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Synthesis of iPF$_{2\alpha}$-V: a new route

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Abstract

We are reporting here on a new synthesis of iPF$_{2\alpha}$-V, and we also disclose the first report on the synthesis of 12-*epi*-iPF$_{2\alpha}$-V. The new total synthesis of iPF$_{2\alpha}$-V reported here is designed to address metabolism and analytical issues. We have used this new route and also performed the total synthesis of 17,17,18,18-tetradeutero-iPF$_{2\alpha}$-V. The availability of the deuterated analog of iPF$_{2\alpha}$-V is the first step in our attempt to quantitate this isoprostane in biological fluids by GC and LC–MS. © 1999 Elsevier Science Ltd. All rights reserved.

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Isoprostanes (iPs) are formed in vivo as a result of free-radical peroxidation of arachidonic acid (AA).[1] Four groups of iPs, namely III, IV, V, VI, can be formed as a result of this (Scheme 1a). They are isomeric with prostaglandins (PGs) which are formed by the action of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) on AA. iPF$_{2\alpha}$-III, a group III isoprostane, has also been detected in the enzymatic reaction of COX-1 and COX-2 on AA.[2,3] This is of relevance due to the recent discovery of COX-2 inhibitor as an anti-inflammatory agent.[4,5] We have recently discovered four members of Group VI isoprostanes in human urine (Scheme 1b).[6–8] We have described two general methods for the synthesis of isoprostanes.[9–11] We have also shown that iPs, and in particular Group VI iPs,[8] can be used to assess the oxidant stress component in diseases such as atherosclerosis[12] and Alzheimer's.[13] Equally, because of the close structural analogy with the PGs, interaction of these iPs with PG receptors are possible.[14,15]

We have recently reported a Diels–Alder synthetic approach to isoprostanes and applied it to the synthesis of iPF$_{2\alpha}$-V.[10] Scheme 2 briefly illustrates the synthesis. The nomenclature of iPs used here is the one we have introduced recently.[16]

This synthesis of iPF$_{2\alpha}$-V allowed us to secure synthon **12** and build first the lower side chain and obtain intermediate **13**. The synthesis described in this report (Scheme 3) was designed to accomplish

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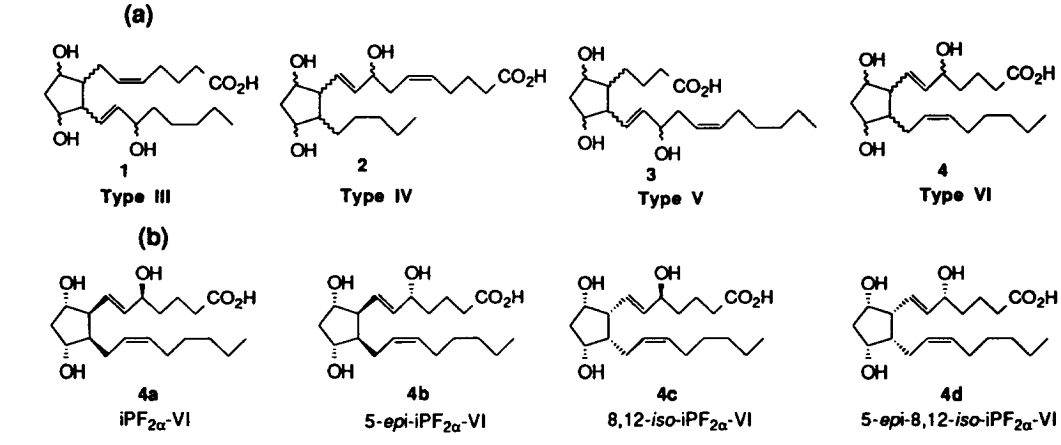
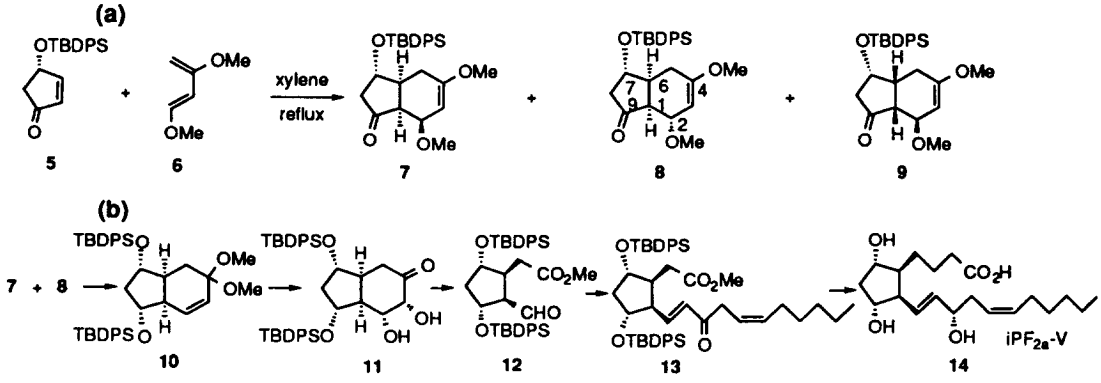


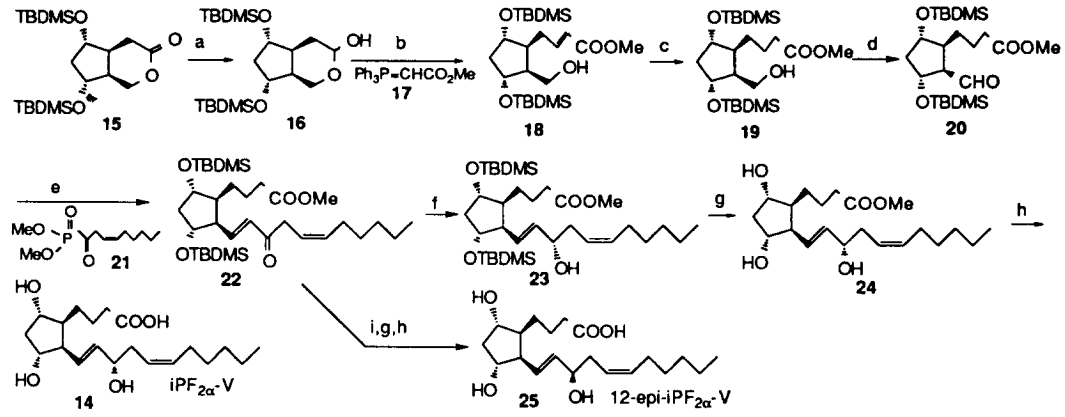
Scheme 1.



Scheme 2.

two objectives. The first was to build the upper side chain first. This would allow us to vary the nature and structural features of the lower side chain while keeping the upper side chain constant. For example, we envisage that some of the intermediates in Scheme 3 en route to the final isoprostane **14** could be used to identify potential metabolites of this isoprostane. It is known that $PGF_{2\alpha}$ metabolism starts with enzymatic oxidation of the 15-hydroxy on the lower side chain, followed by reduction of the 13,14 double bond. If such a process was to occur with iPF$_{2\alpha}$-V, the carbonyl intermediate **22** could be useful in the identification of such a metabolite. Equally, we were also interested in modifying the lower side chain and incorporating four deuterium atoms. This would allow us to develop a GC–MS or LC–MS assay for the quantitation of this isoprostane in biological fluids. The four deuterium atoms could have also been incorporated by the approach shown in Scheme 2. The one described here, however, (Scheme 3) is appreciably shorter in the sense that we are performing fewer synthetic steps involving the precious deuterated derivatives.

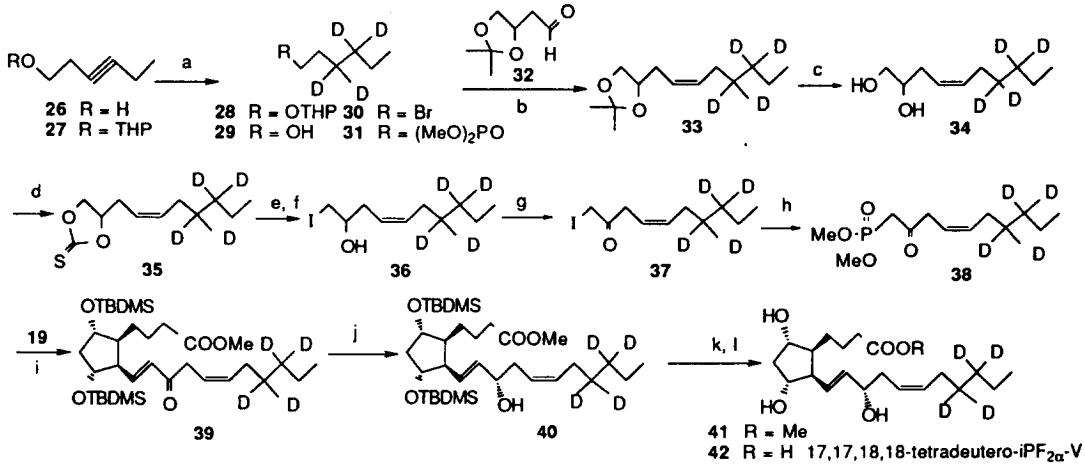
Another reason for undertaking the synthesis reported here (Scheme 3) is the unequivocal confirmation of the structure of iPF$_{2\alpha}$-V prepared by the Diels–Alder approach. When the Diels–Alder project was still developing, we assigned the structures of the Diels–Alder products **7** and **8** based on spectroscopic evidence. We thought it wise at the time to confirm the structures by a chemical proof. This would at the same time provide further credence to the underlying mechanism we proposed for the formation of these Diels–Alder products.[10] We have performed chemical structure correlation at two levels. The first, reported previously, shows the stereochemical equivalency of structure **12** (Scheme 2) and **15**



Scheme 3. Reaction conditions: (a) DIBAL-H, 87–93%; (b) THF, 18 h, 90%; (c) Pd-C, H_2, 91%; (d) Swern oxidation, 88%; (e) $NaN(SiMe_3)_2$, THF, −78°C, 69%; (f) (*S*)-BINAL-H, THF, −100°C, 58%; (g) *n*-Bu_4NF, 95%; (h) KOH, KH_2PO_4 (pH=4.2), 88%; (i) (*R*)-BINAL-H, THF, −100°C, 63%

(Scheme 3) by converting **12** to **15**.[10] The second was made possible by the synthesis reported here. We have compared the *i*$PF_{2\alpha}$-V obtained by the two routes (Scheme 2 and 3) and showed them to be identical in every respect by various chromatographic techniques. Equally, the methyl esters of *i*$PF_{2\alpha}$-V, obtained by the two different routes, were completely equivalent. We have also used *i*$PF_{2\alpha}$-V and confirmed qualitatively its presence in human urine by LC–MS.

Scheme 3 shows the steps involved in the synthesis of *i*$PF_{2\alpha}$-V, starting with bicyclic system **15** prepared as already described.[9,11] DIBAL reduction afforded a mixture of lactol epimers in 87–93% yield. The reaction between the stabilized Wittig reagent **17** and the masked aldehyde **16** affords **18** in 90% yield. Hydrogenation over Pd/C gives **19** in 91% yield. Oxidation of **19** by the swern method proceeds smoothly in 88% yield after chromatography on silica gel. The Wittig reaction with the keto phosphonate **21** affords, after purification, 69% yield of **22**. The preparation of the β,γ-unsaturated ketophosphonate itself is performed as described in Scheme 4 for the tetradeutero analog. This preparation has been made



Scheme 4. Reaction conditions: (a) $[(C_6H_5)_3P]_3RhCl$, D_2, 99%; (b) $LiN(SiMe_3)_2$, THF, −78°C, 77%; (c) 4% aq. H_2SO_4, THF, 62%; (d) $S{=}C(Im)_2$, CH_2Cl_2, 88%; (e) MeI, $ClCH_2CH_2Cl$, 88%; (f) DIBAL-H, 79%; (g) Jones reagent, 76%; (h) $P(OMe)_3$, 52%; (i) NaHMDS, THF, −78°C, 50%; (j) (*S*)-BINAL-H, THF, −100°C, 65%; (k) 48% aq. HF, CH_3CN, 88%; (l) aq. KOH, KH_2PO_4 (pH=4.2), 76%

possible by a very efficient method we developed recently for the preparation of iodohydrins such as **36**.[17] The keto ester **22** was reduced with (*S*)-BINAL-H and after deprotection and hydrolysis gave *i*$PF_{2\alpha}$-V, **14**. In a similar fashion **22** was converted into 12-*epi*-*i*$PF_{2\alpha}$-V, **25**, via an (*R*)-BINAL-H reduction.[18,19]

With the availability of the synthetic tetradeutero *i*$PF_{2\alpha}$-V, work is now in progress to quantitate this isoprostane in urine and other biological fluids.

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18. The NMR data of compound **14**: ^{1}H NMR (CD_3COCD_3) δ 5.53 (dd, *J*=15.3 and 6.3 Hz, 1H), 5.43 (m, 3H), 4.03 (q, *J*=6.3 Hz, 1H) 3.90 (m, 1H), 3.69 (br s, 2H), 2.84 (br s, 1H), 2.63 (td, *J*=8.2 and 3.3 Hz, 1H), 2.38 (m, 1H), 2.25 (m, 2H), 2.04 (m, 4H), 1.63 (m, 2H), 1.54 (m, 1H), 1.38 (m, 10H), 0.88 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (CD_3COCD_3) δ 175.19, 136.91, 132.54, 130.34, 127.39, 77.19, 76.88, 73.44, 54.85, 50.76, 44.72, 37.03, 35.08, 32.81, 30.60, 29.75, 28.61, 24.90, 23.79, 14.90. Electrospray MS *m/z* 353.2 $(M-H)^+$. HRMS (Cl–CH_4) *m/z* calcd for $C_{20}H_{34}O_5$ $[(M+1)-2H_2O]^+$ 319.2274, found 319.2286.
19. The NMR data of compound **25**: ^{1}H NMR (CD_3COCD_3) δ 5.55 (dd, *J*=15.3 and 5.9 Hz, 1H), 5.44 (m, 3H), 4.03 (q, *J*=6.2 Hz, 1H), 3.86 (m, 2H), 3.70 (br s, 2H), 2.87 (br s, 1H), 2.64 (td, *J*=9.5 and 3.2 Hz, 1H), 2.38 (m, 1H), 2.24 (m, 4H), 2.04 (m, 4H), 1.62 (m, 2H), 1.37 (m, 8H), 0.88 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (CD_3COCD_3) δ 175.42, 136.76, 132.51, 130.08, 127.39, 77.17, 76.88, 73.24, 54.72, 50.72, 44.76, 36.97, 35.03, 32.80, 30.60, 29.96, 28.60, 24.82, 23.79, 14.90.