First Total Synthesis of A_2 Isoprostane

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A stereoselective Julia−Lythgoe olefination has allowed the first total synthesis of A_2 isoprostane (**1**), a recently discovered member of the growing isoprostane family. This elusive compound opens up numerous new avenues for the molecular biology of cyclopentenone prostaglandins, which are endowed of intriguing biological effects such as antitumor, antiinflammatory, and antiviral activities.

Isoprostanes (IsoP) are prostaglandin-like compounds produced in humans by a nonenzymatic free radical peroxidation of membrane-bound arachidonic acid.[1]

These oxidation products differ from prostaglandins by the thermodynamically less stable cis stereochemistry relationship between the two side chains on the five-membered ring. This is one of the notable differences between the enzymatic process, yelding the trans products, and free-radical processes, affording the cis structures.[2] The preponderance of the cis stereochemistry in the newly formed cyclopentane ring is consistent with the Beckwith−Houk model of hex-5-enyl radical cyclizations.[3] Another important feature of the nonenzymatic pathway to natural isoprostanes is the absence of control on the absolute stereochemistry of the stereogenic centers of the cyclopentane ring and C-15 hydroxyl group. Besides the well-known F_2-, D_2-, and E_2-IsoPs, in 1999 Morrow and Roberts[4] reported the formation in vivo of two new elusive isoprostanes belonging to the A_2 and J_2 families that are formed presumably through dehydration of D_2- and E_2-IsoPs, respectively.[5] Representative examples of F_2-, D_2-, E_2-, and J_2-IsoPs are reported in Figure 1.

A_2- and J_2-isoprostane could not be isolated from the biological fluids, and no stereochemical assignment was therefore possible. Indeed, in consequence of the radical isoprostane pathway, and in analogy with other isoprostanes,[4] A_2-IsoP **1** should comprise a mixture of four stereoisomers: 15-A_{2c}-IsoP **2**, 15-*epi*-15-A_{2t}-IsoP **3**, 15-A_{2t}-IsoP **4**, and 15-*epi*-15-A_{2c}-IsoP **5**, named accordingly to the isoprostane accepted nomenclature (Figure 2).[5b,6]

Isoprostanes A_2 (**1**) and J_2 (A_2-IsoP and J_2-IsoP) are isomeric of the cyclopentenone prostaglandins A_2 and J_2, respectively, which are reported to exert unique biological effects.[7] Indeed, prostaglandins of A_2 and J_2 series have

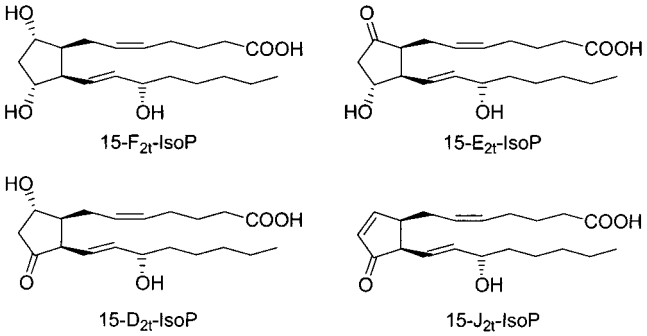

Figure 1. Representative isoprostanes of the F_2, D_2, E_2, and J_2 families.

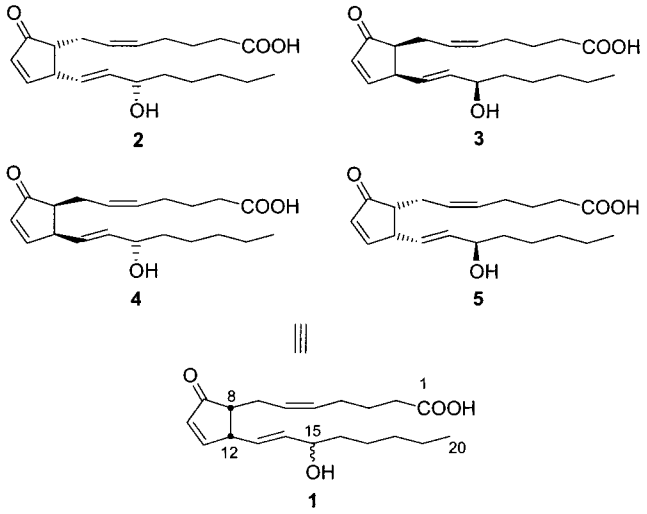

Figure 2. A_2 isoprostane family.

been reported to be active against a wide variety of DNA and RNA viruses, including HIV-1 and influenza virus. They also possess a potent antiinflammatory activity due to the inhibition and modification of the subunit IKKβ of the enzyme IκB kinase. In addition, these compounds induce arrest of cell mitosis at G_1 phase or apoptosis of tumor cells, depending on the cell type. Because of this intriguing biological profile, the investigation of pharmacological properties of cyclopentenone isoprostanes is therefore a very important task. Unfortunately, a detailed evaluation of the biological activities of A_2- and J_2-

(1) (a) Morrow, J. D.; Hill, T. M. K. E.; R. F. Burk, Nammour, T. M.; Roberts, J. L., II. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 9383. (b) Roberts, J. L., II; Morrow, J. D. *Biochim. Biophys. Acta* **1997**, *1345*, 121. (c) Roberts, J. L., II; Morrow J. D. *Prog. Lipid. Res.* **1997**, *36*, 1.

(2) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

(3) (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions. Concepts, Guidelines, and Synthetic Applications*; VCH: New York, 1996. (b) A. L. J. Beckwith, *Tetrahedron* **1981**, *37*, 3073.

(4) Rokach, J.; Khanapure, S. P.; Hwang, S.-W.; Adiyaman, M.; Schio, L.; FitzGerald, G. A. *Synthesis* **1998**, 569.

(5) (a) Chen, Y.; Zackert, E. W.; Roberts, J. L., II; Morrow, J. D. *Biochim. Biophys. Acta* **1999**, *1436*, 550. (b) Y. Chen, J. L. Roberts, J. D., II. Morrow, J.D. *J. Biol. Chem.* **1999**, *274*, 10863.

(6) Taber, D. F.; Morrow, J. D.; Roberts, J. L., II. *Prostaglandins* **1997**, *53*, 63.

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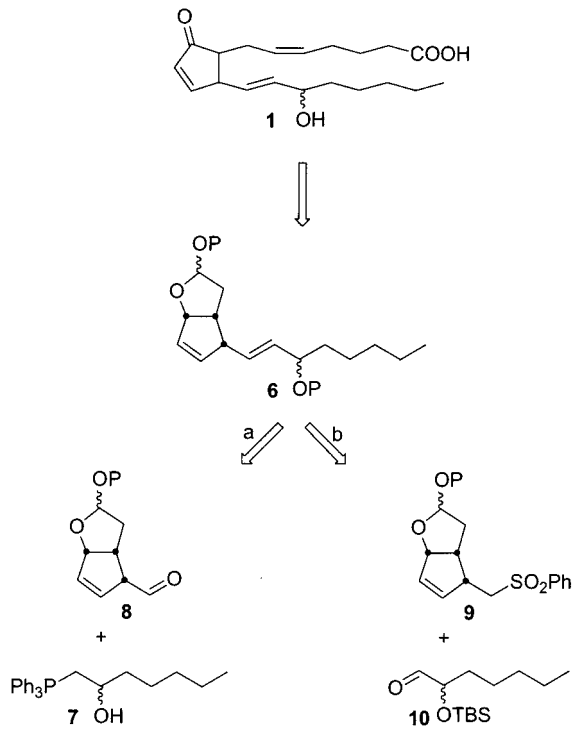
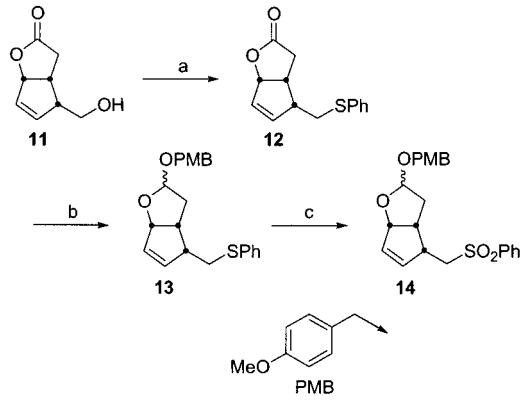
Scheme 1



Scheme 2[a]



[a] Reaction conditions: (a) $(PhS)_2$, Bu_3P, pyridine, rt, 4.5 h, 92%; (b) (1) DIBAL-H, DCM, −78 °C, 1.5 h, 97%; (2) PMB-OH, PTSA, DCM, −20 °C, 16 h, 95%; (c) H_2O_2, 10% mol $(NH_4)_2MoO_4$, MeOH, 0 °C to rt, 16 h, 95%.

IsoP has been prevented so far by poor availability of pure compounds.[5] Thus, the chemical synthesis of A_2- and J_2-isoprostanes is not only a highly challenging goal but is the only way to prepare enough material for biological studies. In achieving these elusive targets by total synthesis, one has to get over the inherent difficulty in installing the two side chains on the cyclopentenone ring with the thermodinamically less favored cis stereochemistry and has to avoid the subsequent easy epimerization of the labile stereogenic centers C-8 and C-12 (prostaglandin numbering). At the onset of our work, we deliberately decided to prepare A_2-IsoP in a non-stereoselective manner in order to collect preliminary information on the biological activity of the mixture of stereoisomers that are expected to occur in nature (see above).

Herein, we describe the first total synthesis of natural A_2-IsoP, and in this context, a method for the efficient construction of cis-disubstituted prostanoid-like cyclopentenones is reported.

Our retrosynthetic disconnection of A_2-IsoP (Scheme 1) followed the well-known prostaglandin chemistry, i.e., a retro-Wittig condensation,[8] which led to the protected *all-cis*-lactol **6** as the key intermediate of the synthesis. Two different tactics for the retrosynthesis of **6** could then be envisioned following either path a or path b. Disconnection along path a led to phosphoniun salt **7**[9] and the easily epimerizable aldehyde **8** with consequent possible erosion of the stereochemical integrity.[10]

Therefore, an unprecedented methodology for the construction of the lower side chain of PGA-like compounds should be envisioned. We reasoned that a highly stereoselective approach, based upon a retro-Julia−Lythgoe olefination, might arise from path b, in which a configurationally stable sulfone **9** and racemic O-TBS-protected aldehyde **10**[11] were the suitable starting compounds. It was anticipated that the unique stereochemical features of the Julia−Lythgoe reaction not only would allow the cis stereochemistry of sulfone **9** to be preserved but also would give rise to the stereodefined *E* double bond required in the lower side chain.[12] As an additional benefit, sulfone **9** could be readily obtained from the known hydroxymethyl lactone **11**[13] by a simple manipulation of functional groups (Scheme 2).

In the event, lactone **11** was treated with diphenyldisulfide in the presence of Bu_3P and pyridine to give the corresponding sulfide **12** in 92% yield.[14] Reduction of lactone **12** with DIBAL-H gave the corresponding lactol in 99% yield, which was immediately protected as *p*-methoxybenzyl ether **13**, in 95% yield, upon exposure to PMB-OH in the presence of a catalytic amount of PTSA.[14] Chemoselective oxidation of sulfide **13** to sulfone **14** was carried out with H_2O_2 in the presence of a catalytic amount of $(NH_4)_2MoO_4$ in methanol at rt.[15] Under these conditions, the carbon−carbon double bond was not affected by the oxidant, and the expected sulfone **14** was obtained in a gratifying 95% yield. The crucial Julia−Lythgoe condensation was then initially accomplished

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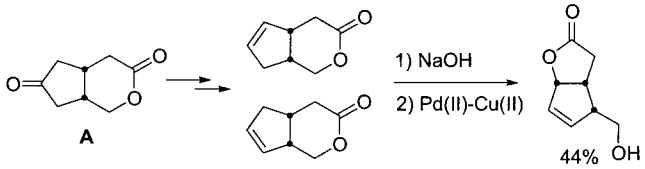
(9) Schwarz, S.; Weber, G.; Depner, J.; Schaumann, J.; Schick, H.; Welzel, H. P. *Tetrahedron* **1982**, *38*, 1261.

(10) Exposure of lactone **11** to Dess−Martin periodinane in $CDCl_3$ at rt gave, after 10 min, three different aldehyde signals in the ^1H NMR spectrum. This behavior is consistent with an easy epimerization of the C-12 stereogenic center and double-bond shift to the more substituted position.

(11) Nicolaou, K. C.; Marron, B. E.; Veale, C. A.; Webber, S. E.; Serhan, C. N. *J. Org. Chem.* **1989**, *54*, 5527.

(12) Kociennski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829.

(13) (a) The syntesis of lactone **11** has been recently accomplished[13b] in a 44% overall yield starting from the known ketolactone A.[13c]



(b) Zanoni, G.; Porta, A.; Meriggi A.; Franzini, M.; Vidari, G. 1,2-Oxopalladation vs. π-Allyl Palladium Route. A Regioconvergent Approach to a Key Intermediate for Cyclopentanoids Synthesis. New Insights into the Pd(II)-Catalyzed Lactonization Reaction. Manuscript in preparation. (c) Garlaschelli, L.; Vidari, G.; Zanoni, G. *Tetrahedron* **1992**, *43*, 9495.

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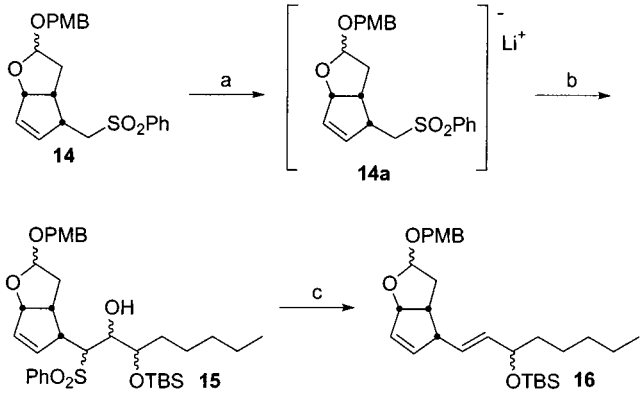
(15) Earl, H. A.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1273.

Scheme 3[a]



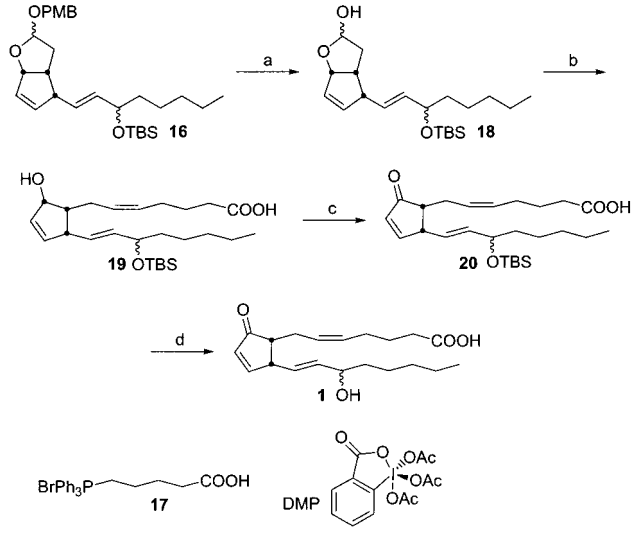
[a] Reaction conditions: (a) BuLi, THF, −78 °C, 45 min; (b) **10** in THF, −78 °C 2 h, 87%; (c) Na(Hg) 10% Na_2HPO_4, MeOH, −40 to −20 °C, 1.5 h, 81%.

according to the modification developed by Wicha.[16] This author showed that efficient coupling of a lithiated sulfone and a protected hydroxy aldehyde required the presence of 1.1 equiv of $BF_3 \cdot Et_2O$. In contrast, in absence of the Lewis acid, the yields of the corresponding Julia adduct dropped dramatically. In our hands, lithiated sulfone **14a** reacted sluggishly with aldehyde **10** (Scheme 3) under the Wicha conditions (BuLi, THF, −78 °C, 15 min, then BF_3 etherate, 15 min, followed by a THF solution of aldehyde **10**, −78 °C, 3 h), affording the corresponding hydroxysulfone **15**, as an inseparable mixture of stereoisomers, in a disappointingly low yield of 20%. By contrast, condensation of lithiated sulfone **14a** with aldehyde **10** in the absence of Lewis acid (BuLi, THF, −78 °C 45 min, followed by addition of **10** in THF, −78 °C, 2 h) smoothly afforded the desired hydroxysulfone **15**, as a mixture of diastereoisomers, in a gratifiyng 87% yield.

On the wave of this observation, upon exposing crude adduct **15** to 10% sodium amalgam in the presence of Na_2HPO_4 in MeOH at −20 °C, we were pleased to obtain the desired key PMB-protected lactol **16** in 81% yield.

With compound **16** in hand, completion of the synthesis of A_2-IsoP proceeded straightforwardly in a few additional steps as outlined in Scheme 4. Thus, standard olefination of the aldehyde function oxidatively released from acetal **16** (DDQ, phosphate buffer pH = 7.2)[17] with the nonstabilized Wittig reagent **17** smoothly gave the corresponding *Z* olefin **19**,[18] as a 1:1 mixture of two epimers at C-15 hydroxyl group. Compound **19** was immediately submitted to the crucial oxidation of the allylic hydroxyl group. Thus, Dess−Martin periodinane[20] oxidation of alchool **19** cleanly furnished the protected cyclopentenone **20**, aqueous HF mediated desilylaion[21] delivered synthetic A_2-IsoP **1** in quantitative yield. The cis stereochemistry of the two side chains on the cyclopentenone ring was unequivocally established by NOE experiment[22] and by comparing the ^1H and ^{13}C NMR spectra of natural PGA_2[22] with synthetic A_2-IsoP. Particular diagnostic was the signal of 12-H at

Scheme 4[a]



[a] Reaction conditions: (a) DDQ, phosphate buffer pH = 7.2, DCM, rt, 3 h, 70%; (b) **17**, *t*-BuOK, THF, rt, 20 min, then **18** in THF, 2 h, 83%; (c) Dess−Martin periodinane, DCM, rt, 3 h, 94%; (d) aq 48% HF, quant.

the ring junction that occurred at δ 3.12 in PGA_2, whereas it was shifted downfield to δ 3.72 in A_2-IsoP. Notably, the signal at about δ 3.10 was negligible in the ^1H NMR spectrum of compound **1**, indicating insignificant contamination by the trans stereoisomer.

Moreover, the ^1H NMR olefinic signals at δ 5.44−5.46 of the lower side-chain double bond of PGA_2 were completely superimposable on those of A_2-IsoP **1**, indicating a complete *E* stereoselectivity in the Julia−Lythgoe olefination.

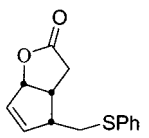
Preliminary biological studies showed a comparable activity of A_2-IsoP with PGA_1 in the electrophoretic mobility shift assay (EMSA) for inhibition of the nuclear factor κB (NF-κB). This factor plays a key role in the activation of HIV-1 transcription and in inflammatory processes.[7]

However, A_2-IsoP was significantly more potent than PGA_1, as shown by EMSA test, in the activation of the heat-shock transcription factor (HSF), which is responsible for the inhibition of viral protein synthesis.[7]

In conclusion, we have described, for the first time, a viable synthesis of the novel elusive isoprostane A_2. Further studies on the stereoselective synthesis of each stereoisomer **2**−**5** of A_2-IsoP as well as on the evaluation of individual biological activities are now in progress.

Experimental Section

4-Phenylsulfanylmethyl-3,3a,4,6a-tetrahydrocyclopenta-[*b*]furan-2-one (12).



To a stirred solution of lactone **11** (97 mg, 0.629 mmol) in 2.5

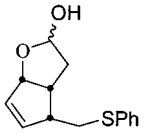
(16) Acmatovich, B.; Baranowska, E.; Daniewski, A. R.; Pankowski, J.; Wicha, J. *Tetrahedron* **1988**, *44*, 4989.
(17) Meyer, S. D.; Miwa, T.; Nakatsuka, M.; Schreiber, S. L. *J.Org.Chem*. **1992**, *57*, 5058.
(18) Chapleo, C. B.; Finch, M. A. W.; Lee, T. V.; Roberts, S. M.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2084.
(19) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(20) Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Tetrahedron Lett.* **1979**, *23*, 2084.

(21) Irradiation of H-12 at δ = 3.72 gave an enhancement of 3.6% of H-8 at δ 2.55. A similar experiment done on PGA_2 gave no observed NOE effect.
(22) Natural PGA_2 was purchased from Cayman Chemical.

mL of dry THF under an argon atmosphere was added solid PhSSPh (412 mg, 1.887 mmol, 3 equiv), the mixture was cooled to 0 °C in an ice bath, and then ^{n}Bu$_3$P (472 μL, 1.887 mmol, 3 equiv) was added dropwise. The ice bath was removed, and the solution was stirred at rt for 4 h.

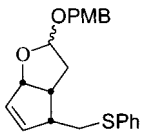
Brine (7 mL) and DCM were then added to the reaction mixture, and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic fractions were washed with brine and dried on $MgSO_4$. Evaporation under reduced pressure gave an oily residue that was purified by flash chromatograpy on silica gel (28 g). Elution with hexanes−EtOAc (8:2) gave sulfide **12** as a colorless oil (131 mg, 86%): IR (liquid film) 3057, 2929, 1770, 1171, 1002, 742, 691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (dd, J = 8.6, 18.2 Hz, 1H), 2.6 (dd, J = 9.6, 18.2 Hz,1H), 2.86 (dt, J = 4.2, 11.8 Hz, 1H), 3.05 (d, J = 6.4 Hz, 1H), 3.12 (bt, J = 2.14, 6 Hz, 1H), 3.28 (m, 1H), 5.45 (dd, J = 1.6, 8 Hz, 1H), 5.9 (dt, J = 6.4, 2.4 Hz, 1H), 6.02 (dt, J = 5.7, 1.3 Hz, 1H), 7.1−7.5 (m, 5H, Ph); ^{13}C NMR (75 MHz) δ 176.6 s, 138.0 d, 135.1 s, 130.0 d, 129.6 d, 129.0 d, 126.7 d, 88.3 d, 45.9 d, 39.4 d, 35.1 t, 29.1 t; EIMS (70 eV) *m*/*z* 246 (30) [M$^+$], 123 (100), 108 (20), 91(10), 77 (30), 65 (20), 52 (12), 45 (25). Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.34; H, 5.76.

4-Phenylsulfanylmethyl-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-ol (12a).



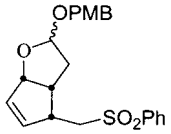
A stirred solution of sulfide **12** (508 mg, 2.065 mmol) in DCM (13 mL) was cooled to −78 °C, and DIBAL-H (2.5 mL, 1 M in hexane, 1.2 equiv) was added dropwise. Stirring was continued for an additional 1 h, and then a saturated solution of NH_4Cl (10 mL) was added at −78 °C. The mixture was gradually warmed to rt, diluted with DCM (30 mL), and acidified with concentrated HCl. The aqueous layer was extracted with DCM (3 × 25), and the combined organic phases were washed with H_2O and brine and dried on $MgSO_4$. Evaporation in vacuo of the volatiles left lactol **12a** (493 mg, 98%), mixture 9:1 of hemiacetals, as a white solid, mp 107−110 °C. Major anomer: IR (liquid film) 3356, 2954, 2922, 1582, 1478, 1282, 1004, 736, 688 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.72 (ddd, J = 4.3, 11.7, 12.3 Hz, 1H), 2.05 (dd, J = 8.0, 12.3 Hz, 1H), 2.8 (bs, OH, 1H); 2.9−3.2 (m, 3H), 3.24−3.36 (m, 1H), 5.24 (d, J = 7.5 Hz, 1H), 5.54 (bd, J = 4.3 Hz, 1H), 5.74−5.82 (m, 2H), 7.15−7.45 (m, 5H, Ph); ^{13}C NMR (75 MHz) δ 134.4 d, 131.6 d, 131.6 s, 129.7 d, 128.9 d, 126.3 d, 99.2 d, 88.4 d, 45.0 d, 41.5 d, 34.8 t, 34.2 t.

2-(4-Methoxybenzyloxy)-4-phenylsulfanylmethyl-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan (13).



The crude lactol **12a** (160 mg, 0.645 mmol) was dissolved in dry DCM (10 mL), and neat PMB-OH (160 μL, 2 equiv) was added. The solution was cooled to −20 °C, and solid PTSA was added with stirring. After 18 h at the same temperature, the reaction was quenched by adding solid $NaHCO_3$ at −20 °C. A saturated solution of $NaHCO_3$ (10 mL) was then added, and the aqueous layer was extracted with DCM (3 × 20 mL). The organic layers were combined, washed with brine, and dried over Na_2SO_4. Elimination of the solvent in vacuo gave an oily residue that was purified by flash chromatograpy on silica gel (14 g). Elution with hexanes−EtOAc (9:1) afforded acetal **13** (225 mg, 95%) as a mixture 9:1 of epimers: R (liquid film) 2909, 1613, 1514, 1248, 1031, 740, 691 cm^{-1}. Major anomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (ddd, J = 4.9, 11.34, 12.2 Hz, 1H), 2.1 (dd, J = 8.1, 12.2 Hz, 1H), 2.85−3.10 (m, 3H), 3.20−3.36 (m, 1H), 3.81 (s, 3H, OMe), 4.43 and 4.67 (AB system of benzylic CH_2, J = 11.8 Hz, 2H), 5.16 (d, J = 7.5 Hz, 1H), 5.20 (d, J = 4.3 Hz, 1H), 5.77 (bd, J = 5.4 Hz, 1H), 5.84 (dt, J = 5.4, 1.5 Hz, 1H), 6.75−7.5 (m, 9H, Ph and PMB); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0 s, 136.1 s, 134.4 d, 131.6 d, 130.3 s, 129.5 d, 129.3 d, 128.9 d, 126.1 d, 113.7 d, 103.4 d, 88.1 d, 68.1 t, 55.2 q, 44.9 d, 41.8 d, 34.6 t, 33.6 t; EIMS (70 eV) *m*/*z* 368 (2) [M$^+$], 230 (35), 169 (38), 121 (100),91 (42), 77 (45). Anal. Calcd for $C_{22}H_{24}O_3S$: C, 71.71; H, 6.56. Found: C, 71.82; H, 6.52.

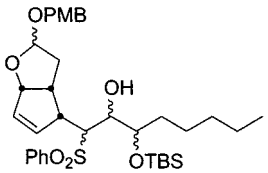
4-Benzenesulfonylmethyl-2-(4-methoxybenzyloxy)-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan (14). Sulfide



acetal **13** (224 mg, 0.583 mmol) was dissolved in MeOH and cooled to 0 °C; to this solution were added solid $(NH_4)_2MoO_4$ (30 mg) and 30% H_2O_2 (680 μL). The temperature was allowed to reach rt, and stirring was continued for 3 h. After addition of an additional 30% H_2O_2 (350 μL) and $(NH_4)_2MoO_4$ (10 mg), the yellow slurry was stirred for an additional 14 h.

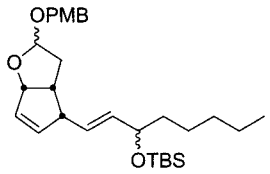
The reaction was quenched by adding solid Na_2SO_3; after 40 min of stirring at rt, MeOH was removed by evaporation in vacuo and the residue was taken up in a saturated solution of NH_4Cl (6 mL) and DCM (10 mL). The aqueous phase was extracted with DCM (3 × 25 mL), and the organic layers were collected, washed with brine, and dried over Na_2SO_4. The crude sulfone obtained from evaporation of volatiles was purified on silica gel (8 g) using hexanes−EtOAc (7:3) as eluent. Sulfone **14** was obtained as a pale yellow viscous oil (229 mg, 94%): IR (liquid film) 3061, 2909, 1612, 1514, 1447, 1304, 1248, 1148, 1086, 1032, 735, 689 cm^{-1}. Major anomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (ddd, J = 4.7, 11.1, 12.6 Hz, 1H), 1.95 (dd, J = 6.3, 12.6 Hz, 1H), 3.08−3.40 (m, 4H), 3.81 (s, 3H, OMe), 4.38 and 4.63 (AB system of benzylic CH_2, J = 11.8 Hz,2H), 5.12 (d, J = 7.5 Hz, 1H), 5.13 (d, J = 4.2 Hz, 1H), 5.70 (bd, J =,5.4 Hz, 1H), 5.84 (dt, J = 5.4, 1.5 Hz, 1H), 6.84−7.96 (m, 9H, Ph and PMB); ^{13}C NMR (75 MHz, $CDCL_3$) δ = 159.0 s, 139.1 s, 133.7 d, 132.7 d, 132.6 d, 130.1 s, 129.3 d, 129.1 d, 127.9 d, 113.6 d, 102.8 d, 87.4 d, 68.0 t, 56.9 t, 55.1 q, 42.3 d, 39.4 d, 34.2 t; EIMS (70 eV) *m*/*z* 400 (1) [M$^+$], 310 (12), 268 (40), 267 (36), 167 (15), 149 (48), 121 (100), 91 (80), 77 (68), 43 (86). Anal. Calcd for $C_{22}H_{24}O_3S$: C, 65.98; H, 6.04. Found: C, 65.79; H, 5.99.

1-Benzenesulfonyl-3-(*tert*-butyldimethylsilanyloxy)-1-[2-(4-methoxybenzyloxy)-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-4-yl]-octan-2-ol (15). Sulfone **14** (685 mg,



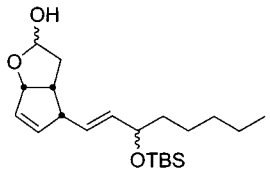
1.71 mmol) was dissolved in dry THF (7.5 mL) and cooled to −78 °C; after the solution was stirred for 10 min, ^{n}BuLi (1.192 mL, 1.6 M in hexane, 1.11 equiv) was added dropwise. After 45 min of stirring at the same temperature, the deep orange solution was slowly added via cannula with aldehyde **10** (486 mg, 1.16 equiv) in dry THF (6 mL). After the solution was stirred at the same temperature for an additional 2 h, a saturated solution of NH_4Cl (15 mL) was added at −78 °C and the temperature was allowed to reach rt. The two layers were separated, and the aqueous phase was extracted with DCM (3 × 50 mL). The organic phases were combined, washed with brine, dried with $MgSO_4$, and evaporated under reduced pressure. The crude adduct was filtered through a short pad of silica gel using hexanes−EtOAc (88:12) as eluant. The crude hydroxysulfone **15** was immediately used in the next step (917 mg, 84.5%).

***tert*-Butyl[3-[2-(4-methoxybenzyloxy)-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-4-yl]-1-pentylallyloxy]dimethylsilane (16).**



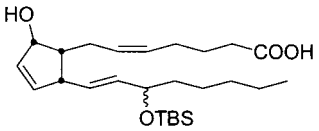
Crude hydroxysulfone **15** (287 mg, 0.4347 mmol) was dissolved in dry MeOH (15 mL) under an argon atmosphere. To the solution was added Na_2HPO_4 (1.5 g), and the slurry was cooled to −40 °C; after 10 min of vigorous stirring, sodium amalgam (2.36 g, 10% of Na) was slowly added portionwise in such a way to keep the temperature below −40 °C. At the end of the addition, the temperature was allowed to reach −20 °C, and stirring was continued for an additional 1.5 h. The mixture was warmed to rt and filtered through a filter paper. Evaporation of volatiles in vacuo under 40 °C gave a residue that was partitioned between DCM (50 mL) and an aqueous saturated solution of $NaHCO_3$. The two phases were separated, and the aqueous layer was reextracted with DCM (3 × 15 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure to give a residue that was purified by flash chromatography on silica gel (SiO_2 10 g). Elution with hexanes−Et_2O (94:6) gave adduct **16** as a colorless oil (171 mg, 81%): IR (liquid film) 2930, 2856, 1612, 1514, 1464, 1249, 1033, 835, 775 cm^{-1}. Major anomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.88 (t, J = 6.5 Hz, 3H), 0.90 (s, 9H), 1.2−1.4 (br m, 6H), 1.4−1.6 (br m, 2H), 1.64−1.96 (m, 2H), 3.24 (br quintuplet, J = 8.6 Hz, 1H), 3.4−3.52 (m, 1H), 3.82 (s, 3H), 4.08 (m, 1H), 4.42 and 4.67 (AB system of benzylic CH_2, J = 11.8 Hz, 2H), 5.14−5.22 (m, 2H), 5.46−5.55 (m, 2H), 5.73 (br d, J = 5.4 Hz, 1H), 5.86 (br d, J = 5.4 Hz, 1H), 6.84−7.35 (AA′BB′ system, J,= 8.6 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0 s, 135.3 d, 135.2 d, 131.3 d, 130.3 s, 129.4 d, 128.2 d, 113.7 d, 103.5 d, 88.3 d, 73.3 d, 68.1 t, 55.1 q, 47.6 d, 42.6 d, 38.4 t, 34.9 t, 31.7 t, 25.8 3xq, 24.8 t, 22.6 t, 18.2 s, 14.0 q, −4.3 q, −4.8 q; ESI-MS m/z 486 [M^+]. Anal. Calcd for $C_{29}H_{46}O_4Si$: C, 71.56; H, 9.53. Found: C, 71.63; H, 9.55.

4-[3-(*tert*-Butyldimethylsilanyloxy)oct-1-enyl]-3,3a,4,-6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-ol (18).



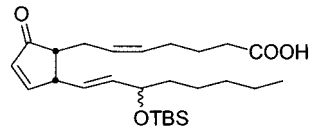
Protected lactol **16** (353 mg, 0.7252 mmol) was dissolved in DCM (11 mL), and pH = 7 phosphate buffer (1 mL) was added at rt under vigorous stirring. To the suspension was added freshly crystallized DDQ (247 mg, 1.088 mmol, 1.5 equiv). After 1.5 h of stirring, the mixture was filtered on a short pad of Celite and washed with DCM (150 mL). The solution was dried over $MgSO_4$, filtered, and concentrated at reduced pressure keeping the water bath below 35 °C. The residue was purified by flash chromatography on silica gel (SiO_2 27 g); elution with DCM−EtOAc (96:4) gave the desidered lactol **18**, mixture 5:1 of hemiacetals, as a colorless oil (161 mg, 61%), which was immediately used in the following step: IR (liquid film) 3416, 2929, 2857, 1463, 1360, 1253, 1032, 836, 775 cm^{-1}. Major anomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.88 (t, J = 6.5 Hz, 3H), 0.90 (s, 9H), 1.2−1.4 (br m, 6H), 1.4−1.6 (br m, 2H), 1.64−1.96 (m, 2H), 2.82 (br s, 1H, OH), 3.24 (br quintuplet, J = 8.6 Hz, 1H), 3.4−3.52 (m, 1H), 4.04−4.15 (m, 1H), 5.24 (d, J = 7.4 Hz,1H), 5.46−5.55 (m, 2H), 5.72 (br d, J = 5.4 Hz, 1H), 5.82 (br d, J = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5 d, 135.3 d, 131.1 d, 128.0 d, 99.0 d, 88.4 d, 73.2 d, 47.4 d, 42.1 d, 38.2 t, 35.5 t, 31.6 t, 25.7 3 × q, 24.7 t, 22.4 t, 18.1 s, 13.8 q, −4.3 q, −4.8 q; ESI-MS m/z 389 [$M + Na^+$].

7-[2-[3-(*tert*-Butyldimethylsilanyloxy)oct-1-enyl]-5-hydroxycyclopent-3-enyl]hept-5-enoic Acid (19).



Solid phosphonium salt **17** (467 mg, 1.026 mmol, 4 equiv) was suspended in dry THF (5 mL) in a two-neck round-bottom flask under an argon atmosphere. To the suspension was added freshly sublimed potassium *tert*-butoxide (236 mg, 2.051 mmol, 8 equiv) portionwise at rt. After being stirred for 20 min, the solution became deeply orange and a THF solution (1.5 mL) of lactol **18** (94 mg, 0.256 mmol) was added via cannula dropwise at rt. Stirring was continued for an additional 2 h, and the reaction was quenched by adding a saturated aqueous solution of NH_4Cl (15 mL) and acetic acid (0.127 mL, 1.05 equiv); Et_2O (20 mL) was added to the mixture and the organic layer was separated, whereas the aqueous phase was extracted with an additional Et_2O (3 × 20 mL). The organic phases were combined, dried on $MgSO_4$, filtered, and concentrated at reduced pressure. The crude acid was purified on silica gel (15 g) using hexanes−EtOAc (8:2) as eluent. The acid **19** (95 mg, 83%) was thus obtained as a pale yellow oil as a 1:1 mixture of epimers at C-15 hydroxyl group: IR (liquid film) 3300−2600 (*OH* and CO*OH*), 2928, 2856, 1713, 1462, 1253, 1065, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02−0.08 (4s, 6H overall), 0.88 (t, J = 6.5 Hz, 3H), 0.9 (s, 9H), 1.28 (br s, 6H), 1.38−1.56 (m, 2H), 1.72 (quintuplet, J = 6.7 Hz, 2H), 2−2.2 (m, 4H), 2.24−2.36 (m, 1H), 2.36 (br t, J = 6.7 Hz, 2H), 3.18 (m, 1H), 4.05 (br q, J = 6.4 Hz, 1H), 4.52 (dd, J = 5.3, 2.6 Hz, 1H), 5.32−5.48 (m, 3H), 5.48−5.64 (m, 1H), 5.96−6.08 (m, 2H); ^{13}C NMR (75 MHz) δ 179.3 (COOH) s, 139.4 d, 135.5 d, 133.0 d, 131.4 d, 129.6 d, 129.2 d, 76.3 d, 73.5 d, 49.8 d,* 49.6 d,* 46.8 d, 38.42 t,§ 38.37 t,§ 33.4 t, 31.8 t, 26.6 t, 25.9 3 × q, 25.0 t, 24.5 t, 24.0 t, 22.6 t, 18.2 s, 14.0 q, −4.3 q, −4.8 q (*,§ doubled signals due to the presence of epimers); ESI-MS (negative ions) m/z 485 [$M + Cl^-$], 449 [$M - H^-$]. Anal. Calcd for $C_{26}H_{46}O_4Si$: C, 69.28; H, 10.29. Found: C, 69.33; H, 10.31.

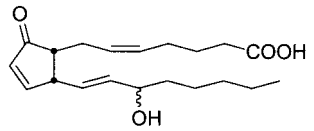
7-[2-[3-(*tert*-Butyldimethylsilanyloxy)oct-1-enyl]-5-oxocyclopent-3-enyl]hept-5-enoic Acid (20).



To a solution of allylic alcohol **19** (76 mg, 0.1686 mmol) in DCM (4 mL) at rt was added solid Dess−Martin periodinane (100 mg, 0.236 mmol, 1.4 equiv) in one portion. After the homogeneous solution was stirred for 3 h, the reaction was quenched by adding dry Et_2O (15 mL) and the suspension was quickly filtered on a short pad of Celite. The Celite layer was washed with Et_2O (3 × 30 mL), and the organic phases were combined and concentrated at reduced pressure WITHOUT HEATING. The residue was purified by flash chromatography on silica gel (SiO_2, 4.5); elution with hexanes−Et_2O (6:4) gave the desidered enone **20** as a colorless oil (70 mg, 93%): IR (liquid film) 3200−2600 (CO*OH*), 2930, 2857, 1712, 1586, 1462, 1251, 1081, 973, 836, 776, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.88 (t, J(H,H) = 6.5 Hz, 3H), 0.9 (s, 9H), 1.28 (br s, 6H), 1.40−1.58 (m, 2H), 1.72 (quintuplet, J = 7.4 Hz, 2H), 1.95−2.18 (m, 3H), 2.36 (br t, J = 7.5 Hz, 2H), 2.42−2.56 (m, 2H), 3.72 (br t, J = 7.2 Hz, 1H), 4.08 (br q, J = 6 Hz, 1H), 5.3−5.6 (m, 4H), 6.22 (dd, J = 1.7, 5.6 Hz, 1H), 7.52 (dt, 1H, J = 2.8, 5.6 Hz,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6 s, 210.5 s, 179.1 s, 179.0 s, 165.2 d, 165.1 d, 138.1 d, 138.0 d, 132.7 d, 132.7 d, 129.8 d, 129.8 d, 128.1 d, 128.1 d, 126.3 d, 126.3 d, 73.0 d, 72.9 d, 49.8 d, 47.6 d, 47.3 d, 38.3 t, 38.2 t,

33.3 t, 31.8 t, 31.7 t, 26.6 t, 26.6 t, 25.9 3 × q, 25.8 3 × q, 24.9 t, 24.8 t, 24.6 t, 24.5 t, 24.4 t, 22.6 t, 18.2 s, 14.0 q, 14.0 q, −4.3 q, −4.4 q, −4.7 q, −4.8 q; ESI-MS *m/z* 919 [2M + Na^+], 471 [M + Na^+]. Anal. Calcd for $C_{26}H_{44}O_4Si$: C, 69.59; H, 9.88. Found: C, 69.48; H, 9,85.

7-[2-(3-Hydroxyoct-1-enyl)-5-oxocyclopent-3-enyl]hept-5-enoic Acid (1).



Aqueous HF (0.15 mL, 48% solution) was added dropwise to enone **20** (37 mg, 0.0825 mmol) dissolved in CH_3CN (3 mL) in a Teflon test tube. The mixture was stirred for 1 h at rt and quenched by addition of silica gel (300 mg); the solid was removed by filtration and the liquid concentrated in vacuo, WITHOUT HEATING. Isoprostane **1** was thus obtained as a colorless oil (27.5 mg, quant), as a 1:1 mixture of epimers at C-15 hydroxyl group: IR (liquid film) ν(3414, 2931, 1705, 1586, 1241, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.9 (t, J = 6.5 Hz, 3H,H_{20}), 1.3 (br s, 6H), 1.48−1.62 (m, 2H), 1.70 (quintuplet, J = 7.3 Hz, 2H), 2.1 (q, J = 7.5 Hz, 2H), 2.15−2.26 (m, 1H), 2.35 (br t, J = 7.3 Hz, 2H), 2.3−2.56 (m, 2H), 3.72 (m, 1H, H_{12}), 4.14 (distorted br q, J = 7 Hz, 1H, H_{15}), 5.3−5.7 (m, 4H), 6.21−6.27 (m, 1H, H_{10}), 7.50 and 7.56 (1dd each, J = 3.2, 6.0 Hz,1H overall, H_{11}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7 s, 210.5 s, 177.5 s 177.4 s, 164.7 d, 164.7 d, 136.7 d, 136.7 d, 133.1 d, 133.1 d, 129.7 d, 129.6 d, 128.7 d, 128.6 d, 128.4 d, 127.9 d, 72.8 d, 72.5 d, 49.5 d, 49.5 d, 47.7 d, 47.1 d, 37.1 t, 37.1 t, 32.9 t, 32.8 t, 31.7 t, 31.7 t, 26.5 t, 26.4 t, 25.0 t, 25.0 t, 24.8 t, 24.3 t, 24.2 t, 22.6 t, 14.0 q; ESI-MS *m/z* 691 [2M + Na^+], 471 [M + Na^+]; HRMS calcd for $C_{20}H_{30}O_4$ 334.2144, found 334.2149.

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Supporting Information Available: ^1H NMR, ^{13}C NMR, and DEPT data for compounds **12**, **14**, **16**, **19**, **20**, and **1**, and ^1H NMR of natural PGA_2. This material is available free of charge via the Internet at http://pubs.acs.org.

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