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Total Synthesis of 15-F_{2t}-Isoprostane by Using a New Oxidative Cyclization of Distonic Radical Anions as the Key Step

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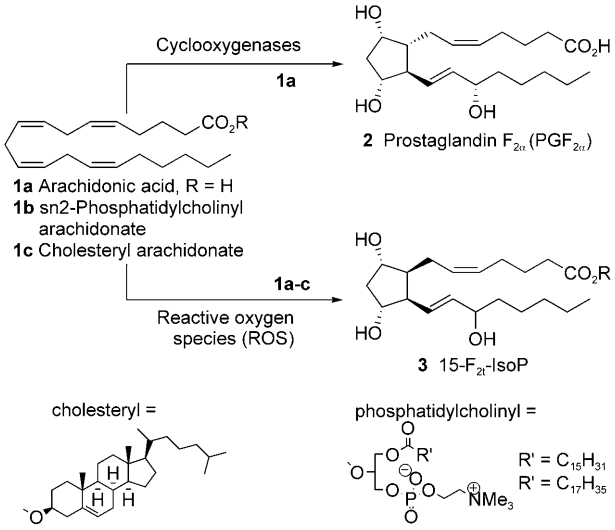
Dedicated to the memory of Professor Peter Welzel

Isoprostanes (IsoPs) **3** are cyclic derivatives of arachidonic acid (**1a**) and are diastereomeric to the enzymatically formed prostaglandins (PGs) **2**.[1] They form in vivo by a free-radical-induced cascade, which consists of peroxidation/double 5-*exo* radical cyclization/oxygenation, predominately from membrane- or low-density lipoprotein (LDL)-bound arachidonic acid derivatives **1b** and **1c**, in much larger quantities than PGs (Scheme 1).[2] In contrast to the strongly regulated biosynthesis of **2**, in which initial hydrogen abstraction occurs exclusively at C13, all bisallylic positions of **1** are subject to hydrogen abstraction under autoxidative conditions. Radical peroxidation/bicyclization/peroxidation cascades give rise to IsoPs **3** as racemic mixtures of regio- and stereoisomers, in which racemic PG-type diastereomers are only formed to a minor extent.[1]

The production of **3** is strongly increased under oxidative stress. The extent of formation of IsoPs **3** is correlated with some of the most incidental human diseases, such as atherosclerosis, pulmonary, and cardiovascular diseases, as well as Alzheimer's disease and other neuronal disorders. Since IsoPs **3** form reliably, today they are considered to be the gold standard for monitoring oxidative stress and pathophysiological conditions in humans in vivo. Monitoring of **3** and the study of their various biological functions requires pure synthetic material because isolation from biological material is scarcely possible. Therefore, recently there has been a great interest in the total synthesis of isoprostanes in a regio- and stereoselective manner. A number of total syntheses of **3** were developed, some of them even before the first isolation of IsoPs. Many of them are, however, multistep syntheses that deliver only small amounts of material.[1a]



Scheme 1.

We have previously developed a number of oxidatively triggered radical cyclizations using easily accessible enolates as cyclization precursors.[3] We present herein preliminary results on a new approach to the total synthesis of **3** using dianions as precursors; this approach bears some relation to the in vivo formation of isoprostanes[1] in that it relies on an oxidatively triggered radical cyclization and oxygenation of the C7–C20 chain.

Our retrosynthetic analysis of **3** calls for an initial disconnection of the C6–C7 bond and leads to functionalized hexyne **4** and cyclopentanecarboxylate **5** (Scheme 2). This disconnection has rarely been applied to the total synthesis

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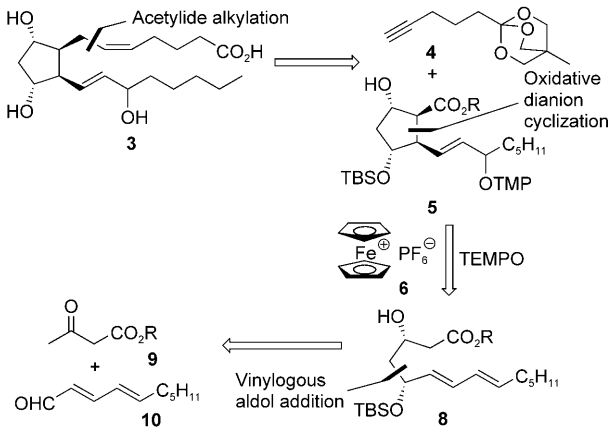
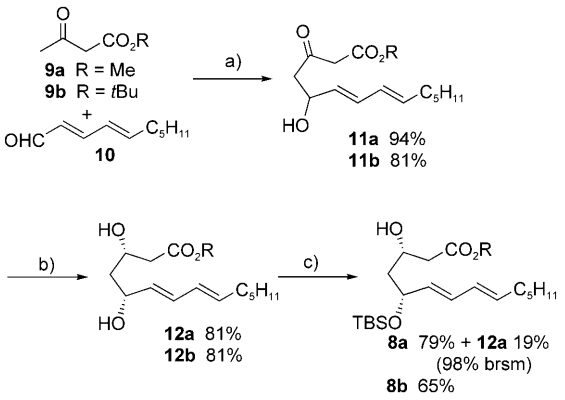


Scheme 2.

of PG,[4] and never to IsoP. The cyclopentane core **5**, with the attached ω chain, will be approached by a new radical anion cyclization starting from the dianion of **8** and ferrocenium hexafluorophosphate (**6**). This strategy will allow the concomittant installation of the oxygen functionality in the 15-position by using the stable free radical 2,2,6,6-tetramethylpiperidine N-oxyl (TEMPO) **7**.[5] Compound **8**, the 5-*tert*-butyldimethylsilyl (TBS)-protected *syn*-3,5-dihydroxy ester is easily accessible from commercially available acetoacetates **9** and (*E,E*)-2,4-decadienal (**10**). The choice of the initial vinylogous aldol addition will allow potential asymmetric approaches in the future.[6] A number of challenges are inherent to the approach, namely, the development of the oxidative dianion cyclization, the adjustment of the correct protecting group pattern, and the alkylation of the densely functionalized cyclopentane core to assemble the full carbon skeleton.

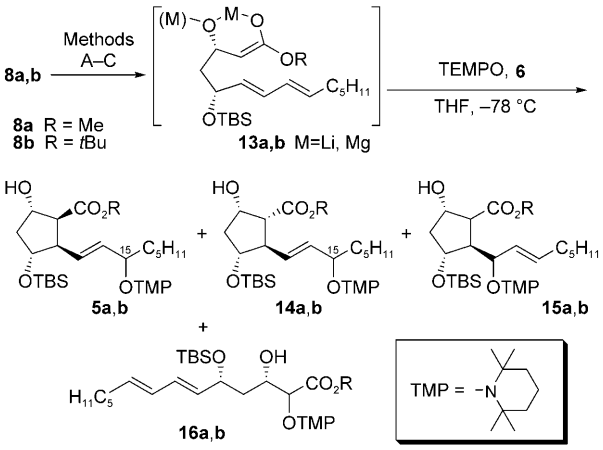
The total synthesis commenced with the assembly of the C7–C20 chain (Scheme 3). The vinylogous aldol addition of the dianion of methyl- (**9a**) or *tert*-butyl acetoacetate (**9b**)



Scheme 3. a) i) NaH (1.1 equiv), THF, 0 °C, hexamethylphosphoramide (HMPA; 1.2 equiv); ii) BuLi (1.05 equiv), −78 °C; iii) **10**, −78 to −45 °C. b) i) Et_2BOMe (1.5 equiv), MeOH/THF (4:1), −78 to −65 °C, 1 h; ii) $NaBH_4$ (1.5 equiv), −78 °C, 3 h; iii) NaOAc, H_2O_2, THF/H_2O, 0 °C, 0.5 h. c) TBSOTf (1.05 equiv), 2,6-lutidine (3 equiv), CH_2Cl_2, −78 °C, 3.5 h (brsm = based on reacted starting materials).

to decadienal **10**[7] proceeded in good yield to give the somewhat thermally labile 5-hydroxy-3-oxoesters **11a** and **11b**. Both esters were reduced in good yields with exclusive *syn* selectivity to give 3,5-dihydroxy esters **12a** and **12b**.[8] The selective monoprotection of **12a** and **12b** was achieved with equimolar amounts of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-lutidine at low temperature. The monosilylated products were isolated in 79 and 65% yield, respectively, accompanied by only small amounts (traces for **8a**, 22% for **8b**) of the disilylated compounds (not shown). The reaction of **12** with TBSOTf is unique with regard to the regioselectivity of the protection because we were not able to introduce the triethylsilyl (TES), methoxymethyl (MOM), or benzyl protecting groups selectively in the 5-position under a variety of conditions.[9]

With compounds **8a**,**b** in hand, we studied their tandem radical anion cyclization/oxygenation reactions (Scheme 4,



Scheme 4. Method A: Lithium diisopropylamide (LDA; 2.5 equiv), LiCl (7 equiv), THF (0.036 M), −78 to −40 °C, 1.5 h, then HMPA (6 equiv) and TEMPO (1.2 equiv). Addition of **6** in small portions at −78 °C until a blue-green color persists for 20 min. Method B: LDA (2.5 equiv), LiCl (7 equiv), THF (0.039 M), −78 to −40 °C, 1.5 h, then HMPA (6 equiv) and TEMPO (0.2 equiv). Addition of a homogeneous mixture of TEMPO (0.8 equiv) and **6** (1.0 equiv) in small portions at −78 °C followed by further addition of **6** until a blue-green color persists for 30 min. Method C: *t*BuMgCl (1.5 equiv) and THF (5 mL), −78 to −50 °C, 40 min, then LDA (2.2 equiv) at −78 to −40 °C, 1 h, THF (15 mL), HMPA (6 equiv) and TEMPO (1.2 equiv). Addition of **6** in small portions at −78 °C until a blue-green color persists for 20 min.

Table 1). Alkoxide enolate dianions **13a**,**b** were generated by deprotonation reactions under a variety of conditions (Scheme 4, Methods A–C). The cyclizations were triggered by single electron transfer (SET) oxidation with **6** in the presence of the stable free radical TEMPO. The partially separable cyclopentanecarboxylates **5** and **14** were the major compounds in moderate to good yields. The yields were not significantly dependent on the size of the ester functionality in **8**, however, the selectivity for the cyclopentane **5a**,**b** with isoprostane configuration was better for the smaller methyl ester **8a** than for the *tert*-butyl ester **8b** (Table 1, entries 1 and 2 versus 4 and 5). The oxidative cyclization reactions

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Table 1. Oxidative cyclizations of dianions **13a**,**b**.

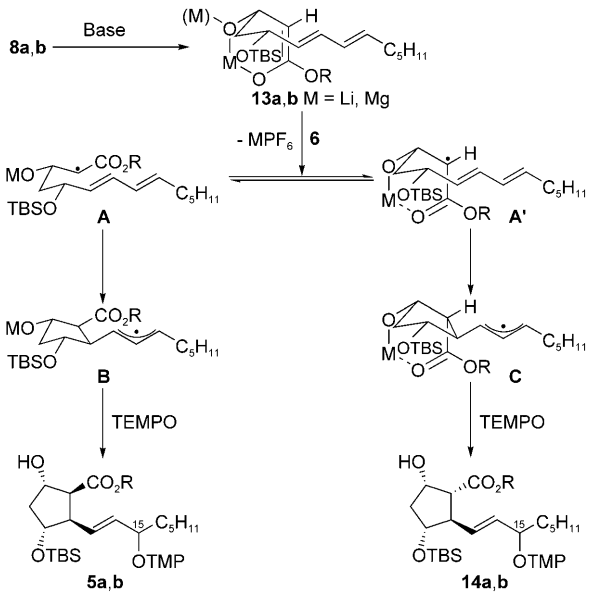
Entry	**8**	Base/additive [equiv]	Method	**5**+**14** [%]	dr **5**(15α/β)/**14**(15α/β)		**15** [%]	**16** [%]
1[a]	**a**	LDA/LiCl/HMPA	A	71	1.4(1:1.1)	1(2:1)	1	8
2[b]	**a**	LDA/LiCl/HMPA	B	62	1.7(1:1.7)	1(3:1)	8	7
3[c]	**a**	*t*BuMgCl/LDA/HMPA	C	41	1(1:1.1)	4.1(2.1:1)	7	19
4[d]	**b**	LDA/LiCl/HMPA	A	58	1.1(1.8:1)	1(1:1.4)	8	–
5[e]	**b**	LDA/LiCl/HMPA	B	61	1.3(2.2:1)	1(1.2:1)	9	–
6[f]	**b**	*t*BuMgCl/LDA/HMPA	C	46	1(1.7:1)	6(1.7:1)	8	17

[a] Scale: 0.65 mmol. [b] Reaction run in triplicate; scale: 3.1 mmol, LiCl (15 equiv), 5% of **8a** recovered. [c] Scale: 0.65 mmol, 12% of **8a** recovered. [d] Scale: 0.7 mmol, 13% of **8b** recovered. [e] Scale: 2.4 mmol, 1% of **8b** recovered. [f] Scale: 0.7 mmol, 23% of **8b** recovered.

could also be scaled up to gram amounts without difficulty (Scheme 4, Method B; Table 1, entries 2 and 5). However, the reagent combinations applied for the double deprotonation of the β-hydroxy ester had a significant impact on the cyclization outcome. Although the formation of the preferred product **5a**,**b** was observed, when the dilithium alkoxide enolate was oxidatively cyclized (Scheme 4, Methods A and B; Table 1, entries 1, 2, 4, and 5), a significant reversal of the diastereoselectivity to cyclopentanecarboxylate **14a**,**b** was found when the magnesium alkoxide enolate was subjected to the oxidative cyclization conditions (Scheme 4, Method C; Table 1, entries 3 and 6). The diastereoselectivity of radical trapping by TEMPO is low, but parallels what is known from in vivo trapping of the corresponding allylic radicals with oxygen itself.[1,5] In the context of the present synthesis this does not matter because this stereocenter will be destroyed during the course of the total synthesis (see below). Small amounts of a cyclized isomer (**15a**,**b**), in which trapping by TEMPO occurred in the 13-position, and of the corresponding acyclic TEMPO-trapped compounds **16a**,**b** were formed in almost all experiments; however, their relative configurations cannot yet be unambiguously assigned.

The stereochemical course of the cyclization may be rationalized as follows (Scheme 5): SET oxidation of the dilithium dianion **13a**,**b** by **6** generates an equilibrium mixture of radical anions **A** and **A′**. In the case of the lithium counterion, the open radical anion **A** is apparently favored over the chelated form **A′** and cyclization occurs preferentially via a Beckwith–Houk transition state to form the cyclic allylic radical anion **B**, which is trapped by TEMPO with a slight preference for a front-side attack, because the back side is blocked somewhat by the ester functions. Nonetheless, cyclization can also proceed via the chelated transition state **A′** to generate allylic radical **C**, which is trapped by TEMPO. In contrast, the chelated radical anion should be much more favored in the SET oxidation of the magnesium dianion, resulting in a rather selective cyclization via transition state **A′**.

Thus, this strategy is suitable for the stereodivergent synthesis of both IsoPs and PGs. IsoPs are currently the more interesting class of natural products, so we proceeded with their synthesis from **5a**,**b**. PGs may, however, be synthesized by an analogous route using **14a**,**b** as the starting materials.



Scheme 5.

The next step in the synthetic strategy called for appending the α chain (Scheme 6). To reach this goal, the esters **5a**,**b** were reduced with lithium aluminum hydride to diol **17**. Ester **5a** was reduced selectively, but the reaction was slow because of steric congestion. The reduction of **5b** was very sluggish, with only 53% of the desired diol **17** isolated; moreover, the corresponding aldehyde and products resulting from silyl deprotection were formed (see the Supporting Information). The following one-pot triflation of the primary alcohol in **17** and TES protection of the secondary alcohol proved to be highly efficient, giving the unstable triflate **18** in good yield. This led to the crucial introduction of the α chain into **18** by an alkylation of the alkynyllithium of orthoester **4**, generated by standard deprotonation with butyllithium in THF/HMPA, which delivered 50% of the desired protected C20-orthoester **19**. The product was formed with 26% of the free alcohol **20** and some of the triethylsilylated derivative of **4** (see the Supporting Information). Thus, a triethylsilyl migration to the acetylide occurred to some extent. Compounds **19** and **20** were deprotected by using TBAF. A one-pot ring opening of the orthoester, saponification according to Corey's procedure,[10] and esterification with trimethylsilyldiazomethane gave **21** cleanly as a mixture of C15 stereoisomers in excellent yield.

At this point, the 2,2,6,6-tetramethylpiperidinyl protecting group was oxidatively cleaved by using *meta*-chloroperbenzoic acid (*m*CPBA).[11] It was important to keep the temper-

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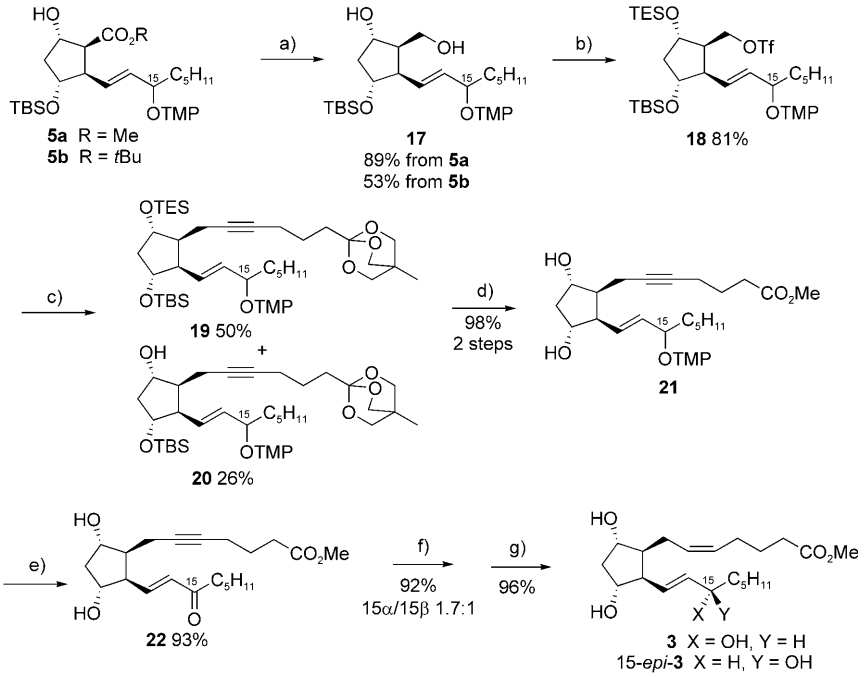

Scheme 6. a) Excess $LiAlH_4$, THF, 2–3 h. b) i) Tf_2O (1.05 equiv), 2,6-lutidine (3.0 equiv), −78 °C, 0.5 h; ii) TESOTf (1.5 equiv), −78 °C, 0.5 h, CH_2Cl_2. c) i) BuLi (3.6 equiv), THF/HMPA, −78 °C, 0.5 h; ii) **4** (3.0 equiv); iii) **18**, −78 to −15 °C, 2.75 h. d) i) Tetrabutylammonium fluoride (TBAF), THF, 0 °C, 4.5 h; ii) $NaHSO_4$, 1,2-dimethoxyethane (DME)/H_2O, 0 to 20 °C, 1 h; iii) LiOH, 0 to 20 °C, 2.5 h; iv) Me_3SiCHN_2, THF/MeOH, RT, 2.25 h. e) *m*CPBA (1.4 equiv), CH_2Cl_2, 0 °C, 10 min. f) i) 0.2 M diisobutylaluminium hydride (DIBAL-H; 12 equiv), 2,6-di-*tert*-butyl-4-methylphenol (13.2 equiv) in toluene, −95 to −78 °C, 2 h; ii) −50 °C, 3 h; iii) −50 to −10 °C, 1.25 h. g) Lindlar catalyst, 1 bar H_2, EtOH/EtOAc/pyridine, RT, 24 h.

ature low, the reaction time as short as possible, and to use neutral workup conditions, because the 12-position of **22** proved to be quite sensitive to epimerization under both basic and acidic conditions. Although several methods exist to reduce the keto function at the 15-position of **22** to the alcohol stereoselectively,[1a] we chose Yamamoto's DIBAL-H/2,6-di-*tert*-butyl-4-methylphenol method, which was used to prepare the 15α-alcohols in the PG derivatives selectively.[12] 5,6-Dehydro-IsoP was obtained in high yield as a 1.7:1 mixture of 15α/15β-alcohols. Thus, the method proved to be less selective for the IsoP skeleton than for the PG system. However, since both alcohols are formed in vivo and both display potent biological activity in some assays,[13] they were separated and individually subjected to (*Z*)-selective Lindlar semihydrogenation of the alkyne units in ethanol/ethyl acetate/pyridine to give **3** and its 15-epimer (15-*epi*-**3**) in excellent yields. The presence of ethanol was crucial to the success of the hydrogenation; in its absence no reaction occurred.

In conclusion, we achieved the total synthesis of the most prominent isoprostane diastereomer, **3**, and its 15-epimer, 15-*epi*-**3**, by applying a conceptually new strategy, which includes a new oxidative radical anion cyclization/oxygenation methodology. This allows, in principle, the stereodivergent preparation of both IsoP and PG skeletons from the same precursor, as well as the introduction of the α chain by linking C6 and C7 instead of the more common formation of the C5−C6 or C7−C8 bonds. The synthesis was achieved in twelve steps in an overall yield of 14% for each epimer of **3**, starting from **9a**, which is more suitable, and compares well to existing syntheses of **3**.[1a] The methodology developed should also allow the selective and stereodivergent preparation of the hundreds of constitutional, regio-, and stereoisomers of IsoP, the biological activities of which have not yet been determined, owing to the lack of pure synthetic material. Research in this area is being actively pursued and will be reported in due course.

Acknowledgements

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Keywords: cyclization · electron transfer · prostanoids · radical ions · total synthesis

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