Pergamon

Tetrahedron Letters 42 (2001) 4333–4336

TETRAHEDRON LETTERS

Synthesis of the two main urinary tetranor metabolites of 15-F_{2t}-isoprostane

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Received 27 March 2001; revised 30 April 2001; accepted 6 May 2001

Abstract—The first synthesis of two main urinary tetranor metabolites of 15-F_{2t}-isoprostane methyl ester is described using L-glucose as starting material.

F_2-isoprostanes (F_2-isoP), a complex family of 32 stereoisomers to cyclooxygenase derived $PGF_{2\alpha}$, are products o f non-enzymatic free radical-catalyzed peroxidation of arachidonic acid.[1–3] Since these compounds are now widely used as indices of lipid peroxidation in vivo,[2–5] knowledge of their metabolic fate may be useful, in general, to better define their overall formation. In fact, the identification of major metabolites of F_2-isoP might help in finding new analytical targets to monitor in addition to or instead of the parent compounds. Moreover, given that selected F_2-isoP isomers have potent biological effects,[2–5] it is important to establish whether and how these isomers are specifically degraded, in order to relate their levels in vivo to a putative biological effect. To date, the only F_2-isoP metabolites identified and most studied were 2,3-dinor-5,6-dihydro-15F_{2t}-isoP[6–8] and putative tetranor isomers of 15-F_{2t}-isoP.[7,9]

In connection with our program directed towards the synthesis of isoprostanes and neuroprostanes, we now report the first total synthesis of two main urinary tetranor metabolites of 15F_2-isoP **1** and **2** from commercially available L-glucose (Fig. 1).

The synthesis of 2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F_{2t}-isoP methyl ester **1**, is shown in Schemes 1 and 2. The first six steps leading to iodo derivative **4** were assessed in 84% overall yield by using iodo pathway, according to our procedure.[10] Treatment of compound **4** with $ZnCl_2$ in ethanethiol at −15°C afforded the diol–thioacetal **5** in 88% yield, which was protected into dibenzoyl ether **6** in the presence of benzoyl chloride in pyridine at room temperature in 90% yield. Removal of the thioacetal group under neutral conditions ($HgO/HgCl_2$) in acetone/water gave the unstable aldehyde **7**, which was immediately used in the following steps without further purification. The aldehyde **7** reacted with the ylide derived from the 3-(tetrahydropyranyloxypropyl)triphenyl phosphonium bromide **8**[11] and KHMDS to afford the pure *cis*-β,γ-ethylenic derivative **9** in 74% yield. No trace of

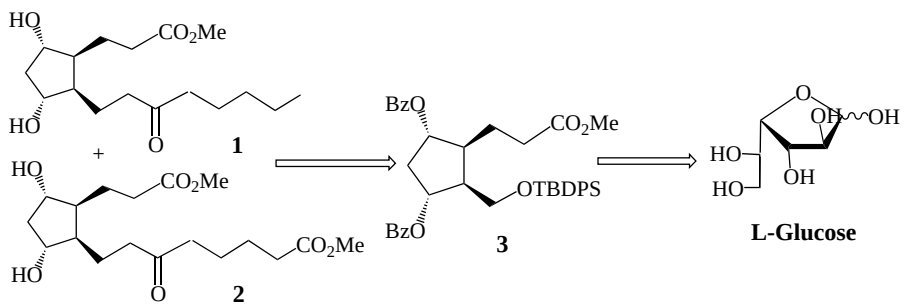

Figure 1. Retrosynthesis scheme.

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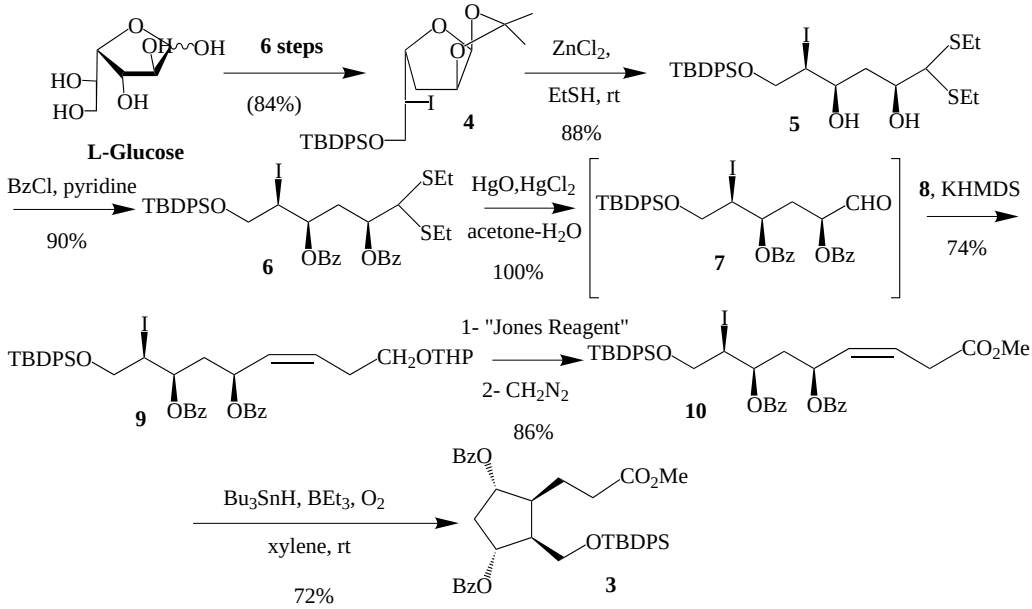
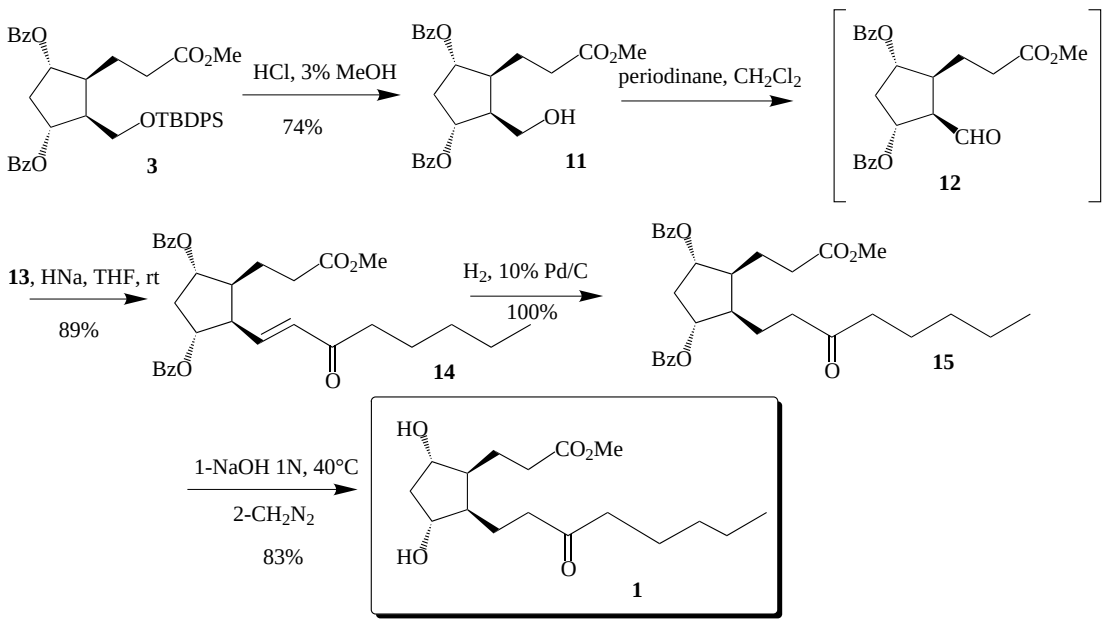
PII: S0040-4039(01)00754-7



Scheme 1.



Scheme 2.

the *trans* compound could be detected by ^{13}C and ^{1}H NMR analysis.

Oxidation of the protected primary alcohol **9** gave the corresponding acid, which in the presence of an excess of diazomethane was transformed in 86% yield into the methyl ester **10**. The radical precursor **10** was converted to highly funtionalized hex-5-enyl radical then the intramolecular cyclization was achieved[12] to yield 72% of the protected *syn–anti–syn* cyclopentane compound **3**.[13] The *tert*-butyldiphenylsilyl ether **3** was converted into the alcohol **11** in 74% yield, with a solution of 3% hydrogen chloride in methanol/ethyl ether (1:1, v/v).[14] Dess–Martin oxidation[15] of **11** with periodinane in CH_2Cl_2 gave the unstable aldehyde **12**, which was immediately used in the next step without purification to avoid any epimerization of the aldehyde. It is important to note that this Dess–Martin oxidation gave a higher yield avoiding any epimerization than our first attempts using Swern conditions. The condensation of **12** with diethyl oxoheptyl–phosphonate **13**, in the presence of NaH, in anhydrous THF, afforded the *trans*-α,β-enone **14** in 89% overall yield from the alcohol **11**. Reduction of the *trans* double bond on the ω chain, was achieved using H_2 on 10% Pd/C, giving the corresponding oxo derivative **15** in 100% yield. Finally, cleavage of the ester functions of **15** with 1N NaOH, followed by treatment with diazomethane gave the 2,3,4,5-tetranor-

15-oxo-5,6,13,14-tetrahydro-15F_{2t}-isoP methyl ester **1** in 83% yield (Scheme 2).

The synthesis of 20-carboxy-2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F_{2t}-isoP dimethyl esters **2** from **12** is shown in Scheme 3. The condensation of **12** with diethyl [6-(methoxycarbonyl)-2-oxohexyl]phosphonate **16**,[16] in the presence of NaHMDS, in anhydrous THF at −78°C, afforded the *trans*-α,β-enone **17** in 64% overall yield from the alcohol **11**.

During the Horner–Wadsworth–Emons reaction, it was not possible to avoid the formation of the compound **18** derived from the elimination of the benzoyl group at C11 (Scheme 3). Reduction of the *trans* double bond on the ω chain, was achieved using H_2 on 10% Pd/C, giving the corresponding oxo derivative. Finally, cleavage of the ester functions with 1N NaOH, followed by treatment with diazomethane gave the 20-carboxy-2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F_{2t}-isoP dimethyl esters **2** in 83% yield

In conclusion, we describe the first stereoselective synthesis of 2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F_{2t}-isoP methyl ester **1** in 17 steps and 20-carboxy-2,3,4,5-tetranor-15-oxo-5,6,13,14-tetrahydro-15F_{2t}-isoP dimethyl esters **2** in 18 steps from commercially available L-glucose. This route allows the enantiospecific synthesis of two main urinary metabolites of 15F_{2t}-isoP, which provides the basis for the development of methods of assay for its quantification in different fluids. Such studies are currently being investigated.

Supplementary material

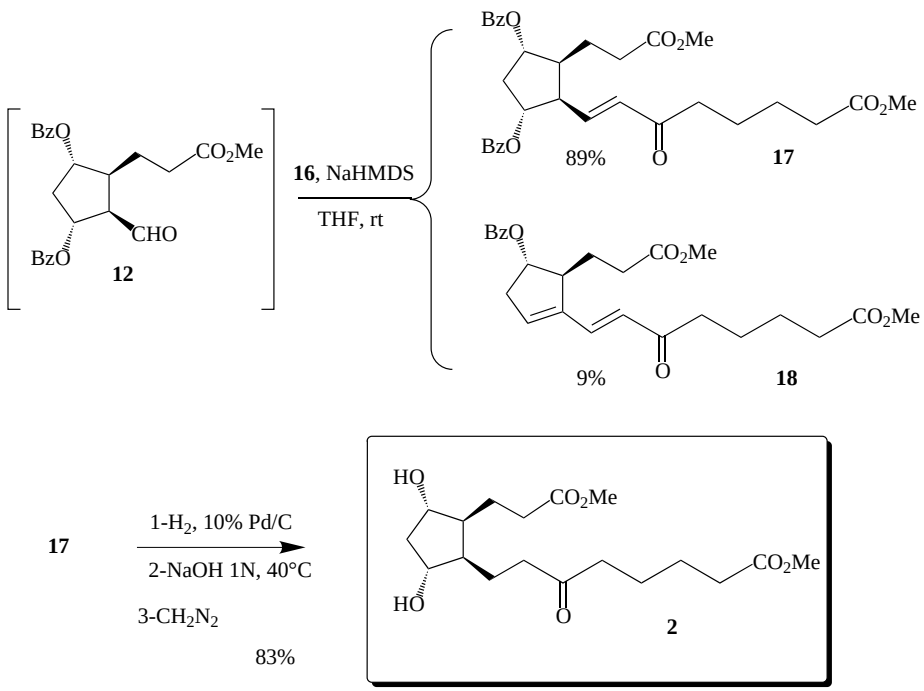
Full experimental data for the compounds **3**, **1** and **2**.

(1*R*,2*S*,3*S*,4*S*)-1,4-Bis-*O*-(benzoyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-(methoxycarbonylethyl)cyclopentane-1,4-diol (**3**):

IR: $\nu = 1715$ cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.09 (s, 9H), 1.94–1.70 (m, 2H), 1.90 (dq, 1H, $J = 15.7$ Hz, $J = 4.15$ Hz, $J = 2.82$ Hz), 2.37 (t, 2H, $J = 8.62$ Hz), 2.59–2.49 (m, 1H), 2.64–2.54 (m, 1H), 2.95 (dt, 1H, $J = 15.7$ Hz, $J = 7.4$ Hz), 3.60 (s, 3H), 3.70 (dd, 1H, $J = 10.95$ Hz, $J = 5.14$ Hz), 3.86 (dd, 1H, $J = 10.95$ Hz, $J = 5.14$ Hz), 5.31 (dq, 1H, $J = 6.14$ Hz, $J = 4.15$ Hz, $J = 7.4$ Hz), 5.40 (dt, 1H, $J = 7.4$ Hz, $J = 2.82$ Hz), 7.38–7.31 (m, 4H), 7.45–7.35 (m, 2H), 7.45–7.36 (m, 4H), 7.57–7.49 (m, 2H), 7.71–7.63 (m, 4H), 8.06–7.95 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 19.1, 23.2, 26.9, 32.7, 39.4, 45.0, 48.8, 51.5, 61.7, 77.4, 79.2, 127.8, 128.3, 129.6, 129.8, 130.3, 132.9, 132.9, 135.6, 135.7, 166.0, 166.1, 173.4. Anal. calcd for $C_{40}H_{44}O_7Si$: C, 72.26; H, 6.67. Found: C, 72.24; H, 6.68. $[\alpha]_D^{20} = +11.5$ ($c = 10^{-3}$, MeOH).

20-Carboxy-2,3,4,5-tetranor-5,6,13,14-tetrahydro-15-oxo-15-F_{2t}-isoprostane dimethyl esters (**2**)

IR: $\nu = 3409,1732,$ 1713 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.31–1.44 (m, 1H), 1.35–1.48 (m, 1H), 1.51–1.60 (m, 1H), 1.53–1.60 (m, 2H), 1.54–1.64 (m, 2H), 1.59–1.71 (m, 1H), 1.65–1.77 (m, 1H), 1.94–2.02 (m, 1H), 1.97–2.05 (m, 1H), 2.29 (t, 2H, $J = 7.13$ Hz), 2.32–2.43 (m, 2H), 2.32–2.423 (m, 1H), 2.35–2.44 (m, 2H), 2.49 (t,



Scheme 3.

2H, $J=7.30$ Hz), 3.64 (s, 3H), 3.65 (s, 3H), 3.85–3.91 (m, 1H), 3.90–3.95 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 21.6, 23.1, 23.2, 24.4, 32.7, 33.8, 41.1, 42.4, 42.9, 48.8, 48.9, 51.5, 51.6, 76.0, 76.2, 174.0, 210.5. Anal. calcd for $C_{18}H_{30}O_7$: C, 60.32; H, 8.44. Found: C, 60.35; H, 8.42. $[\alpha]_D^{20}=+1.13$ ($c=10^{-3}$, MeOH).

2,3,4,5-Tetranor-5,6,13,14-tetrahydro-15-oxo-15-F_{2t}-isoprostane methyl ester (**1**)

IR: $\nu=3415$, 1736, 1712 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H, $J=6.97$ Hz), 1.16–1.30 (m, 2H), 1.22–1.32 (m, 2H), 1.32–1.45 (m, 1H), 1.36–1.49 (m, 1H), 1.52–1.61 (m, 1H), 1.50–1.60 (m, 2H), 1.59–1.72 (m, 1H), 1.66–1.79 (m, 1H), 1.95–2.03 (m, 1H), 1.98–2.07 (m, 1H), 2.33–2.44 (m, 3H), 2.35–2.43 (m, 2H), 2.49 (dd, 2H, $J=7.3$ Hz, $J=7.8$ Hz), 3.65 (s, 3H), 3.87–3.93 (m, 1H), 3.91–3.97 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 13.9, 21.7, 22.4, 23.1, 23.5, 31.4, 32.7, 41.1, 42.9, 48.9, 49.0, 51.6, 76.0, 76.3, 174.0, 211.3. Anal. calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 64.97; H, 9.61. $[\alpha]_D^{20}=+1.34$ ($c=10^{-3}$, MeOH).

Acknowledgements

The authors thank Professor Valdimir Bezuglov, Moscow (Russia) and Dr. Chiara Chiabrando, Milan (Italy) for helpful discussions.

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