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Stereodivergent Synthesis of All 15-F_2 Isoprostanes

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Isoprostanes,[1] lipid metabolites generated from free radical oxidation of membrane-bound arachidonic acid (**1**),[2] have received considerable attention since their discovery over a decade ago. Unlike the prostaglandins, these lipid oxidation products are not necessarily formed under enzymatic control. It is not surprising, therefore, that a variety of isoprostane stereo- and regioisomers have been detected in the biological fluids of organisms (including humans) subjected to oxidative stress.[3]

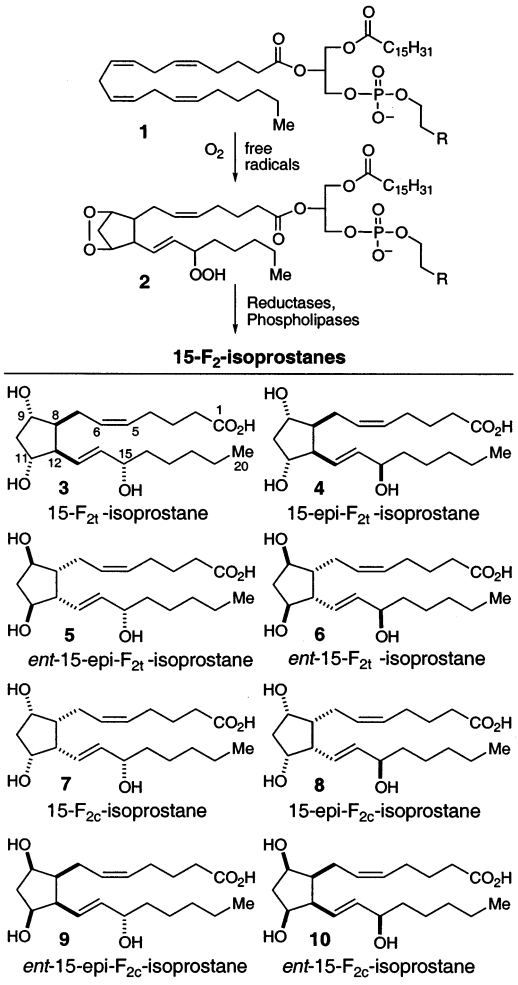
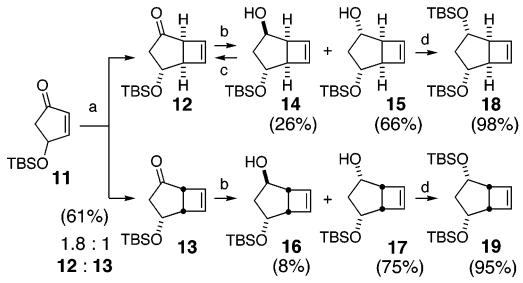


Figure 1. The 15-F_2 family of isoprostanes.

Given the role of lipid oxidation in illnesses such as atherosclerosis, cancer, diabetes, liver, and neurodegenerative diseases,[4] it is critical to develop a better understanding of the biological functions of the isoprostanes. In a few cases, these lipid metabolites have been reported to be potent vasoconstrictors,[5] smooth muscle growth factors,[6] platelet aggregation factors,[7] as well as to possess other biological activities;[8] however, for the most part, the function and cellular targets of the isoprostanes are unclear. As an initial step toward studying the biological role of these molecules, we report herein the synthesis of a complete library of known and anticipated 15-F_2 isoprostanes (**3**−**10**, Figure 1).[9,10]

An effective synthetic strategy for accessing all of the 15-F_2 isoprostanes requires certain notable features. A stereodivergent approach is most appropriate where the isoprostane isomers are generated late from a common isoprostanoid intermediate.[11] The requisite tetra-substituted cyclopentane ring can be accessed rapidly through a ring-opening metathesis of an appropriately functionalized bicyclo[3.2.0]heptenyl ring system.[12] In this regard, the synthesis of the 15-F_2 isoprostane library commences with the known (±)-TBS-4-hydroxy-2-cyclopentenone **11**, which is readily available from furfuryl alcohol in two steps.[13] The [2 + 2] photocycloaddition between **11** and acetylene gives an inseparable mixture of the desired bicyclo[3.2.0]heptenones **12** and **13** (Scheme 1);[14] these photoadducts will lead, respectively, to the 15-F_{2t} and 15-F_{2c} series isoprostanes.

Scheme 1. Preparation of the Ring-Opening Metathesis Substrates[a]



[a] (a) Acetylene, acetone, *hν* (61% yield @ 83% conv; *exo*-**12**:*endo*-**13** = 1.8:1); (b) DiBAl-H, $PhCH_3$, −78 °C; (c) PCC, CH_2Cl_2; (d) TBSCl, DMAP, Et_3N, CH_2Cl_2.

DiBAl-H reduction of ketones **12** and **13** (as a mixture) led to a diastereomeric mixture of **14**, **15**, **16**, and **17**, all of which can be separated by silica gel chromatography. While the reduction of the cyclobutene **13** led to the formation of desired *syn*-dihydroxylated product **17** with acceptable selectivity (**17**:**16** ≈ 9:1), the reduction of the cyclobutene **12** was less selective (**15**:**14** = 2.5:1). Other reducing agents, such as Red-Al, $NaBH_4$, and LAH, provided more of the undesired *anti*-dihydroxylated product **14**. In either case, the minor undesired isomer **14** can be recycled back to **12** by oxidation with PCC, followed by reduction with DiBAl-H to provide **15** (51%, two steps). The *meso*-cyclobutenes **18** and **19**

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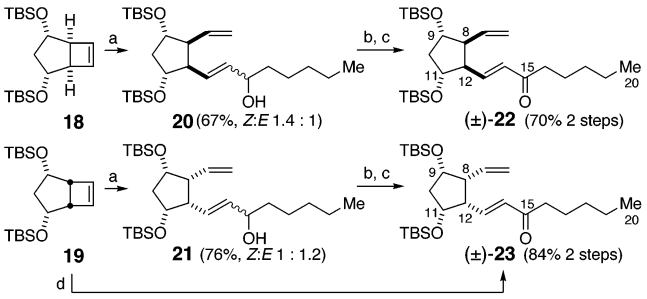
Scheme 2. Side-Chain Construction through Ring-Opening Metatheses[a]

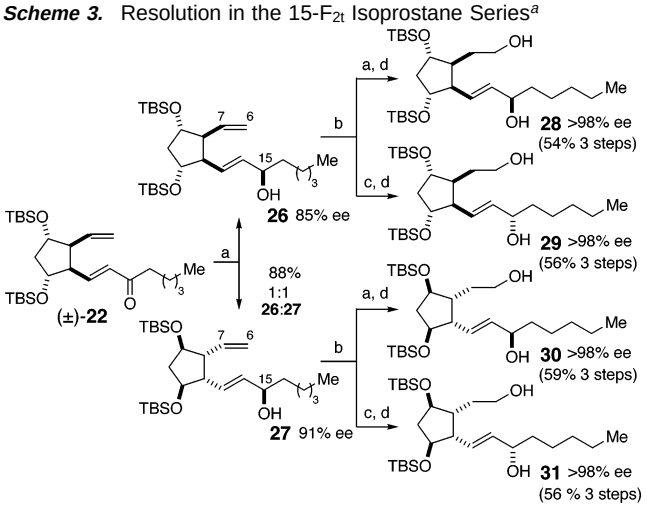


[a] (a) $(IMesH_2)(PCy_3)Cl_2Ru{=}CHPh$, (**24**), CH_2Cl_2, oct-1-en-3-ol; (b) PCC, CH_2Cl_2; (c) I_2 (1 mol %), CH_2Cl_2; (d) cat. **24**, benzene, oct-1-en-3-one, 80 °C.

can then be prepared in high yield by treatment of alcohols **15** and **17** with TBSCl.

The *cis* side chains of the isoprostanes can now be introduced through ring-opening metatheses of the bis-silylated bicyclo[3.2.0]-heptenediols **18** and **19** (Scheme 2).[15] Grubbs' *N*-heterocyclic carbene-containing catalyst **24** with excess octen-3-ol generates the ring-opened products **20** and **21**, as mixtures of isomers in 67% and 76% yield, respectively. In each case, the *Z*-olefin isomers could be converted to the desired *E*-stereochemistry through a PCC oxidation, followed by an iodide-catalyzed isomerization to provide *trans*-enones **22** and **23**.[10e] Alternatively, cyclobutene **19** could be converted to enone **23** directly in 55% yield through a ring-opening metathesis with oct-1-en-3-one. Unfortunately, this enone cross-metathesis was not successful with cyclobutene **18**.

Scheme 3. Resolution in the 15-F_{2t} Isoprostane Series[a]

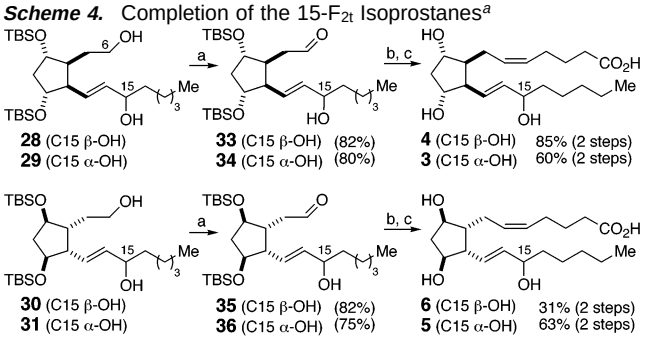


[a] (a) (*S*)-2-Methyl-CBS-oxazoborolidine (**25**), catecholborane, toluene, −78 °C; (b) PCC, CH_2Cl_2; (c) (*R*)-2-methyl-CBS-oxazoborolidine (**32**), catecholborane, toluene, −78 °C; (d) 9-BBN; NaOOH.

With the lower side chain (C13−C20) in place, the remaining steps involve installation of the upper side chain and resolution of the various stereoisomers. Racemic enone (±)-**22** serves as the substrate for the resolution. Asymmetric catalytic reduction of (±)-**22** using (*S*)-2-methyl-CBS-oxazoborolidine (**25**) and catecholborane[16] produced enantiomerically enriched diastereomeric alcohols **26** and **27**, which can be separated by silica gel chromatography (Scheme 3).[17] The individual alcohols were then reoxidized with PCC to the corresponding enantiomerically enriched enones (−)-**22** and (+)-**22**.

Pure 15-F_{2t} isoprostane isomers are now accessible from a second catalytic asymmetric reduction of the enantiomerically enriched enones (−)-**22** and (+)-**22**. Reduction of (−)-**22** with (*S*)-2-methyl-CBS-oxazoborolidine (**25**) produced the 15-*R* alcohol **26** as the major diastereomer (Scheme 3). Hydroboration of the reaction mixture with 9-BBN, followed by oxidative workup, provided the enantiomerically pure diol **28**. Similarly, reduction of enone (+)-**22** with **25**, followed by the hydroboration, generates enantiomerically pure diol **30**. The enantiomerically pure C15-epimers, **29** and **31**, are prepared by reducing the enantiomerically enriched enones (−)-**22** and (+)-**22**, respectively, with the opposite enantiopode of the reduction catalyst, (*R*)-2-methyl-CBS-oxazoborolidine (**32**).

Scheme 4. Completion of the 15-F_{2t} Isoprostanes[a]



[a] (a) TEMPO, NCS, $Bu_4N^+Cl^-$, CH_2Cl_2/H_2O; (b) $(Ph_3P(CH_2)_4CO_2H)^+Br^-$, KHMDS, THF; (c) TBAF, THF.

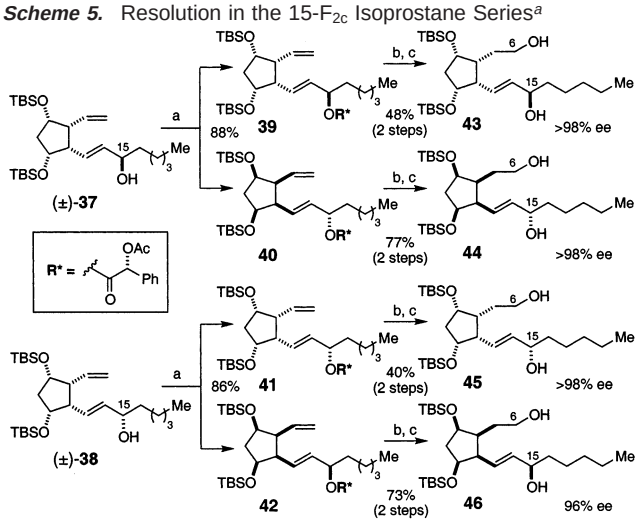
The final steps of synthesis of the 15-F_{2t} isoprostanes are outlined in Scheme 4. Selective oxidation of the primary alcohol (C6) in the presence of an allylic alcohol (C15) for diols **28**−**31** was accomplished under phase transfer conditions using catalytic TEMPO with NCS as the reoxidant.[18] Wittig olefination proceeded selectively to produce exclusively the *Z*-olefin stereochemistry at the newly formed C5−C6 double bond. Deprotection of the TBS groups with TBAF in THF then yields the desired 15-F_{2t} isoprostanes **3**−**6**.[10a]

The use of the same strategy to resolve the 15-F_{2c} isoprostanes was met with some difficulty. CBS-reduction of enone (±)-**23** gave the desired diastereomeric alcohols, however, each in less than 30% ee. As an alternative, a more classical approach was pursued (Scheme 5). The diastereomeric allylic alcohols, (±)-**37** and (±)-**38**, were prepared through a $NaBH_4$ reduction of (±)-**23** (80% yield). Allylic alcohol (±)-**37** was acylated with (*R*)-*O*-acetylmandelic acid chloride (**47**) to give the diastereomeric esters **39** and **40**.[19] Similarly, esters **41** and **42** were prepared from (±)-**38**. The esters could be separated by silica gel chromatography yielding the enantiomerically enriched diastereomers. The acetyl mandelate esters were then removed under reductive conditions, and the resulting isomers were hydroborated to give diols **43**−**46** in an enantiomerically pure fashion.

The synthesis of the 15-F_{2c} isoprostane isomers could then be completed in a manner similar to the 15-F_{2t} isoprostanes. Selective oxidation of diols **43**−**46** to the corresponding hydroxyaldehydes, Wittig olefination, and deprotection furnished the individual 15-F_{2c} isoprostanes **7**−**10** (Scheme 6).[10b]

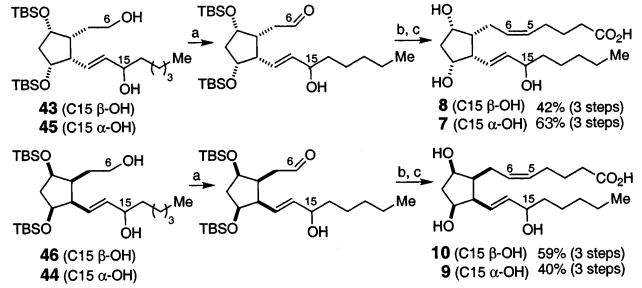
The first synthesis of all 15-F_2 isoprostane has been accomplished. This synthesis includes the preparation of both known, as well as anticipated, members of this class of lipid metabolites. The stereodiversifying strategy allows for the preparation of the 15-F_2 isoprostanes from a common starting material in an efficient manner. A ring-opening metathesis serves as the key transformation for introducing the isoprostane side chains. Separation of the 15-F_{2t} stereoisomers was achieved using a catalytic asymmetric reduction protocol, while separation of the 15-F_{2c} isoprostane isomers was accomplished using chiral auxiliaries. The availability

Scheme 5. Resolution in the 15-F_{2c} Isoprostane Series[a]



[a] (a) *R*-Ph(AcO)CHCOCl (**47**), DMAP, Et_3N, CH_2Cl_2; separate diastereomers; (b) DiBAl-H; (c) 9-BBN; NaOOH.

Scheme 6. Completion of the 15-F_{2c} Isoprostanes[a]



[a] (a) TEMPO, NCS, TBACl, CH_2Cl_2/H_2O; (b) $(Ph_3P(CH_2)_4CO_2H)^+Br^-$, KHMDS, THF; (c) TBAF, THF.

of this complete 15-F_2 isoprostane library allows for the side-by-side comparison of these lipid metabolites in a variety of biological assays.

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Supporting Information Available: Compound characterization and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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