Selective Synthesis of ent-15-epi-F$_2$-Isoprostane and a Deuterated Derivative

Manami Shizuka, Marc L. Snapper*
Department of Chemistry, Eugene F. Merkert Chemistry Center, Boston College, 2609 Beacon Street, Chestnut Hill, MA 02467, USA
Fax +1(617)5521442; E-mail: marc.snapper@bc.edu
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Abstract: Isoprostanes are an emerging class of lipid metabolites whose physiological properties are not well understood. The selective synthesis of ent-15-epi-F$_2$-isoprostane, an isomer active in a preliminary screening assay is described. The synthesis features a regioselective cross-metathesis on an enantiomerically enriched divinyl cyclopentyl intermediate to selectively differentiate the side-chains of the target. The route provides the isoprostane, as well as a $d_4$-labeled analogue, in 14 steps from readily available starting materials.

Key words: asymmetric synthesis, metathesis, olefination, lipids

Isoprostanes are produced upon non-enzymatic, free radical peroxidation of phosphatidyl arachidonates (Scheme 1).\(^1\) In addition to possible activities within the lipid bilayer, hydrolytic release of these soluble lipid oxidation products may also lead to a variety of physiological responses. The biological activities of the isoprostanes that have been identified to date typically involve inflammatory responses, as well as activities related to smooth muscle growth factors,\(^2\) and platelet aggregation factors.\(^3\) These lipid metabolites are also recognized as important indicators of oxidative stress,\(^4\) particularly in human maladies such as Alzheimer’s disease,\(^5\) diabetes,\(^6\) and cancer.\(^7\) While progress has been made in understanding the formation and distribution of the isoprostanes, significant questions remain regarding the physiological roles for these endogenous metabolites.

Total synthesis has begun to provide useful quantities of isoprostanes and derivatives required for their further study.\(^8\) In this regard, we disclosed the preparation of all eight 15-F$_2$-isoprostane isomers via a stereodivergent strategy (Figure 1).\(^9\) The key intermediate in the synthesis was obtained from a [2+2] photocycloaddition between an enone and acetylene, followed by a ring-opening cross-metathesis.\(^10\) Subsequent resolution of the racemic diastereomers by an asymmetric CBS-reduction provided the individual isoprostanes isomers in an enantiomerically enriched manner. This sequence offered simultaneous access to the complete library of 15-F$_2$-isoprostanes from a common synthetic precursor 1.

Preliminary screening of the eight diastereomeric 15-F$_2$-isoprostanes in a whole blood platelet aggregation inhibition assay indicated that the unknown ent-15-epi-F$_2$-iso-

Scheme 1 Formation of the 15-F$_2$-isoprostanes

prostane was more active than the known inhibitor, 15-F$_{2\alpha}$-isoprostane.\(^11\) To further study this particular isoprostane isomer, we modified our synthetic strategy toward the 15-F$_2$-isoprostanes to provide access to any specific isoprostane isomer. Herein, we describe how a regioselective olefin cross-metathesis of an enantiomerically enriched divinyl intermediate provides ent-15-epi-F$_{2\alpha}$-isoprostane and a mass-labeled derivative in an enantioselective manner.

Our synthesis of ent-15-epi-F$_{2\alpha}$-isoprostane begins with enone 4, generated efficiently and selectively from an enzymatic desymmetrization of meso-diol 2 (with pancreatin lipase).\(^12,13\) Enone 4 can be accessed by functional group manipulations from 3 in 80% overall yield (Scheme 2).\(^14\)

A photochemical [2+2] cycloaddition between enone 4 and acetylene generates a mixture of bicyclo[3.2.0]heptenones 5 and 6 (5:6 = 2:1, Scheme 3). DIBAL-H reduction of the mixture yields isomers 7, 8, 9, and 10, which are separable by silica gel chromatography. The reduction favors the desired hydroxyl stereochemistry by an 84:16 ratio. The major product 7 could be isolated and the remaining fractions could be oxidized with PCC back to a mixture of 5 and 6. Preliminary results show that the un-
desired syn-endo photoadduct 6 can be photoisomerized using a Vycor filter to a 1:1 ratio of the desired syn-exo 5 isomer and the starting syn-endo 6. This isomerization between the two diastereomers is likely occurring through a 1,3-acyl migration.\(^{15}\) Given the reoxidation and isomerization pathways, in principle, all undesired isomers can be used to increase the overall yield of adduct 7; however, in practice only cyclobutene 8 was routinely recycled.

Ring-opening cross-metathesis (ROCM) of syn-exo compound 7 in benzene using Grubbs’ catalyst 11 under an ethylene atmosphere generates the divinyl species 13 in 87% yield (Scheme 4).\(^{10,16}\) High dilution is required to avoid ring-opening metathesis polymerization (ROMP). In contrast, cross-metathesis (CM) of divinyl compound 13 with oct-1-en-3-one finds optimal conditions under higher concentration in CH\(_2\)Cl\(_2\) at 40 °C with 5 mol% Hoveyda–Grubbs catalyst 12. This leads to the desired mono-CM product in high selectivity; none of the other regioisomeric cross-metathesis product is observed and only trace amount of the double cross-metathesis product is obtained.\(^{17}\) The newly formed enone in the desired product is formed exclusively with \(E\)-stereoselectivity. The high regioselectivity of the cross-metathesis could arise through ruthenium coordination by the free hydroxyl group on the cyclopentyl ring, although steric hindrance of the silyl protecting group on the other hydroxyl functionality may also play a role in dictating the selectivity of the reaction.

When cyclobutene 7 was subjected to a direct ROCM with oct-1-en-3-one using Hoveyda–Grubbs catalyst 12, the desired compound 14 was not obtained; mainly ROMP of the cyclobutene was observed. Furthermore, Grubbs’ catalyst 11 was unreactive in a ROCM with oct-1-en-3-one; only starting materials were recovered. Since the two metatheses require different reaction conditions, it was necessary to run these transformations in a stepwise fashion.

Silyl protection of the free hydroxyl group, followed by an asymmetric catalytic reduction of enone 14 with (R)-2-methyl-CBS-oxazaborolidine\(^{18}\) and catecholborane led to alcohol 15 in high yield and diastereomeric excess (>95:5...
Scheme 4 Installation of the isoprostanyl side-chains through a regio- and stereoselective cross-metathesis. Reagents and conditions: (a) ethylene, 5 mol% 11, benzene (0.01 M), 87%; (b) oct-1-en-3-one, 5 mol% 12, CH₂Cl₂, (0.2 M), 40 °C, 70–90%; (c) TBSCI, Et₃N, DMAP, CH₂Cl₂, 99%; (d) (R)-2-methyl-CBS-oxazaborolidine, catecholborane, toluene, –78 °C; 99%.

In addition, this route also allowed for the preparation of a tetradeuterated analogue of ent-15-epi-F₂t-isoprostane.21 Exhaustive reduction of methyl sorbate under D₂ gave 17 in 60% yield (Scheme 6). Weinreb amide22 formation, followed by vinyl group addition provided tetradeu tero- enone 18. Enone 18 was then used for the cross-metathesis partner with 13 as described in Scheme 4. The rest of the synthesis was carried out in an analogous manner to that shown in Schemes 4 and 5 to yield d₄-ent-15-epi-F₂t-isoprostane.

d₄-ent-15-epi-F₂t-isoprostane was used as an internal standard in a GC/MS assay to detect isoprostanes in human urine.23 Four diastereomeric 15-F₂t-isoprostanes were separated on an achiral GC column.24 Although the known 15-F₂t-isoprostane was not detected in this assay, preliminary results revealed that the ent-15-epi-F₂t-isoprostane (or its enantiomer) was present in the urine sample.

In summary, we have achieved a stereoselective synthesis of ent-15-epi-F₂t-isoprostane through a regio- and stereoselective ring-opening cross-metathesis/cross-metathesis sequence. Enzymatic acylation generates the starting enone 4 as a single enantiomer. Photocycloaddition with acetylene followed by functional group manipulations provides an enantiomerically enriched precursor for the key metatheses. A catalyst-controlled asymmetric reduction completes one of the 15-F₂t-isoprostanyl side-chains and allows for the installation of the second side-chain. The overall sequence provides efficient access to ent-15-epi-F₂t-isoprostane and allows for the selective access of any of the 15-series isoprostanes. Further biological and chemical studies of ent-15-epi-F₂t-isoprostane are underway.
sensitive solids were transferred in a glove box. Unless otherwise stated, reactions were stirred with a Teflon-covered stir bar. Concentration refers to the removal of solvent under reduced pressure using a Büchi rotary evaporator. Silica gel column chromatography was performed using Baxter brand gel silica gel 60 Å (230–400 mesh ASTM). Cerium ammonium molybdate was used as the TLC staining reagent. IR spectra (FTIR) were recorded on a Nicolet 210 FT-IR spectrometer, and reported in wave numbers (cm⁻¹). 1H NMR and 13C NMR spectra were measured on a Varian Gemini-400 instrument at 400 MHz (1H NMR) and 100 MHz (13C NMR). Chemical shifts are reported with the solvent as the internal standard [CDCl₃: δ = 7.26 (1H NMR), δ = 77.0 (13C NMR)]. Enantiomer ratio was determined by chiral GLC analysis (Supelco BetaDEX 120 column (30 m × 0.25 mm). Optical rotations were measured on a Rudolph Research Analytical Autopol IV polarimeter. High-resolution mass spectral (HRMS) analyses were performed on a Micromass LCT ESI-MS (positive mode) at the Mass Spectrometry Laboratory at Boston College.

4-(t-Butylidimethylsiloxy)cyclopent-2-enone (4)

Monocarbonate 3 was obtained from literature procedure after recrystallization with hexane–benzene as white needle-like crystals (55% yield, >99% ee). The optical purity was established by chiral GLC analysis. Acetate 3 (957 mg, 6.74 mmol) and DMAP (411 mg, 3.37 mmol) were dissolved in CH₂Cl₂ (67 mL) at 0 °C. Et₃N (2.80 mL, 20.2 mmol) and TBSCL (2.03 g, 13.5 mmol) were added to the mixture at 0 °C. The solution was warmed to 23 °C and stirred for 12 h. The mixture was diluted with CH₂Cl₂ (60 mL) and washed with aq 0.5 M HCl (2 × 40 mL), aq sat. NaHCO₃ (1 × 50 mL) and brine (1 × 50 mL). The organic layer was dried (MgSO₄) and filtered, and solvent was removed under reduced pressure to give TBS-protected cyclopentenyl acetate (5) (not shown) as a colorless oil.

In a 3.0 L-photochemical vessel, enone 4 (432 mg, 1.80 mmol) in benzene (2.0 mL) was added to the mixture and stirred for 2 h. The solution was diluted with CH₂Cl₂ (20 mL) and washed with brine (2 × 50 mL). The aqueous layer was back-extracted with CH₂Cl₂ (3 × 25 mL) and the combined organic layers were dried (MgSO₄) and filtered. The solvent was removed under reduced pressure and the residue was dissolved in acetone (2.80 L). A Pyrex immersion well containing a medium-pressure mercury vapor lamp was placed in the immersion well and the stirred solution was irradiated with constant bubbling of acetylene for a total of 42 h (reaction progress monitored by GC). Solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (hexanes–EtOAc, 20:1, 10:1, 5:1) to give a mixture of 5 and 6 (δ = 2:1, 86% conv., 1.73 g, 74% yield, based on recovered starting material (BRSMI)). The 1H NMR and 13C NMR were identical to published results.

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4-(t-Butylidimethylsiloxy)bicyclo[3.2.0]hept-6-en-2-ones (5, 6)

In a 3.0 L-photochemical vessel, enone 4 (2.40 g, 11.3 mmol) was dissolved in aceton (2.80 L). A Pyrex immersion well containing a Pyrex sleeve (~3.5 mm thickness) was placed into the vessel and the solution was sparged with acetylene for 5 min. A 100 W medium-pressure mercury vapor lamp was placed in the immersion well and the stirred solution was irradiated with constant bubbling of acetylene for a total of 42 h (reaction progress monitored by GC). Solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (hexanes–EtOAc, 20:1, 10:1, 5:1) to give a mixture of 5 and 6 (δ = 2:1, 86% conv., 1.73 g, 74% yield, based on recovered starting material (BRSMI)). The 1H NMR and 13C NMR were identical to published results.

IR (film): 3530 (b), 3040 (w), 2953 (s), 2854 (m), 1459 (m), 1408 (s), 1253 (m), 1068 (s), 1053 (s), 1002 (s), 835 (s), 773 (s), 697 cm⁻¹ (m).

1H NMR (CDCl₃, 400 MHz): δ = 6.05 (1 H, d, J = 2.8 Hz), 5.99 (1 H, d, J = 3.6 Hz), 4.18 (1 H, d, J = 3.6 Hz), 4.00 (1 H, d, J = 11.2, 4.4 Hz), 3.36 (1 H, s), 3.23 (1 H, s), 3.10 (1 H, d, J = 11.2 Hz), 2.31 (1 H, d, J = 14.0, 4.4 Hz), 1.87 (1 H, d, J = 14.4 Hz), 0.89 (9 H, s), 0.09 (6 H, s).

13C NMR (CDCl₃, 100 MHz): δ = 140.3, 138.7, 73.9, 57.2, 56.5, 40.4, 26.2, 18.4, –4.38, –4.50.

HRMS (ESI⁺): m/z calc for C₁₁H₂₀O₂Si + Na (M + Na): 263.1443; found: 263.1443.

4-(t-Butylidimethylsiloxy)-2,3-dimethyleneocta-2,7-dien-1-ol (13)

Grubbs catalyst 11 (74.0 mg, 89.8 µmol) was stirred in benzene (87.9 mL) and sparged with ethylene (balloon) for 5 min. Cyclobutene 7 (432 mg, 1.80 mmol) in benzene (2.0 mL) was added to the mixture and stirred under an ethylene atmosphere (balloon) at 23 °C for 15 h. The mixture was opened to air and ethyl vinyl ether (1.0 mL) was added and stirred for 5 min. Silica gel (4.20 g) was then added and stirred for another 15 min. The slurry was filtered through a plug of silica gel and washed with hexanes–EtOAc (3:1, 30 mL). The filtrate was concentrated and purified by silica gel chromatography (hexanes–EtOAc, 5:1) to obtain 13 as a clear yellow oil (426 mg, 88%); [α]₂₀⁺0.16 (c = 0.37, CHCl₃).

IR (film): 3359 (b), 2955 (s), 2928 (s), 2857 (s), 1639 (w), 1471 (m), 1256 (s), 1089 (b), 912 (s), 836 (m), 773 (s), 697 cm⁻¹ (m).

1H NMR (CDCl₃, 400 MHz): δ = 5.66 (1 H, ddd, J = 17.1, 10.2, 8.8 Hz), 5.06–5.51 (1 H, m), 5.14–5.06 (3 H, m), 5.03 (1 H, ddd, J = 6.0, 1.0, 0.5 Hz), 4.06–4.01 (2 H, m), 2.84 (1 H, ddd, J = 8.5, 8.3, 5.4 Hz), 2.77 (1 H, ddd, J = 8.8, 8.3, 3.1 Hz), 2.36 (1 H, dt, J = 14.1, 6.5 Hz), 2.00 (1 H, d, J = 6.7 Hz), 1.69 (1 H, dt, J = 14.1, 4.0 Hz), 0.88 (9 H, s), 0.05 (6 H, s).

HRMS (ESI⁺): m/z calc for C₁₃H₂₄O₂Si + Na (M + Na): 263.1443; found: 263.1445.

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13C NMR (CDCl3, 100 MHz): δ = 137.3, 137.0, 116.8, 116.7, 77.4, 76.7, 56.6, 55.7, 43.4, 26.2, 18.4, -4.1, -4.3.

HRMS (ESI+): m/z calculated for C16H20O3Si + Na (M + Na): 291.1756; found: 291.1753.

1-[3-(tert-Butyl(dimethyl)silyl)-5-hydroxy-2-vinylcyclopentyl]oct-1-en-3-ol (14)

Divinyl compound 13 (425 mg, 1.58 mmol) and oct-1-en-3-one (300 mg, 2.37 mmol) were dissolved in CH2Cl2 (8.0 mL). Hoveyda–Grubbs catalyst 12 (50.0 mg, 0.09 mmol) was added and the mixture was heated to 40 °C. The mixture was stirred for 5 h, then cooled to 23 °C and opened to air. Ethyl vinyl ether (2.0 mL) was added and the mixture was stirred for 5 min. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (hexanes–EtOAc, 5:1) to obtain 14 as a light brown oil (429 mg, 74%; [α]D20 +11 (c 0.30, CHCl3). IR (film): 3425 (b), 2956 (s), 2928 (s), 2857 (s), 1669 (m), 1625 (m), 1563 (m), 1459 (m), 1417 (m), 1373 (m), 1370 (m), 1168 (m), 1167 (m), 774 (m), 767 (s), 566 (s), 557 (s), 434 (s), 262 (s), 184 (s), -4.1, -4.3.

1H NMR (CDCl3, 400 MHz): δ = 6.67 (1 H, dd, J = 15.8, 9.0 Hz), 6.19 (1 H, dd, J = 15.8, 1.1 Hz), 5.49 (1 H, dd, J = 16.4, 10.8, 9.6 Hz), 5.09–5.04 (2 H, m), 4.13 (1 H, t, J = 7.3, 4.7 Hz), 4.08 (1 H, dt, J = 5.9, 3.1 Hz), 3.01 (1 H, dd, J = 8.3, 5.5 Hz), 2.88–2.83 (1 H, m), 2.50 (2 H, t, J = 7.3 Hz), 2.39 (1 H, dd, J = 14.3, 7.2, 5.7 Hz), 2.12 (1 H, d, J = 7.5 Hz), 1.74 (1 H, dt, J = 13.8, 3.3 Hz), 1.64–1.56 (2 H, m), 1.35–1.24 (4 H, m), 0.91–0.87 (3 H, m), 0.89 (9 H, s), 0.06 (6 H, s).

13C NMR (CDCl3, 100 MHz): δ = 200.2, 193.6, 151.0, 135.9, 130.6, 119.6, 77.3, 76.6, 57.1, 54.2, 43.6, 41.0, 31.8, 26.6, 24.3, 22.8, 18.4, 14.3, -4.1, -4.2.

HRMS (ESI+): m/z calculated for C16H20O3Si + Na (M + Na): 291.1756; found: 291.1753.

1-[3-(5-Bis(tert-butyl(dimethyl)silyl)-5-hydroxy-2-vinylcyclopentyl]oct-1-en-3-ol (15)

Enone 14 (362 mg, 0.99 mmol) and DMAP (60.2 mg, 0.49 mmol) were dissolved in CH2Cl2 (9.9 mL). Et3N (412 µL, 2.96 mmol) and TBSCl (297 mg, 1.97 mmol) were added to the mixture. The solution was stirred at 23 °C for 12 h. The mixture was diluted with CH2Cl2 (40 mL) and washed with 0.5 M HCl (2 × 15 mL), aq sat. NaHCO3 (1 × 20 mL), and brine (1 × 20 mL). The organic layer was dried (MgSO4), filtered, and solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (hexanes–EtOAc, 4:1) to afford 15 as a colorless oil (232 mg, 64%; [α]D20 +15.6 (c 2.40, CHCl3). IR (film): 3388 (b), 2956 (s), 2925 (s), 2857 (s), 1647 (m), 1468 (m), 1363 (m), 1258 (m), 1061 (m), 851 (m), 770 (m), 666 cm–1 (m).

1H NMR (CDCl3, 400 MHz): δ = 5.51 (1 H, dd, J = 15.4, 9.9 Hz), 5.37 (1 H, dd, J = 15.4, 6.5 Hz), 4.06 (1 H, q, J = 6.4 Hz), 3.90–3.84 (2 H, m), 3.73–3.60 (2 H, m), 3.28–3.16 (1 H, m), 1.98–1.87 (4 H, m), 0.91–0.89 (2 H, m), 0.89 (9 H, s), 0.88–0.86 (1 H, m), 0.87 (9 H, s), 0.07 (6 H, s), 0.02 (6 H, s).

13C NMR (CDCl3, 100 MHz): δ = 135.5, 129.5, 76.7, 76.2, 72.9, 61.3, 56.4, 46.0, 44.4, 37.4, 32.4, 31.9, 25.9, 25.2, 22.7, 18.2, 18.1, 14.2, -3.9, -4.4, -4.5.

HRMS (ESI+): m/z calculated for C19H36O2Si2Na (M + Na): 523.3615; found: 523.3625.

Diol IV (232 mg, 0.463 mmol) and Bu4NCl (25.7 mg, 92.6 µmol) were stirred in CH2Cl2 (3.8 mL) and H2O (carbonate buffer, pH 8.6, 3.8 mL) at 23 °C. NCS (68.0 mg, 0.509 mmol) and TEMPO (14.5 mg, 92.6 µmol) was added to the mixture and stirred for 5 h. The mixture was diluted with CH2Cl2 (10 mL) and the CH2Cl2 layer washed with brine (2 × 15 mL). The aqueous layer was back-extracted with CH2Cl2 (3 × 15 mL) and the combined organic layers were dried (MgSO4), filtered, and concentrated. The residue was purified by silica gel chromatography (hexanes–EtOAc, 3:1; 1:1) to obtain the aldehyde 16 as a thick orange oil (184 mg, 99%, BSRM) and starting material (49 mg, 80% conv.), t-ButOK (329 mg, 2.94 mmol) in THF (4.9 mL) was added to a stirred solution of carboxybutyltriphenylphosphonium bromide (651 mg, 1.47 mmol) in THF (3.1 mL) at 23 °C. After this bright orange ylde solution was stirred for 20 min, it was syringed into a stirred solution of the aldehyde (183 mg, 0.37 mmol) in THF (1.1 mL). After the reaction was stirred for 3.5 h, aq sat. NH4Cl (15 mL) and glacial AcOH (1 mL) were added. The solution was extracted with EtOAc (3 × 10 mL), dried (MgSO4), filtered, and concentrated. The residue was purified by silica gel chromatography (hexanes–EtOAc–AcOH, 5:1:0) to obtain TBS-protected-isoprostane V (not shown) as a colorless oil (200 mg, 93%). TBAF (1 M in THF, 2.69 mL, 2.69 mmol) was added to neat V (196 mg, 0.37 mmol) at 23 °C and stirred overnight. The mixture was opened to air and diluted with EtOAc (5.0 mL) and washed with aq sat. NaHCl (2 × 5 mL) solution. The aqueous layer was back-extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (1 × 25 mL). The solution was dried (MgSO4), filtered, and solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (EtOAc–MeOH–AcOH, 20:1:0.1) to obtain ent-15-epi-F2-isoepi.
tane as a pale yellow oil (104 mg, 87%); \([\text{H}]_{20}\text{.} -1.1 \text{ (c 0.55, MeOH).}

IR (film): 3363 (b), 2999 (w), 2923 (m), 2847 (m), 1698 (s), 1405 (w), 1235 (w), 1052 (m), 965 cm\(^{-1}\) (m).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 5.59 (1, \text{ dd, } J = 15.3, 6.6 \text{ Hz}), 5.52-5.40 (3, \text{ m}), 4.12 (1, \text{ q, } J = 6.4 \text{ Hz}), 4.04-4.00 (2, \text{ m}), 3.94-3.52 (3, \text{ br s}), 2.78 (1, \text{ dq, } J = 8.6, 3.9 \text{ Hz}), 2.44 (1, \text{ H, dt, } J = 14.7, 6.9 \text{ Hz}), 2.32 (2, \text{ H, t, } J = 6.4 \text{ Hz}), 2.21-2.04 (4, \text{ m}), 1.99-1.90 (1, \text{ m}), 1.74-1.61 (3, \text{ m}), 1.60-1.45 (2, \text{ m}), 1.39-1.25 (6, \text{ m}), 0.88 (3, \text{ H, t, } J = 6.5 \text{ Hz}).

\(^13\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 176.5, 135.2, 129.7, 129.4, 129.2, 76.5, 76.4, 73.1, 53.8, 50.8, 42.3, 37.3, 32.6, 31.8, 27.0, 26.3, 25.2, 24.4, 22.7, 14.2.

HRMS (ESI\(^+\): m/z calcd for C\(_{20}\)H\(_{30}\)D\(_4\)O\(_5\) + Na (M + Na): 377.2304; found: 377.2290.

\(d_{4}\)-ent-15-ei-F2t-Isoprostane

The synthesis was carried out analogously as above, starting with cross-metathesis of the appropriate \(d_{4}\)-oct-1-en-3-one and divinyl cyclooctane 13.\(^{20}\) \([\text{H}]_{20}\text{.} -0.6 \text{ (c 0.33, MeOH).}

IR (film): 3420 (b), 2930 (m), 2873 (m), 1709 (s), 1413 (w), 1255 (m), 1193 (w), 1060 (m), 966 cm\(^{-1}\) (m).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 5.56 (1, \text{ dd, } J = 15.2, 6.8 \text{ Hz}), 5.48-5.40 (3, \text{ m}), 4.18 (1, \text{ H, br s}), 4.14 (1, \text{ q, } J = 6.0 \text{ Hz}), 4.00-4.01 (2, \text{ m}), 2.81-2.76 (1, \text{ m}), 2.43 (1, \text{ H, dt, } J = 14.8, 6.8 \text{ Hz}), 2.32 (2, \text{ H, t, } J = 6.5 \text{ Hz}), 2.21-2.04 (4, \text{ m}), 1.98-1.93 (1, \text{ m}), 1.70-1.61 (3, \text{ m}), 1.54-1.46 (2, \text{ H, m}), 1.34-1.24 (4, \text{ H, m}), 0.89-0.84 (3, \text{ H, m}).

\(^13\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 178.5, 135.6, 130.1, 129.7, 129.4, 76.6, 76.5, 73.2, 53.8, 50.9, 42.4, 32.7, 27.0, 26.4, 24.4, 23.5, 14.1.

HRMS (ESI\(^+\): m/z calcd for C\(_{20}\)H\(_{30}\)D\(_4\)O\(_5\) + Na (M + Na): 381.2550; found: 381.2555.

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References

(1) For free radical peroxidation of arachidonic acid, see:


(14) For a more recent and convenient approach to this intermediate, see: Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. Nature (London) 2006, 443, 67.
(17) Regioselectivity was determined by COSY NMR.
(19) Selectivity was determined by 1H NMR (estimated detection limits of 20:1) by comparison with authentic samples of each diastereomer.
(24) More details on the setup and results of the GC/MS detection assay may be obtained by contacting the authors.
(27) Data shown for a 74% yield reaction. Yields range from 70–90%, depending on catalyst purity.
(28) This compound is the major isomer; however, it is in a mixture of isomers of lower deuterium incorporation.