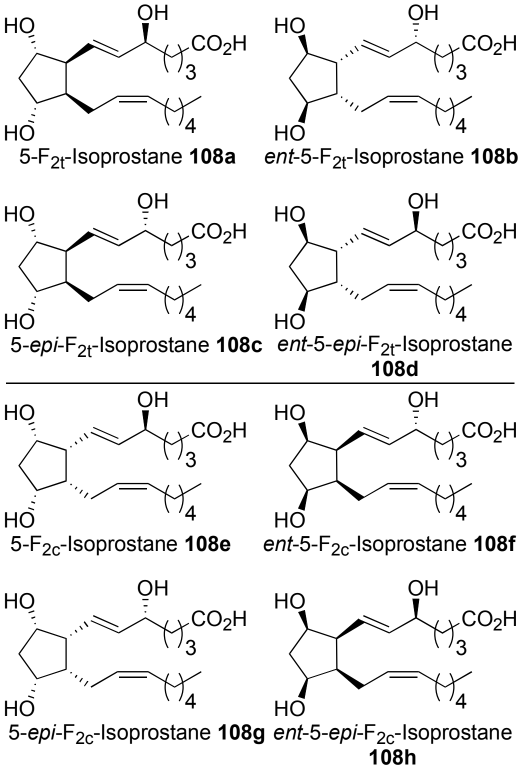
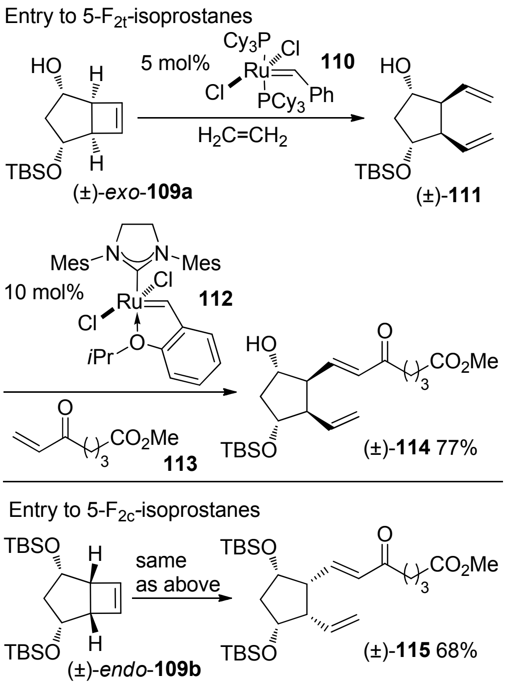
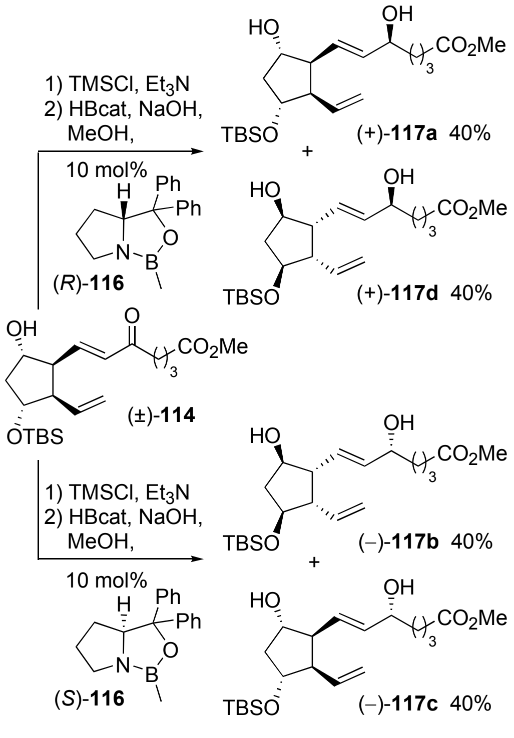


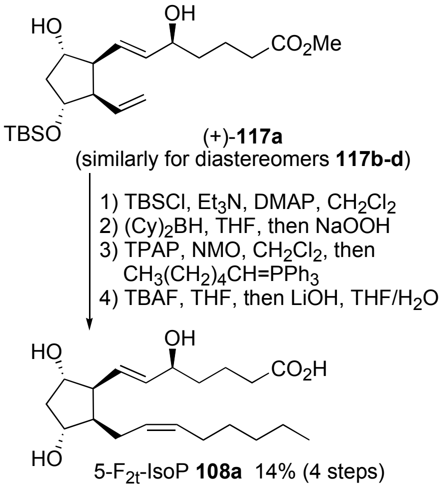
Fig. 2. **The eight diastereomeric 5-F_2-IsoP**



Scheme 16. **Approach to the 5-F$_{2t}$- and 5-F$_{2c}$ cyclopentane cores**



Scheme 17. **Enantiodivergent reduction of racemic enone 114**

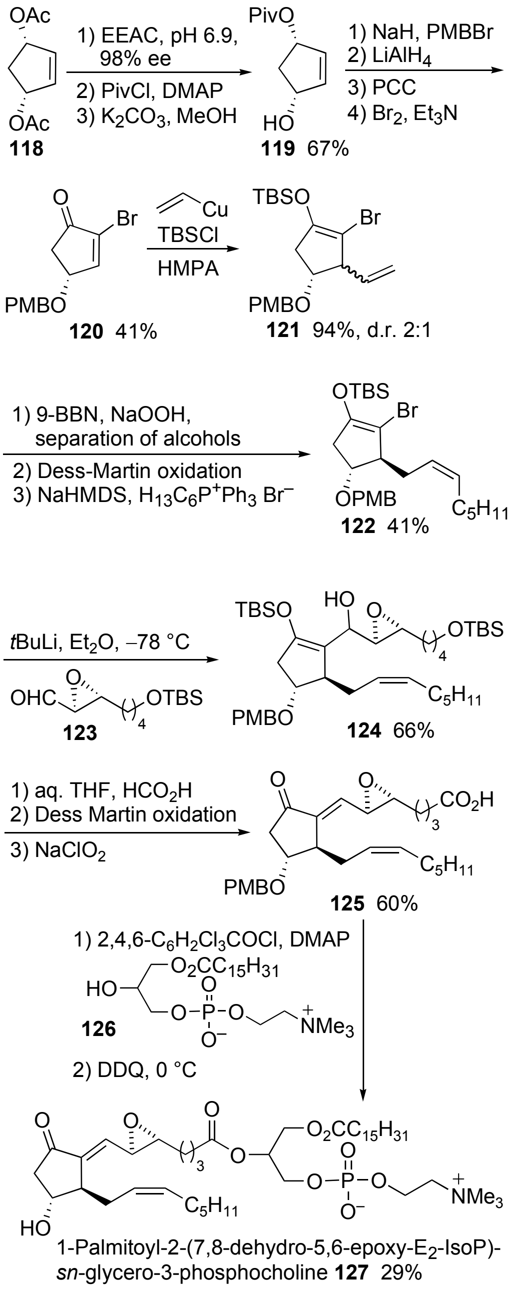


Scheme 18. **Completion of the total syntheses of the diastereomeric 5-F$_2$-IsoPs 108**

4. Epoxy-Isoprostane Syntheses

Jung's Synthesis

E$_2$-Epoxyisoprostane phospholipid (PEIPC) **127** has important biological activities related to atherosclerosis (Scheme 19). The total synthesis of **127** was initially achieved in 2005 (ref.[56]), but was recently significantly improved[57]. Chiral pivalate **119** was prepared from *meso*-diacetate **118** by enzymatic deacetylation with electric eel acetylcholine esterase (EEAC), protection with pivaloyl chloride and saponification of the remaining acetyl group in 67% yield[58]. Pivalate **119** was converted uneventfully to 2-bromocyclopentenone **120** in 41% yield in four steps, namely protection of the free alcohol as a PMB ether, reductive deprotection of the pivalate, oxidation of the alcohol to the ketone by PCC, and α-bromination. The introduction of the C12-C13 unit was accomplished by a 1,4-addition of vinylcopper to enone **120** in the presence of TBSCl to afford an inseparable 2:1 *trans/cis* mixture of enol ethers **121**. Hydroboration/oxidation of the terminal olefin afforded a separable mixture of terminal alcohols, which were individually converted to the aldehydes by a Dess-Martin oxidation. The ω-chain was attached by a Wittig reaction, affording the C8–C20 subunit **122**. The introduction of the α-chain was accomplished by a lithium-halogen exchange in **122**, followed by the nucleophilic addition to chiral aldehyde **123** furnishing the C20 compound **124**. A one-pot deprotection of the silyl enol ether and subsequent dehydration at the C7–C8 position, followed by a two-step oxidation of the terminal alcohol gave epoxy acid **125**. Treatment of the free acid with commercially available 1-lysophosphatidylcholine **126** as previously described[56] and subsequent oxidative deprotection of the PMB group gave 1-palmitoyl-2-(5,6-epoxy-7,8-

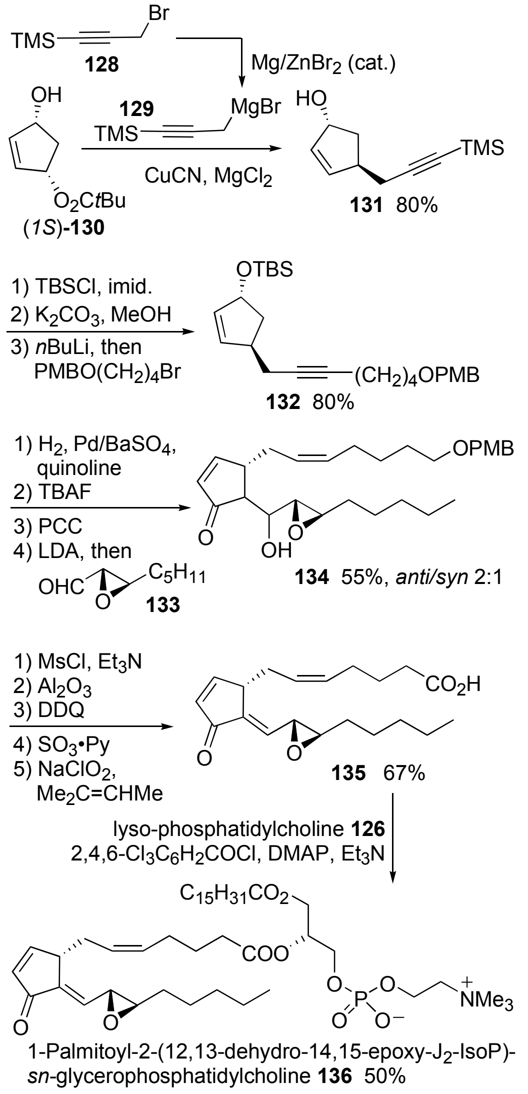


Scheme 19. **Jung's total synthesis of 5,6-epoxy-E$_2$-IsoP**

dehydro-E$_2$-IsoP)-*sn*-glycero-3-phosphocholine **127** after 17 linear steps in 0.8% overall yield from *meso*-diacetate **118**.

Kobayashi's Synthesis

Kobayashi et al. reported the total synthesis of 12,13-dehydro-14,15-epoxy-J$_2$-IsoP palmitoylphosphatidyl choline **136** (ref.[59]), which started with the ZnBr$_2$-catalyzed formation of propargylic Grignard reagents such as **129** from TMS-protected propargylic bromide **128** (Scheme 20)[60]. A copper-promoted allylic substitution of enantiopure monoester (*1S*)-**130** gave acetylene **131**. The alcohol was subsequently protected as a TBS ether, the trimethylsilyl group at the alkyne was cleaved by K$_2$CO$_3$ and the free alkyne was after deprotonation alkylated with the corresponding benzyloxybutyl bromide furnishing substituted silyloxy cyclopentene **132** with the complete C1–C7 alkyl chain. A Lindlar hydrogenation of the alkyne unit, deprotection of the silyl ether group and oxidation of the free alcohol set the stage for the crucial aldol addition, which was performed by kinetic deprotonation of the cyclopentenone by LDA and addition of epoxy aldehyde **133.** The resulting aldol adduct **134** was obtained as a 2:1 *anti/syn* mixture at the newly formed stereocenters in 55%



Scheme 20. **Kobayashi's synthesis of epoxy-J$_2$-IsoP**

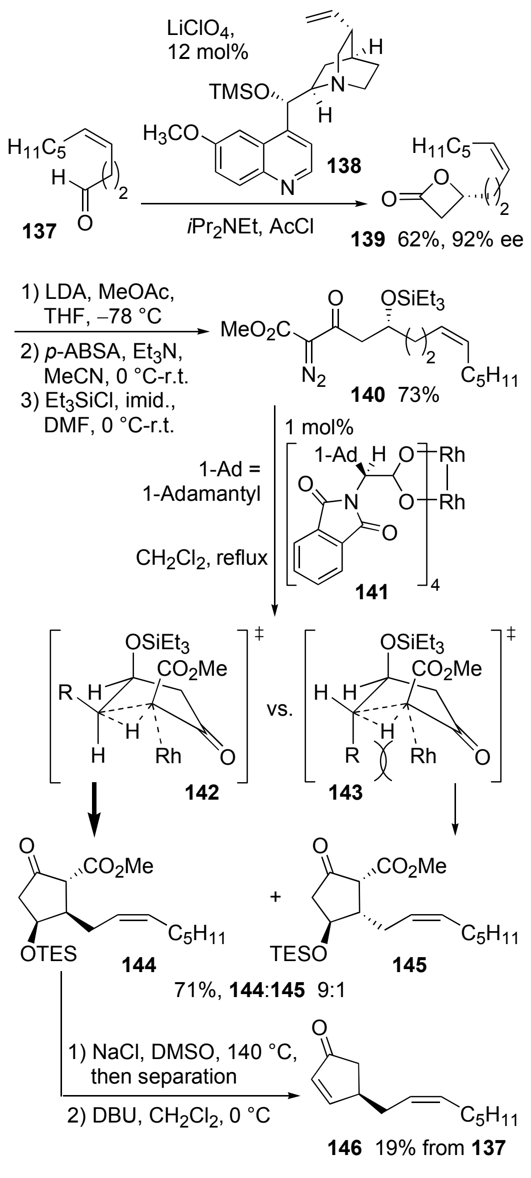
yield over the four steps. The functionality of the C20 precursor was subsequently adjusted by dehydration at the C12–C13 positions, oxidative deprotection of the PMB group with DDQ, and a two-step oxidation of the terminal alcohol providing free 12,13-dehydro-14,15-epoxy-J$_2$-IsoP **135**. A Yamaguchi esterification with commercially available lyso-1-palmitoyl-phosphatidylcholine furnished the desired target molecule **136** over 14 steps in 12% yield from cyclopentenol **130**.

Carreira's Synthesis

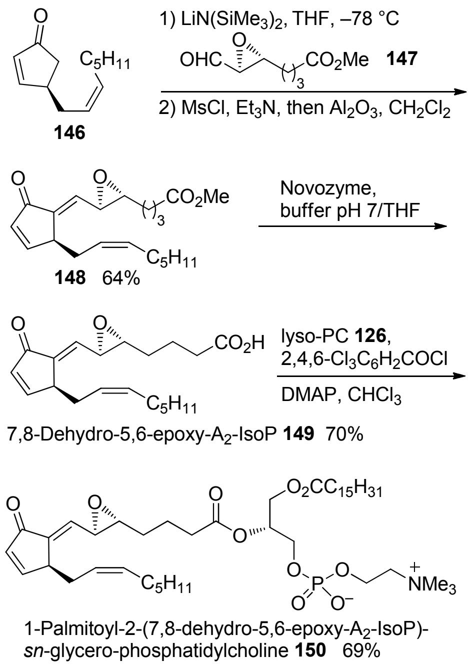
Carreira published most recently total syntheses of 7,8-dehydro-5,6-epoxy-A$_2$-IsoP, 7,8-dehydro-5,6-epoxy-E$_2$-IsoP and their phosphatidylcholine esters[61]. The synthesis commenced with the preparation of β-lactone **139** from (*Z*)-4-decenal **137** by an asymmetric [2+2] ketene-aldehyde cycloaddition catalyzed by modified cinchona catalyst **138** under Nelson conditions[62]. A Claisen condensation with methyl acetate yielded a δ-hydroxy-β-ketoester, which was subjected to diazo transfer with *p*-acetamidobenzenesulfonyl azide (ABSA) and protection of the hydroxy group giving diazo ester **140** in 73% yield. A 1,5-C-H insertion catalyzed by [Rh$_2$(*S*-PTAD)$_4$] **141** afforded cyclopentanone carboxylates **144** and **145** in 71% yield with 9:1 11,12-*cis:trans* selectivity. (For the application of Rh-catalyzed intramolecular cyclopropanations of α-diazoketones in the total syntheses of IsoP see ref.[5]).

The diastereoselectivity of the C-H insertion can be rationalized by a preferred transition state **142**, in which the bulky rhodium catalyst and the alkyl chain are in a favorable *trans*-orientation as supposed to the minor isomer, which may arise *via* transition state **143**. The initially 8,11-*cis*-oriented methyl cyclopentanone carboxylate epimerized at the 8-position, giving the thermodynamically more stable cyclopentanone carboxylates **144** or **145**. Cyclopentenone **146** with full ω-chain was prepared by Krapcho decarboxylation to the corresponding β-silyloxy cyclopentanone, which allowed separation of the C11-C12 *cis*- and *trans*-diastereomers, and subsequent elimination of the silanol group by DBU.

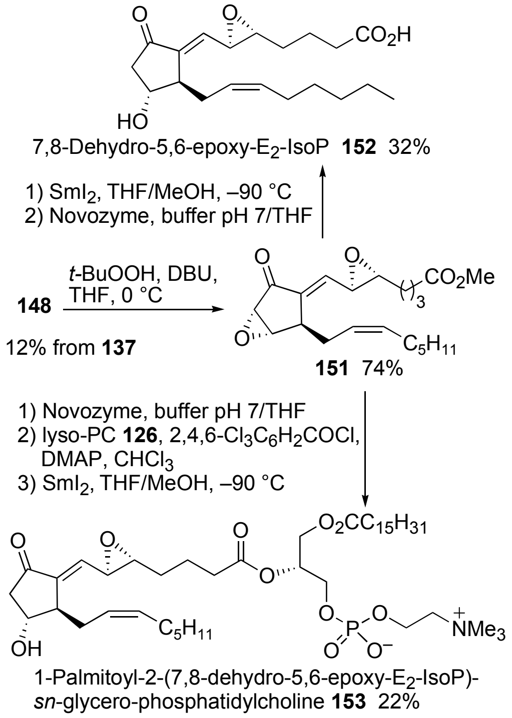
The assembly of the C1-C8-chain was accomplished by a modified Kobayashi approach[63] using a base-mediated aldol addition of **146** with 2,3-epoxyaldehyde



Scheme 21. **Carreira's synthesis of the epoxy-IsoP C8-C20 subunit 146**



Scheme 22. **Completion of the total synthesis of 7,8-dehydro-5,6-A$_2$-IsoP phosphatidylcholine**



Scheme 23. **Epoxy-E_2-IsoP from epoxy-A_2-IsoP**

147 (Scheme 22). Dehydration of the C7-C8 position provided epoxy-A_2-IsoP methyl ester **148**. Its enzymatic hydrolysis gave the free 7,8-dehydro-5,6-epoxy-A_2-IsoP **149**, which was transformed to 1-palmitoyl-2-(7,8-dehydro-5,6-epoxy-A_2-IsoP)-*sn*-glycero-phosphatidylcholine **150** by treatment with lyso-PC **126** under Yamaguchi esterification conditions. Hence, **149** was synthesized over 10 linear steps in 7.8% yield from (*Z*)-4-decenal **137**, whereas **150** was assembled in 11 linear steps and 5.4% yield.

The epoxidation of the ring double bond of **148** in the presence of the exocyclic double bond using *tert*-butyl hydroperoxide and DBU occurred selectively, giving diepoxide **151** as a single diastereomer in 74% yield. Reductive opening with SmI_2 furnished the β-hydroxy cyclopentanone regioselectively in 54% yield. Subsequent enzymatic ester hydrolysis afforded 7,8-dehydro-5,6-epoxy-E_2-IsoP **152**, which was prepared in 12 linear steps and 2.7% yield from **137**. In contrast, initial ester hydrolysis of **151** followed by esterification with lyso-PC **126** and subsequent reduction of the epoxide with SmI_2 gave 1-palmitoyl-2-(7,8-dehydro-5,6-epoxy-E_2-IsoP)-*sn*-glycero-phosphatidylcholine **153** in 22% yield for the three steps. Hence the total synthesis of **153** was accomplished in 13 linear steps and 1.8% overall yield.

5. Total Syntheses of NeuroP

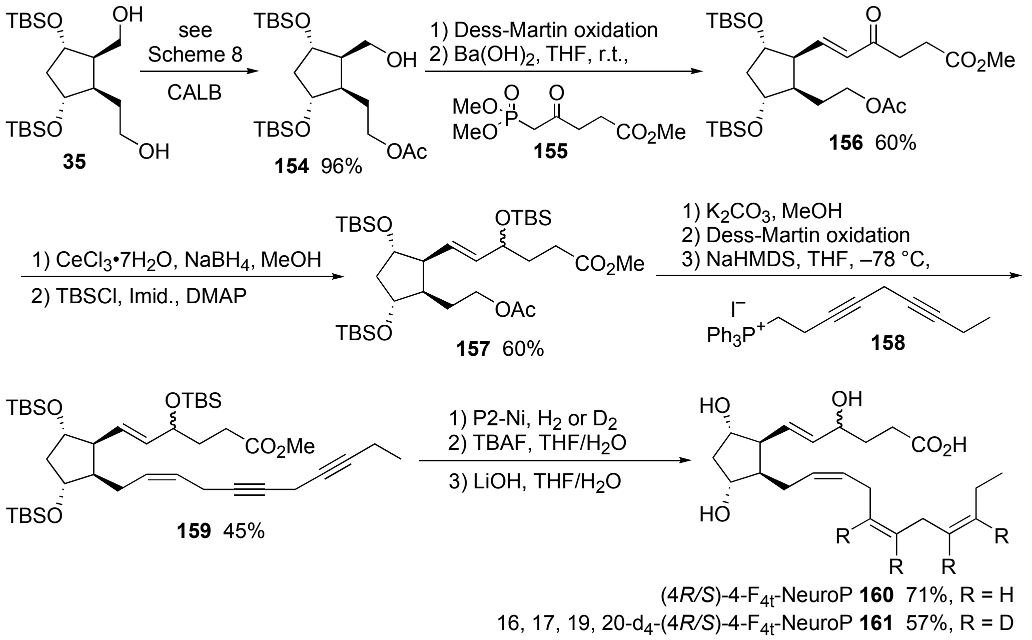
The Galano-Durand Syntheses

The convenient enzymatic access to monoprotected diols (*vide supra*, Scheme 8) permitted the total synthesis of more challenging isoprostanoids having skipped triene or triyne side chains as illustrated by a synthesis of (4*R/S*)-4-F_{4t}-NeuroP **160** and its deuterated analog **161** (ref.[64]). Starting from diol **35**, the enzymatic monoacetylation provided monoacetate **154** in excellent yield. A Dess-Martin oxidation and a HWE olefination with β-keto phosphonate **155**, using the conditions developed by Paterson et al.[65], afforded enone **156** in 60% yield. A Luche reduction of **156** gave a mixture of diastereomeric alcohols, which were protected as TBS derivatives. Compound **157** was isolated in 60% yield over 2 steps. Saponification of the acetate group with K_2CO_3 in MeOH, followed by oxidation of the resulting alcohol and Wittig olefination using diynyl phosphonium salt **158** in the presence of NaHMDS at –78 °C gave the skipped enediyne precursor **159** in 45% yield over 3 steps. The crucial hydrogenation or deuteration of the skipped diyne unit was best performed by using P2-Ni (generated from $Ni(OAc)_2 \bullet 4H_2O$, $NaBH_4$, $NH_2CH_2CH_2NH_2$)[66] in order to avoid overreduction[67] and afforded the desired target molecules, (4*R/S*)-4-F_{4t}-NeuroP **160** and its tetradeuterated derivative **161**, after final deprotection of the silyl groups and saponification in 71% and 57% yield over 3 steps. Despite that the synthesis of (4*R/S*)-4-F_{4t}-NeuroP **160** required up to 20 steps in the longest linear sequence, the ease and scale-up options of this synthesis allowed to synthesize approx. 50 mg in one batch.

Compared to NeuroP partially reduced 7-F_{2t}-Dihomo-IsoP and 17-F_{2t}-dihomo-IsoP metabolites of adrenic acid (AdA) **48** and **49** were similarly synthesized (*cf.* Fig. 1)[32,36]. Other NeuroP derivatives have been very recently synthesized *via* this bicyclic strategy[68] because of the newly discovered anti-arrhythmic activity of 4(*R/S*)-4-F_{4t}-NeuroP, which will be published in due course.

Taber's synthesis

Taber et al. described a novel approach toward the synthesis of the four enantiomerically pure diastereomers of 13-F_{4t}-NeuroP (Scheme 25)[69]. The key step consisted of a thermal diastereoselective ene cyclization of 1,6-dienes to the 1,2-*cis*-cyclopentane skeleton based on the original discovery by Sarkar[70]. Starting from the well-known 2-cyclopentene-1,4-diaceate precursor **118** ozonolysis and a double Wittig homologation of the intermediate dialdehyde resulted in a clean conversion to the desired 1,6-diene **162** in 63% yield. A series of steps including deprotection of the acetate, silylation with TBDPSCl, monoepoxidation with *m*CPBA, oxidative epoxide cleavage, and a Horner-Wadsworth-Emmons reaction with phosphonoacetate furnished the precursor **163** for the ene reaction in a good 37% overall yield.

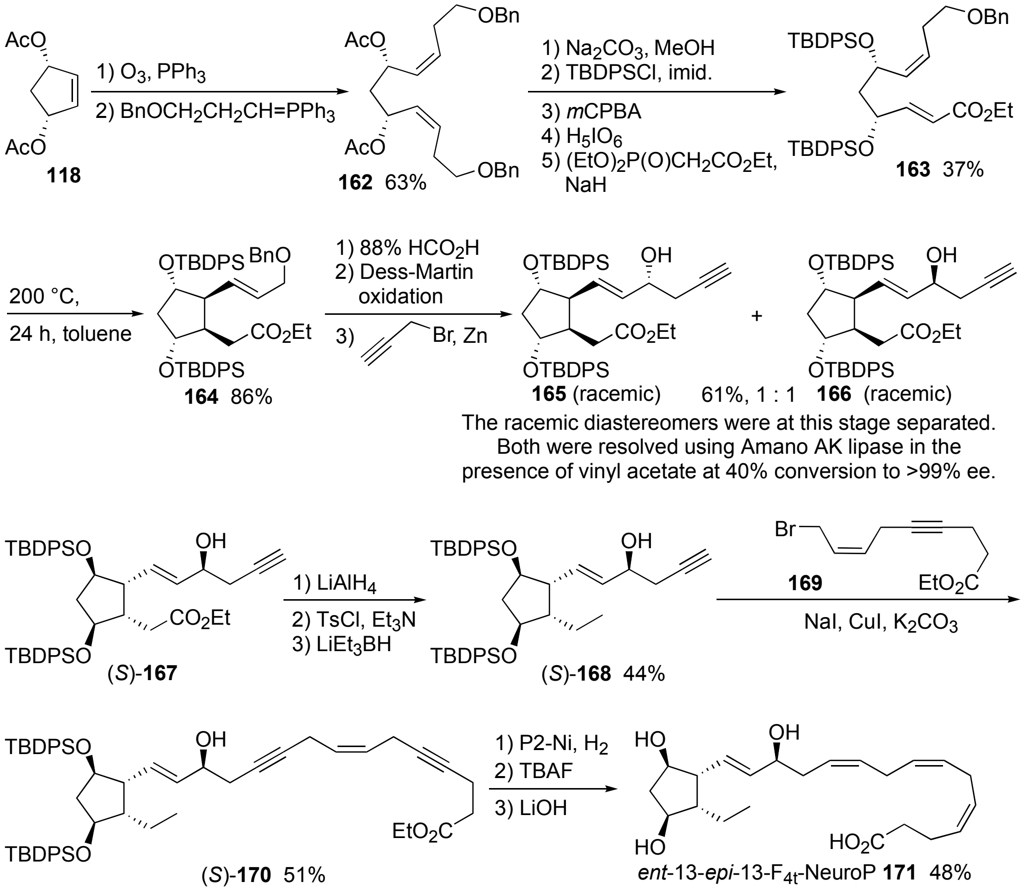


Scheme 24. **Durand's total synthesis of (4*R/S*)-4-F$_{4t}$-NeuroP and its deuterated analog**

Whereas the Lewis acid catalyzed variant of the ene reaction of **163** led to a mixture of *cis*- and *trans*-substituted cyclopentane isomers, the thermal ene reaction gave as predicted exclusively the *cis*-diastereoisomer **164** in 86% yield. Three further steps, namely benzyl ether deprotection, Dess-Martin oxidation and nucleophilic propargylation, provided the separable diastereoisomers **165** and **166**. An enzymatic resolution was carried out to access the four individual enantiomers, which served subsequently as central intermediates for the total syntheses of the individual 13-F$_{4t}$-NeuroP isomers. The further steps are illustrated for (*S*)-**167**. Three transformations served to reduce the ester function to the ethylcyclopentane (*S*)-**168** in 44% yield. Coupling of (*S*)-**168** with allylic bromide **169** provided the skipped 1,4,7-enediyne substrate (*S*)-**170** in 51% yield in a 3:1 ratio with the corresponding S$_N$2′ adduct (not shown). Semihydrogenation using P2-Ni afforded the desired (*Z*,*Z*,*Z*)-triene in 64% yield accompanied by a minimal trace of over-reduced products, which were easily separated. Interestingly, an analogous P2-Ni reduction with the corresponding triyne compound resulted in a complex mixture of products. Deprotection of the TBS ether and saponification of the ester unit by LiOH furnished *ent*-13-*epi*-13-F$_{4t}$-NeuroP **171** in 19 steps and 0.8% overall yield from **118**. The other three diastereoisomers were also obtained using this strategy, which is like Durand's limited to obtaining natural products with the *trans-cis-trans* ring stereochemistry, but furthermore so far also to F-type IsoPs and NeuroPs.

6. Conclusions and Outlook

The current review shows that the field of total synthesis of isoprostanes developed significantly over the last few years, since twenty diverse total syntheses were reported. A common trend is the increasing application of transition metal and enzymatically catalyzed key steps to provide enantiomerically enriched compounds. Many of the reported strategies involve new methodology to synthesize the cyclopentane ring selectively and with a desired ring substitution pattern. One or both side chains are appended subsequently by olefination or nucleophilic addition reactions. Many of the reported syntheses approach IsoP derivatives, but an increasing number of publications dealt with the synthesis of the least investigated class of oxidatively formed lipid metabolites, the neuroprostanes. For the future, it will be important to concentrate on more diversity-oriented synthetic strategies, which will allow the total synthesis of multiple ring-substituted IsoP classes by late-stage diversification of common precursors with the full C18, C20, and C22 skeletons. This will streamline the access to the available metabolites for biological studies even more.



The racemic diastereomers were at this stage separated. Both were resolved using Amano AK lipase in the presence of vinyl acetate at 40% conversion to >99% ee.

Scheme 25. **Taber's diastereoselective thermal intramolecular ene approach to NeuroP**

REFERENCES

1. *Oxidative Stress in Vertebrates and Invertebrates: Molecular Aspects of Cell Signaling* (Farooqui T., Farooqui A. A., eds.), Wiley-Blackwell, Hoboken 2012.
2. *Oxidative Stress: Diagnostics, Prevention, And Therapy* (Andreescu S., Hepel M., eds.), *ACS Symposium Series*, Vol. 1083 ACS Washington, DC 2011.
3. *Polyunsaturated Fatty Acids: Sources, Antioxidant Properties and Health Benefits* (Catalá A., ed.), Nova Science Publishers, Hauppauge, NY 2013.
4. *Lipid Peroxidation* (Catalá A., ed.), InTech, Rijeka 2012.
5. Jahn U., Galano J.-M., Durand T.: Angew. Chem. Int. Ed. *47*, 5894 (2008).
6. Yin H., Xu L., Porter N. A.: Chem. Rev. *111*, 5944 (2011).
7. Porter N. A.: J. Org. Chem. *78*, 3511 (2013).
8. *Prostaglandins: Biochemistry, Functions, Types and Roles* (Goodwin G. M., ed.), Nova Science Publishers, Hauppauge, NY 2010.
9. Das S., Chandrasekhar S., Yadav J. S., Gree R.: Chem. Rev. *107*, 3286 (2007).
10. *Prostaglandins, Leukotrienes and Essential Fatty Acids* (Horrobin D. F., Manku M. S., Sirois P., Borgeat P., eds.), Churchill Livingstone, Edinburgh 2002.
11. Marks F., Fürstenberger G.: *Prostaglandins, Leukotrienes, and Other Eicosanoids*, Wiley-VCH, Weinheim 1999.
12. Milne G. L., Yin H., Hardy K. D., Davies S. S., Roberts II L. J.: Chem. Rev. *111*, 5973 (2011).
13. Jahn U., Galano J.-M., Durand T.: Prostaglandins Leukotrienes Essent. Fatty Acids *82*, 83 (2010).
14. Galano J.-M., Mas E., Barden A., Mori T. A., Signorini C., De Felice C., Barrett A., Opere C., Pinot E., Schwedhelm E., Benndorf R., Roy J., Le Guennec J.-Y., Oger C., Durand T.: Prostaglandins Other Lipid Mediators *107*, 95 (2013).
15. Higdon A., Diers A. R., Oh J. Y., Landar A., Darley-Usmar V. M.: Biochem. J. *442*, 453 (2012).
16. *Biomarkers For Antioxidant Defense And Oxidative Damage: Principles And Practical Applications* (Aldini G., Yeum K.-J., Niki E., Russell R. M., eds.),

Blackwell, Ames 2010.
17. El Fangour S., Guy A., Vidal J.-P., Rossi J.-C., Durand T.: J. Org. Chem. *70*, 989 (2005).
18. Pinot E., Guy A., Guyon A.-L., Rossi J.-C., Durand T.: Tetrahedron: Asymmetry *16*, 1893 (2005).
19. Pinot E., Guy A., Fournial A., Balas L., Rossi J.-C., Durand T.: J. Org. Chem. *73*, 3063 (2008).
20. Mueller M. J.: Prostaglandins, Leukotrienes Essent. Fatty Acids *82*, 71 (2010).
21. Auvinet A.-L., Eignerová B., Guy A., Kotora M., Durand T.: Tetrahedron Lett. *50*, 1498 (2009).
22. Noyori R., Tomino I., Tanimoto Y., Nishizawa M.: J. Am. Chem. Soc. *106*, 6709 (1984).
23. Perlikowska W., Mikołajczyk M.: Synthesis *2009*, 2715.
24. Mikołajczyk M., Perlikowska W.: Synthesis *2007*, 1225.
25. Perlikowska W., Mikołajczyk M.: Tetrahedron: Asymmetry *22*, 1767 (2011).
26. Miura A., Kuwahara S.: Tetrahedron *65*, 3364 (2009).
27. Vázquez-Romero A., Cárdenas L., Blasi E., Verdaguer X., Riera A.: Org. Lett. *11*, 3104 (2009).
28. Vázquez-Romero A., Verdaguer X., Riera A.: Eur. J. Org. Chem. *2013*, 1716.
29. Iqbal M., Evans P., Lledó A., Verdaguer X., Pericàs M. A., Riera A., Loeffler C., Sinha A. K., Mueller M. J.: ChemBioChem *6*, 276 (2005).
30. Robert F., Milet A., Gimbert Y., Konya D., Greene A. E.: J. Am. Chem. Soc. *123*, 5396 (2001).
31. Oger C., Brinkmann Y., Bouazzaoui S., Durand T., Galano J.-M.: Org. Lett. *10*, 5087 (2008).
32. Oger C., Bultel-Poncé V., Guy A., Durand T., Galano J.-M.: Eur. J. Org. Chem. *2012*, 2621.
33. Suzuki T., Morita K., Tsuchida M., Hiroi K.: Org. Lett. *4*, 2361 (2002).
34. Oger C., Marton Z., Brinkmann Y., Bultel-Poncé V., Durand T., Graber M., Galano J.-M.: J. Org. Chem. *75*, 1892 (2010).
35. Brinkmann Y., Oger C., Guy A., Durand T., Galano J.-M.: J. Org. Chem. *75*, 2411 (2010).
36. De Felice C.; Signorini C., Durand T., Oger C., Guy A., Bultel-Poncé V., Galano J.-M., Ciccoli L., Leoncini S., D'Esposito M., Filosa S., Pecorelli A., Valacchi G., Hayek J.: J. Lipid Res. *52*, 2287 (2011).
37. Elsner P., Jetter P., Brödner K., Helmchen G.: Eur. J. Org. Chem. *2008*, 2551.
38. Helmchen G., Goeke A., Lauer G., Urmann M., Fries J.: Angew. Chem. Int. Ed. *29*, 1024 (1990).
39. Bindra J. S., Grodski A., Schaaf T. K., Corey E. J.: J. Am. Chem. Soc. *95*, 7522 (1973).
40. Veselý I., Kozmík V., Dědek V., Paleček J., Mostecký J., Stibor I.: Collect. Czech. Chem. Commun. *54*, 1683 (1989).
41. Blanchette M. A., Choy W., Davis J. T., Essenfeld A. P., Masamune S., Roush W. R., Sakai T.: Tetrahedron Lett. *25*, 2183 (1984).
42. Jahn U., Dinca E.: Chem. Eur. J. *15*, 58 (2009).
43. Jahn U., Dinca E.: J. Org. Chem. *75*, 4480 (2010).
44. Muzart J.: Synthesis *1993*, 11 .
45. Chang C.-T., Patel P., Kang N., Lawson J. A., Song W.-L., Powell W. S., FitzGerald G. A., Rokach J.: Bioorg. Med. Chem. Lett. *18*, 5523 (2008).
46. Lawson J. A., Kim S., Powell W. S., FitzGerald G. A., Rokach J.: J. Lipid Res. *47*, 2515 (2006).
47. Hwang S. W., Adiyaman M., Khanapure S., Schio L., Rokach J.: J. Am. Chem. Soc. *116*, 10829 (1994).
48. Patel P., Chang C.-T., Kang N., Lee G.-J., Powell W. S., Rokach J.: Tetrahedron Lett. *48*, 5289 (2007).
49. Chang C.-T., Patel P., Gore V., Song W.-L., Lawson J. A., Powell W. S., FitzGerald G. A., Rokach J.: Bioorg. Med. Chem. Lett. *19*, 6755 (2009).
50. Kim S., Lawson J. A., Praticò D., FitzGerald G. A., Rokach J.: Tetrahedron Lett. *43*, 2801 (2002).
51. Pandya B. A., Snapper M. L.: J. Org. Chem. *73*, 3754 (2008).
52. Schrader T. O., Snapper M. L.: Tetrahedron Lett. *41*, 9685 (2000).
53. Schrader T. O., Snapper M. L.: J. Am. Chem. Soc. *124*, 10998 (2002).
54. Shizuka M., Snapper M. L.: Synthesis *2007*, 2397.
55. Shizuka M., Schrader T. O., Snapper M. L.: J. Org. Chem. *71*, 1330 (2006).
56. Jung M. E., Berliner J. A., Angst D., Yue D., Koroniak L., Watson A. D., Li R.: Org. Lett. *7*, 3933 (2005).
57. Jung M. E., Berliner J. A., Koroniak L., Gugiu B. G., Watson A. D.: Org. Lett. *10*, 4207 (2008).
58. Jung M. E., Kers A., Subbanagounder G., Berliner J. A.: Chem. Commun. *2003*, 196.
59. Acharya H. P., Miyoshi K., Takashima Y., Ogawa N., Kobayashi Y.: Heterocycles *76*, 1181 (2008).
60. Acharya H. P., Miyoshi K., Kobayashi Y.: Org. Lett. *9*, 3535 (2007).
61. Egger J., Bretscher P., Freigang S., Kopf M., Carreira E. M.: Angew. Chem. Int. Ed. *52*, 5382 (2013).
62. Zhu C., Shen X., Nelson S. G.: J. Am. Chem. Soc. *126*, 5352 (2004).
63. Acharya H. P., Kobayashi Y.: Angew. Chem. Int. Ed. *44*, 3481 (2005).
64. Oger C., Bultel-Poncé V., Guy A., Balas L., Rossi J.-C., Durand T., Galano J.-M.: Chem. Eur. J. *16*, 13976 (2010).
65. Paterson I., Yeung K.-S., Smaill J. B.: Synlett *1993*, 774.
66. Brown C. A., Ahuja V. K.: J. Chem. Soc., Chem. Commun. *1973*, 553.
67. Oger C., Balas L., Durand T., Galano J.-M.: Chem. Rev. *113*, 1313 (2013).
68. Le Guennec J.-Y., Galano J.-M., Oger C., Thireau J., Roy J., Bultel-Poncé V., Guy A., Durand T.: *Methods and pharmaceutical composition for the treatment and prevention of cardiac arrhythmias.* 5-EP12306519.3, December 2012.

69. Taber D. F., Reddy P. G., Arneson K. O.: J. Org. Chem. *73*, 3467 (2008).
70. Sarkar T. K., Ghorai B. K., Nandy S. K., Mukherjee B., Banerji A.: J. Org. Chem. *62*, 6006 (1997).

E. Jahn[a], T. Durand[b], J.-M. Galano[b], and U. Jahn[a] (*[a] Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Prague, Czech Republic, [b] Institut des Biomolécules Max Mousseron, CNRS 5247, Faculté de Pharmacie, Universités de Montpellier I et II ENSCM, Montpellier, France):* **Recent Approaches to the Total Synthesis of Phytoprostanes, Isoprostanes and Neuroprostanes as Important Products of Lipid Oxidative Stress and Biomarkers of Disease**

Isoprostanes (IsoP) are important biologically active metabolites of arachidonic and eicosapentaenoic acids in mammals and humans. IsoPs are becoming the gold-standard biomarkers for monitoring oxidative stress. Their *in-vivo* detected amounts can be correlated with a number of diseases. Similarly, phytoprostanes derived from α-linolenic acid and neuroprostanes from docosahexaenoic acid are other tools for the determination of oxidative stress in plants and the human brain, respectively. To further develop the field, it becomes more and more important to develop total syntheses of these metabolites since this is the only way of obtaining reasonable amounts of pure compounds to study their biological effects and to quantify lipid oxidative stress. In this review, new synthetic strategies, developed in 2008–2013 are summarized, showing the significant advancement in the field.