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General Strategy for the Synthesis of B_1 Phytoprostanes, Dinor Isoprostanes, and Analogs

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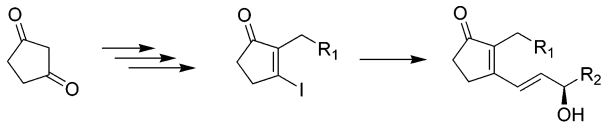

The synthesis of the phytoprostane B_1 types I and II is achieved in high overall yield (35−53%) by only two principal transformations starting from 1,3-cyclopentanedione. The first side chain is attached via O-acylation of the 1,3-dione followed by rearrangement and reduction to give the 2-alkyl-1,3-diones **4a**−**c**. After conversion into the corresponding vinylic iodides **5a**−**c**, the second side chain is introduced by transition metal catalysis following Heck- or Sonogashira-type protocols. The whole spectrum of the phytoprostane B_1 types I, II, and the dinor isoprostane B_1 type III and some structural analogs are rapidly accessible along the same general protocol.

Introduction

Phytoprostanes (or dinor isoprostanes) belong to a novel group of bioactive compounds that are produced in plants from α-linolenic acid (octadeca-9,12,15-trienoic acid) in a free-radical process without participation of enzymes.[1] They are generated ubiquitously at a low background level, but after tissue damage their concentration increases dramatically in response to oxidative stress. Their structure and their pattern of functionalization are reminiscent of mammalian prostaglandins, which are, however, formed by specific enzymes from arachidonic acid. Since phytoprostanes and the mammalian isoprostanes result from a nonenzymatic free radical process, the primary products are racemic. This does not exclude that later enzyme-controlled modifications may result in chiral compounds that show different biological activities upon interactions with enzymes or receptors. Their nomenclature follows the established isoprostane/prostaglandin terminology.[2] As outlined in Figure 1, the cyclopentanoid skeleton results from α-linolenic acid via either the 12- or the 13-hydroperoxy radical or from γ-linolenic acid via the 9- or 10-hydroperoxy radical, leading to two series of regioisomeric products.

The primarily formed endoperoxides (phytoprostanes G_1) are labile and readily suffer reduction, rearrangements, or elimination of water, which further enhances the structural and functional diversity within the family of the phytoprostanes.[1] The phytoprostanes B_1 (Figure 1) represent stable end products of lipid peroxidation and transformation sequence. According to Loeffler et al.,[3] in particular the phytoprostanes of the B_1-series represent important signal molecules that help the plant to cope with stress factors, such as damage or infection. First analyses with small microarrays of the model plant *A. thaliana* demonstrate that the B_1-type phytoprostanes lead to the up-regulation of detoxification and defense responses. γ-Linolenic acid is another polyunsaturated fatty acid found in quite high amounts in several plant species, such as *Ribes nigrum* (black currant), *Oenothera californica* (evening primrose), or *Borago officinalis* (borage). It is also a minor compound in many animal lipids. Analogous to the formation of phytoprostanes type I and II from α-linolenic acid, γ-linolenic acid can be converted into the dinor isoprostanes type III and IV (Figure 1).[1] Despite their biological importance in plant species, such compounds can bind in animals to genuine receptors of the structurally related prostaglandins.[4] Their pronounced and diverse biological activities in plants and animals prompted us to develop short and

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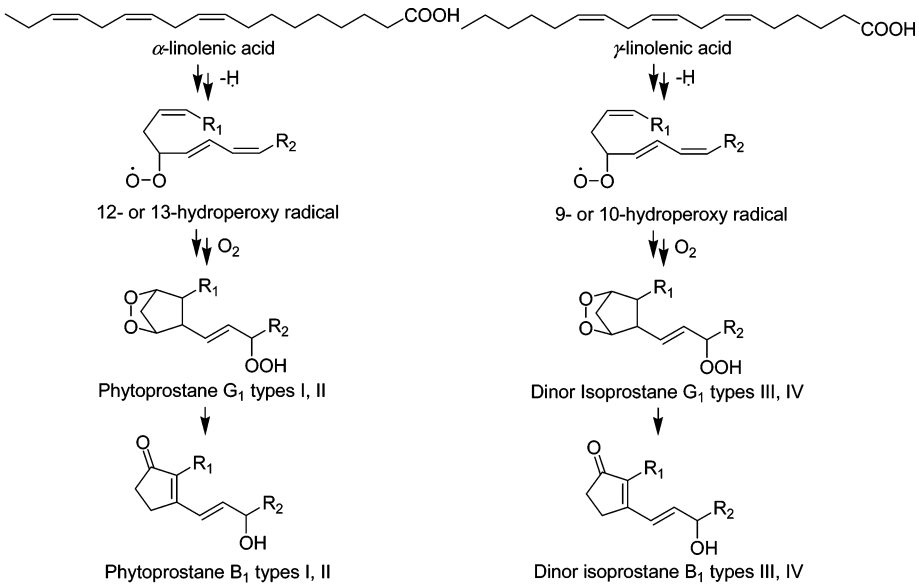
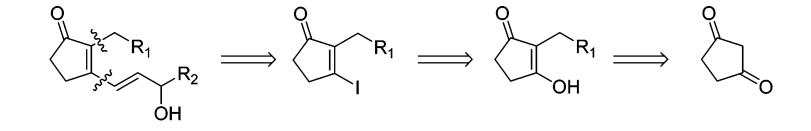


	PPB_1 type I	PPB_1 type II	$DIPB_1$ type III	$DIPB_1$ type IV
R_1	$(CH_2)_7COOH$	CH_2CH_3	$(CH_2)_4COOH$	$(CH_2)_4CH_3$
R_2	CH_2CH_3	$(CH_2)_7COOH$	$(CH_2)_4CH_3$	$(CH_2)_4COOH$

FIGURE 1. Origin and structures of phytoprostanes (PP) B_1 and dinor isoprostanes (DIP) B_1.

SCHEME 1. Retrosynthesis of Phytoprostane B_1 Types I and II and Dinor Isoprostane B_1 Type III



	PPB_1 type I	PPB_1 type II	$DIPB_1$ type III
R_1	$(CH_2)_6COOMe$	CH_3	$(CH_2)_3COOMe$
R_2	CH_2CH_3	$(CH_2)_7COOMe$	$(CH_2)_4CH_3$

efficient strategies to synthesize a broad range of these compounds in high yield and defined stereochemistry. Moreover, the general strategy should be also applicable to synthesize enantiopure compounds or structural analogues without the need for additional synthetic transformations. Here we report on a general strategy that allows synthesizing several members of the phytoprostanes B_1 and selected isoprostanes B_1 by only two key transformations starting from 1,3-cyclopentanedione in high overall yield.

Results and Discussion

Phytoprostanes or dinor isoprostanes have been obtained by autoxidation of α-linolenic acid[5] or by multistep syntheses[6−8] utilizing Pd(0) catalysts and organotin reagents for alkylation. For example, racemic prostaglandin PGB_1 and coriolic acid were obtained along such routes in good overall yield. Recently, Fangour et al. reported a novel but, again, lengthy approach to chiral phytoprostane B_1 types I and II.[9] This route afforded *R*/*S* phytoprostanes B_1 type I and II in moderate yields. Based on our previous protocol to tetrahydrodicranenone B,[10] a naturally occurring cyclopentenone derivative, that shares many structural features with the phytoprostanes B_1, we developed a flexible protocol that allowed the preparation of a whole spectrum of these compounds using only two key operations (Scheme 1) to introduce the two different sides with different chain lengths and a different degree of functionalization.

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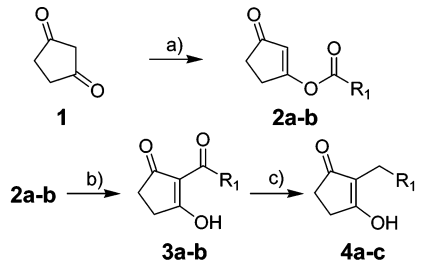
SCHEME 2. Synthesis of 2-Alkylcyclopentane-1,3-diones[a]



	R_1	Compound yield (%)
PPB_1 type I	$(CH_2)_6COOMe$	**2a** (98), **3a** (92), **4a** (89)
$DIPB_1$ type III	$(CH_2)_3COOMe$	**2b** (98), **3b** (85), **4c** (83)

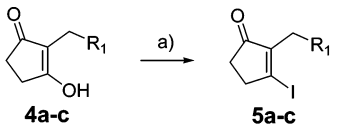
[a] Reagents and conditions: (a) 1.1 equiv of $ClOCR_1$, 1 equiv of pyridine, $C_2H_4Cl_2$, 20 h; (b) 0.4 equiv of acetone cyanohydrine, 1.4 equiv of Et_3N, CH_3CN, 24 h; (c) 3 equiv Et_3SiH, CF_3COOH containing 1% $LiClO_4$, 24 h.

The synthetic approach includes (i) C-alkylation of 1,3-cyclopentanedione and (ii) a transition metal catalyzed introduction of the second side via an alkenyl iodide derived from the C-alkylation product. Particularly well-suited for the second alkylation proved to be functionalized terminal 1-alken-3-ols or 1-alkyn-3-ols using the Heck or Sonogashira protocol.[11,12]

Synthesis of Phytoprostanes B_1 Types I, II, Dinor Isoprostane B_1 Type III and Analogs. Details of the first synthetic steps of the methyl ester of PPB_1 type I and $DIPB_1$ type III are outlined in Scheme 2. Since the direct alkylation of cyclopentane-1,3-dione **1** led to O-alkylation rather than C-alkylation, we used the two-step procedure of Lakhvich et al., which first O-acylates the enolate of cyclopentane-1,3-dione **1** with acylhalides, e.g., methyl 7-(chlorocarbonyl)heptanoate giving **2a** in 98% yield.[13] Subsequent treatment of the resulting enol ester with acetone cyanohydrine or, less efficiently, Lewis acids such as $AlCl_3$, $ZnCl_2$, or 4,4-dimethylaminopyridine,[14] promoted the rearrangement of **2a** to the C-alkylated hydroxy-diketone **3a** (92%).

Reduction of the exocylic ketofunction was best achieved with triethylsilane in trifluoroacetic acid containing 1% of lithium perchlorate and afforded the key intermediates **4a,c** in 89% and 83% yield.[15] The monoalkylated precursor **4b** for phytoprostane B_1 type II synthesis was commercially available and could directly be used for further reactions. The 2-alkylcyclopentane-1,3-diones **4a**−**c** were converted into the corresponding vinyliodides **5a**−**c** by heating with PPh_3 and I_2 in dry acetonitrile in the presence of triethylamine (Scheme 3).[10] Previously reported conditions using imidazole as base or a solvent mixture of diethyl ether and acetonitrile resulted in lower yields.[16]

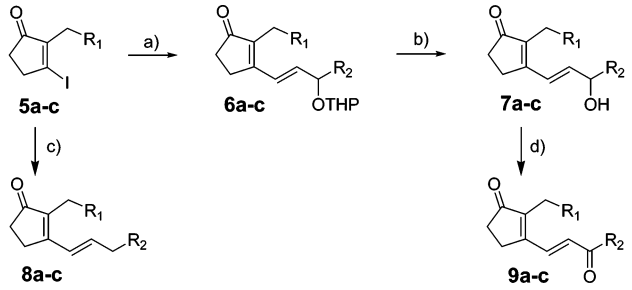
SCHEME 3. Iodination of 2-Alkylcyclopentane-1,3-diones[a]



	R_1	Compound yield (%)
PPB_1 type I	$(CH_2)_6COOMe$	**5a** (68)
PPB_1 type II	CH_3	**5b** (77)
$DIPB_1$ type III	$(CH_2)_3COOMe$	**5c** (82)

[a] Reagents and conditions: (a) 1.125 equiv of PPh_3, 1.125 equiv of I_2, 1.1 equiv of Et_3N, CH_3CN, 24 h.

SCHEME 4. Vinylation of 3-Iodocyclopentenones 5a−c[a]



	R_1	R_2	Compound yield (%)
PPB_1 type I	$(CH_2)_6COOMe$	CH_2CH_3	**7a** (65), **8a** (97), **9a** (81)
PPB_1 type II	CH_3	$(CH_2)_7COOMe$	**7b** (69), **8b** (59), **9b** (86)
$DIPB_1$ type III	$(CH_2)_3COOMe$	$(CH_2)_4CH_3$	**7c** (52), **8c** (70), **9c** (78)

[a] Reagents and conditions: (a) 1.67 equiv of $CH_2CHCH(OTHP)R_2$, 2 equiv Et_3N, $Pd(OAc)_2$·$2PPh_3$, 24 h, 100 °C; (b) $CH_3COOH/THF/H_2O$, 45 °C, 20 h; (c) 1.67 equiv of $CH_2CHCH_2R_2$, 2 equiv of Et_3N, $Pd(OAc)_2$·$2PPh_3$, 24 h, 4d, 100 °C (40 °C); (d) 1.05 equiv of Bobbitt's reagent (4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate), silica gel, CH_2Cl_2, 5 h.

The second side chain was introduced in a Heck-type alkylation of the vinylic iodides **5a**−**c** with protected terminal 1-alken-3-ols using a 2:1 mixture of PPh_3 and $Pd(OAc)_2$ as catalyst in the presence of triethylamine (Scheme 4). Best results were obtained with the tetrahydropyranylethers of the 1-alken-3-ols.[17] The corresponding trimethylsilyl-protected alkenols gave low yields (13−29%). The free alcohols **7a**−**c** were obtained after cleavage of the protective group of **6a**−**c** with $CH_3COOH/THF/H_2O$ (Scheme 4).[11,17] Alkylation with (*R*)-(−)-oct-1-en-3-ol-THP afforded the chiral dinor isoprostane (−)-(*R*)-**7c** along the same protocol.

Vinylation with non-functionalized terminal alkenes proceeded with high yield and without formation of by products (Scheme 4c). During oxidative stress, phytoprostanes could perhaps be further oxidized to their corresponding diketones. The diketones might have interesting biological activity owing

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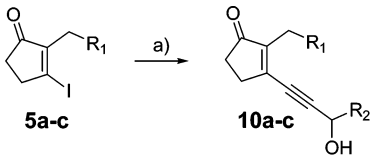
SCHEME 5. Alkynylation of 3-Iodocyclopentenones 5a−c with Acetylenes[a]



	R_1	R_2	Comp. yield (%)
PPB_1 type I	$(CH_2)_6COOMe$	CH_2CH_3	**10a** (88)
PPB_1 type II	CH_3	$(CH_2)_7COOMe$	**10b** (91)
$DIPB_1$ type III	$(CH_2)_3COOMe$	$(CH_2)_4CH_3$	**10c** (86)

[a] Reagents and conditions: (a) 1.5 equiv of $CHCC(OH)R_2$, 0.07 equiv of $PdCl_2(PPh_3)_2$, 0.15 equiv of CuI, 1.2 equiv of Et_3N, DMF, 24 h.

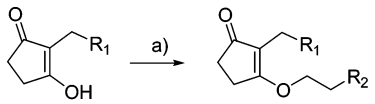
to the presence of two Michael acceptors. Since the direct coupling with terminally unsaturated alken-3-ones failed as a result of reductive elimination of the side chain double bond, the phytoprostanes **7a−c** were converted into the diketones **9a−c** by oxidation of the hydroxy function with Bobbitt's reagent (4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate) in the presence of silica gel (Scheme 4d).[18,19] The diketones of phytoprostane B_1 types I and II and dinor isoprostane B_1 type III **9a−c** were obtained in good yield and without competing side reactions. Other mild oxidants, for example, MnO_2, required long reaction times and resulted in low yields (15−23%.) Interestingly, both enantiomers of each regioisomer showed nearly the same biological activity in all tested species.[3] Some of these defense reactions caused by phytoprostane treatment might be comparable to those of jasmonates, but there are also significant differences.

Synthesis of Acetylenic Phytoprostane Analogs. The introduction of an acetylene moiety instead of the (*E*)-allyl alcohol into the phytoprostanes changes the electronic and steric properties of the molecules, which may result in altered biological properties. The side chain of type II was synthesized from methyl undec-10-ynoate using a procedure similar to the allylic oxidation with SeO_2.[20] The central vinylic iodides **5a−c** proved to be excellent substrates for a Sonogashira-type vinylation with simple or substituted terminal acetylenes.[12] The same reaction could be also achieved with the THP-ether of (*R*)-(+)-oct-1-yn-3-ol and yielded (*R*)-(+)-**10c** in 70%. In general, yields were found to be consistently higher than those for the Heck-type alkylation (Scheme 5).

Attempts to reduce the triple bond with the system Zn(Cu/Ag)[21] were not successful, since the resulting (*Z*)-alkenes readily underwent rapid isomerization to the more stable (*E*)-alkenes.

Synthesis of O-Alkylated Phytoprostane Analogs. The ether oxygen of the second side chain has two electron lone pairs that could mimic the function of the double bond of the natural phytoprostanes. Such O-alkylated substances can easily be

SCHEME 6. O-Alkylation of Alkylhydroxycyclopentenones[a]



	R_1	R_2	Comp. yield (%)
PPB_1 type I	$(CH_2)_6COOMe$	CH_2CH_3	**11a** (42)
PPB_1 type II	CH_3	$(CH_2)_7COOMe$	**11b** (74)
$DIPB_1$ type III	$(CH_2)_3COOMe$	$(CH_2)_4CH_3$	**11c** (48)

[a] Reagents and conditions: (a) 1 equiv of $X(CH_2)_2R_2$, 1.5 equiv of NaH, DMSO, 24 h.

synthesized by reaction of 3-hydroxy-2-alkylyclopent-2-enone **4a−c** with sodium hydride and the corresponding haloester (see Scheme 6).

Bioactivity of Phytoprostanes B_1 and Their Analogs. Bioactive phytoprostanes are produced in stressed or damaged leaf tissue without participation of enzymes.[3] To test whether these compounds also play a role in plant−insect interactions, we tested the phytoprostanes **7a,b**, **8a,b**, **and 9a,b** and their ether analogs **11a,b** for their ability to induce volatile biosynthesis on lima bean plants.[22] Freshly cut plantlets were immediately placed into aqueous solutions (1.0 mM) of the phytoprostanes, and the emitted volatiles were monitored.[23] Both types of phytoprostanes showed a rather weak activity and induced a volatile pattern that had been previously observed upon treatment of lima bean leaves with the channel-forming peptaibol alamethicin.[24] The ether-analogs proved to be inactive. The same compounds exhibited at 10 mM a rather weak antimicrobial activity against the plant pathogen *Erwinia amylovora*; only the diketones **9a−c** and the acetylenes **10a−c** were effective down to 1 mM. Preliminary data obtained from microarrays covering the whole genome of *Arabidopsis thaliana* demonstrated a high activity for the diketone analog of phytoprostane B_1 type I (**9a**). The transcript level of many gene families was affected. In particular, the heat shock proteins (HSPs) and different glutathione-*S*-transferases (GSTs), as well pathogenesis-related proteins (PRs) strongly responded to the treatment with **9a**. Details on the results for the other phytoprostanes and their analogs on the whole genome level of *A. thaliana* will be reported in due course.

Experimental Section

***O*-Alkylation of Cyclopentane-1,3-dione, General Procedure. Methyl 3-Oxocyclopent-1-enyl-octanedioate (2a).** To a solution of cyclopentane-1,3-dione **1** (3.14 g, 32 mmol, 1 equiv) and pyridine (2.6 mL, 32 mmol, 1 equiv) in 150 mL of absolute dichloroethane was added methyl 7-(chlorocarbonyl)heptanoate (5 mL, 35.2 mmol, 1.1 equiv) in 75 mL of absolute dichloroethane. The mixture was kept at room temperature for 20 h. It was then washed with water,

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diluted HCl, saturated $NaHCO_3$, and water again. After drying over Na_2SO_4, the solvent was distilled off on a rotary evaporator, and the chromatographically pure enol ester **2a** was obtained as a light yellow solid (8.4 g, 98%). Mp: 44−47 °C. IR ν (cm^{-1}): 1776 (C═O), 1731 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.31−1.42 (m, 4H), 1.6−1.73 (m, 4H), 2.31 (t, J = 7.5 Hz, 2H), 2.42−2.45 (m, 2H), 2.52 (t, J = 7.4 Hz, 2H), 2.73−2.75 (m, 2H), 3.66 (s, 3H), 6.21 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.3, 24.8, 28.7, 28.8, 28.9, 33.4, 34.0, 34.5, 51.6, 116.6, 169.3, 174.2, 179.7, 206.9. EI-MS: $[M + H]^{+\bullet}$ 268 (1), 171 (100), 139 (63), 125 (3), 111 (70), 99 (52), 83 (82), 74 (11), 69 (69), 59 (25), 55 (91). HR-MS calcd for $C_{14}H_{20}O_5$ ($M^{+\bullet}$) 268.131074, found 268.130173.

Methyl 3-Oxocyclopent-1-enyl-glutarate (2b). Synthesized from 2 g (20.4 mmol) cyclopentane-1,3-dione **1**, 1.64 mL (820.4 mmol) pyridine, 100 mL absolute dichloroethane, 3.7 g (22.4 mmol) methyl 4-(chlorocarbonyl)butanoate in 50 mL absolute dichloroethane. Yield: 4.53 g (98%), yellow oil. IR ν (cm^{-1}): 1782 (C═O), 1737 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.98−2.04 (m, 2H), 2.41−2.45 (m, 4H), 2.62 (t, J = 7.22 Hz, 2H), 2.73−2.75 (m, 2H), 3.68 (s, 3H), 6.21 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.7, 28.9, 32.7, 33.4, 33.6, 51.9, 116.7, 168.7, 173.2, 179.7, 206.9. EI-MS: $[M - 31]^{+\bullet}$ 195 (13), 167 (13), 129 (100), 101 (57), 69 (11), 59 (42), 55 (21). HR-MS calcd for $C_{10}H_{11}O_4$ ($[M - 31]^{+\bullet}$) 195.065734 (− CH_3O), found 195.065903.

O−C-Isomerization of Enol Esters 2a,b, General Procedure. Methyl 8-(2-Hydroxy-5-oxocyclopent-1-enyl)-8-oxo-octanoate (3a). To a solution of methyl 3-oxocyclopent-1-enyl octanedioate **2a** (6 g, 22.4 mmol, 1 equiv) in 60 mL of absolute CH_3CN were added triethylamine (4.4 mL, 31.3 mmol, 1.4 equiv) and acetone cyanohydrine (0.8 mL, 9 mmol, 0.4 equiv). The mixture was stirred at room temperature for 24 h and then treated with 100 mL of diluted HCl. After extraction 3× with $CHCl_3$, the combined organic extracts were washed with water, dried over Na_2SO_4, and evaporated (yellow solid, 5.53 g, 92%). Mp: 51−53 °C. IR ν (cm^{-1}): 1737 (C═O), 1703 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.28−1.4 (m, 4H), 1.57−1.66 (m, 4H), 2.29 (t, J = 7.4 Hz. 2H), 2.48−2.51 (m, 2H), 2.72−2.75 (m, 2H), 2.89 (t, J = 7.5 Hz, 2H), 3.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 23.9, 24.8, 28.6, 28.9 (2C), 33.8, 34.1, 38.4, 51.6, 114.2, 174.3, 199.9, 201.8, 204.4. EI-MS: $M^{+\bullet}$ 268 (29), 250 (5), 237 (23), 218 (28), 195 (23), 167 (8), 153 (92), 140 (95), 125 (100), 97 (20), 87 (17), 74 (12), 69 (32), 59 (11), 55 (32). HR-MS calcd for $C_{14}H_{20}O_5$ ($M^{+\bullet}$) 268.131074, found 268.130988.

Methyl 5-(2-Hydroxy-5-oxocyclopent-1-enyl)-5-oxopentanoate (3b). Synthesized from 4 g (17.7 mmol) methyl 3-oxocyclopent-1-enyl glutarate **3a** in 40 mL of absolute CH_3CN, 3.5 mL (24.8 mmol) triethylamine, 0.65 mL (7.1 mmol) acetone cyanohydrine. Yield: 3.4 g (85%), yellow solid. Mp: 35−37 °C. IR ν (cm^{-1}): 1735 (C═O), 1699 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.94−2.0 (m, 2H), 2.39 (t, J = 7.45 Hz, 2H), 2.49−2.51 (m, 2H), 2.74−2.76 (m, 2H), 2.97 (t, J = 7.22 Hz, 2H), 3.66 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.0, 28.3, 33.3, 33.7, 38.0, 51.7, 114.5, 173.5, 199.9, 201.2, 203.7. EI-MS: $M^{+\bullet}$ 226 (72), 208 (10), 195 (57), 166 (74), 153 (98), 140 (25), 125 (100), 97 (22), 74 (39), 69 (58), 59 (28), 55 (60). HR-MS calcd for $C_{11}H_{14}O_5$ ($M^{+\bullet}$) 226.084124, found 226.084606.

Reduction of 3a,b, General Procedure. Methyl 8-(2-Hydroxy-5-oxocyclopent-1-enyl)octanoate (4a). To a solution of methyl 8-(2-hydroxy-5-oxocyclopent-1-enyl)-8-oxooctanoate **3a** (5 g, 18.7 mmol, 1 equiv) in 90 mL of trifluoroacetic acid containing 1% of lithium perchlorate was added in portions triethylsilane (8.9 mL, 56 mmol, 3 equiv). The mixture was left overnight at room temperature. The acid was distilled off and the residue was cooled and washed 3× with cold hexane. Then the residue was treated with $CHCl_3$, filtered, and evaporated (white solid, 4.21 g, 89%). Mp: 91−93 °C. IR ν (cm^{-1}): 1739 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.29−1.4 (m, 4H), 1.58−1.67 (m, 6H), 2.29 (t, J = 7.4 Hz, 2H), 2.49−2.52 (m, 2H), 2.72−2.75 (m, 2H), 2.89 (t, J = 7.3 Hz, 2H), 3.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 6.5, 6.9, 21.1, 25.0, 28.0, 29.1, 29.2, 29.5, 30.6, 34.2, 51.7, 118.6, 174.8, 198.6. EI-MS: $M^{+\bullet}$ 254 (27), 223 (27), 181 (24), 153 (17), 139 (36), 125 (61), 112 (100), 99 (12), 83 (19), 74 (7), 69 (14), 59 (10), 55 (41). HR-MS calcd for $C_{14}H_{22}O_4$ ($M^{+\bullet}$) 254.151809, found 254.152723.

Methyl 5-(2-Hydroxy-5-oxocyclopent-1-enyl)pentanoate (4c). Synthesized from 2.5 g (11.1 mmol) methyl 5-(2-hydroxy-5-oxocyclopent-1-enyl)-5-oxopentanoate **3b** in 55 mL trifluoroacetic acid conainng 1% of lithium perchlorate and 5.3 mL (33.2 mmol) triethylsilane. Yield: 1.94 g (83%), white solid. Mp: 126−128 °C. IR ν (cm^{-1}): 1737 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.43−1.48 (m, 2H), 1.58−1.64 (m, 2H), 2.18 (t, J = 7.45 Hz, 2H), 2.34 (t, J = 7.45 Hz, 2H), 2.55 (s, 4H), 3.66 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.5, 24.4, 27.6, 31.0, 33.8, 35.7, 51.7, 174.0, 177.4, 197.6, 198.7. EI-MS: $M^{+\bullet}$ 212 (46), 181 (57), 152 (36), 139 (100), 125 (53), 111 (67), 83 (22), 74 (17), 59 (29), 55 (40). HR-MS calcd for $C_{11}H_{16}O_4$ ($M^{+\bullet}$) 212.104859, found 212.104912.

Iodination of C-Alkylated Cyclopentan-1,3-diones 4a−c, General Procedure. Methyl 8-(2-Iodo-5-oxocyclopent-1-enyl)-octanoate (5a). To a solution of triphenylphosphine (3.5 g, 13.3 mmol, 1.125 equiv) in 120 mL of dry CH_3CN was added iodine (3.4 g, 13.3 mmol, 1.125 equiv) in one portion. This slurry was stirred for 2 h at room temperature, and methyl 8-(2-hydroxy-5-oxocyclopent-1-enyl)-octanoate **4a** (3 g, 11.8 mmol, 1 equiv) was added in one portion followed by immediate addition of triethylamine (1.8 mL, 13 mmol, 1.1 equiv). The resulting mixture was heated to 80 °C for 1 h, stirred over night at room temperature, and then heated again to 90 °C for 1 h. Ether was added, and the mixture was filtered and evaporated. The residue was loaded onto a silica column using petrol ether/diethyl ether (1:2) as eluent (light yellow oil, 2.94 g, 68%). IR ν (cm^{-1}): 1737 (C═O), 1704 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.28−1.44 (m, 8H), 1.59−1.64 (m, 2H), 2.21−2.31 (m, 4H), 2.49−2.51 (m, 2H), 2.98−3.0 (m, 2H), 3.65 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.0, 27.3, 27.5, 29.1 (2C), 29.4, 34.2, 36.9, 39.3, 51.6, 133.9, 151.5, 174.4, 202.5. EI-MS: $M^{+\bullet}$ 364 (23), 333 (35), 291 (8), 249 (19), 237 (100), 222 (34), 205 (84), 177 (11), 145 (18), 69 (13), 59 (27), 55 (43). HR-MS calcd for $C_{14}H_{21}IO_3$ ($M^{+\bullet}$) 364.053547, found 364.054787.

2-Ethyl-3-iodocyclopent-2-enone (5b). Synthesized from 4.5 g (17.9 mmol) triphenylphosphine in 150 mL dry CH_3CN, 4.7 g (17.9 mmol) iodine, 2 g (15.9 mmol) 2-ethylcyclopentane-1,3-dione **4b**, 2.4 mL (17.5 mmol) triethylamine. Column: petrol ether/diethyl ether (1:1). Yield: 2.9 g (77%), yellow oil. IR ν (cm^{-1}): 1709 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.0 (t, J = 7.55 Hz, 3H), 2.25−2.3 (m, 2H), 2.5−2.52 (m, 2H), 2.97−3.0 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.9, 21.1, 36.9, 39.3, 133.2, 152.6, 202.4. EI-MS: $M^{+\bullet}$ 236 (100), 127 (2), 109 (24), 81 (32). HR-MS calcd for $C_7H_9IO_3$ ($M^{+\bullet}$) 235.969817, found 235.969070.

Methyl 5-(2-Iodo-5-oxocyclopent-1-enyl)pentanoate (5c). Synthesized from 2.1 g (8 mmol) triphenylphosphine in 60 mL dry CH_3CN, 2 g (8 mmol) iodine, 1.5 g (7.1 mmol) methyl 5-(2-hydroxy-5-oxocyclopent-1-enyl)pentanoate **4c**, 1.1 mL (7.8 mmol) triethylamine. Yield: 1.82 g (82%), yellow solid. Mp: 46−48 °C. IR ν (cm^{-1}): 1739 (C═O), 1688 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.43−1.49 (m, 2H), 1.61−1.67 (m, 2H), 2.25−2.28 (m, 2H), 2.33 (t, J = 7.55 Hz, 2H), 2.5−2.52 (m, 2H), 2.98−3.0 (m, 2H), 3.66 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.8, 26.8, 27.2, 33.9, 36.9, 39.4, 51.7, 134.2, 151.0, 174.1, 202.4. EI-MS: $M^{+\bullet}$ 322 (14), 290 (49), 249 (72), 222 (15), 195 (15), 163 (84), 129 (54), 115 (59), 100 (69), 87 (58), 59 (100), 55 (78). HR-MS calcd for $C_{11}H_{15}IO_3$ ($M^{+\bullet}$) 322.006597, found 322.006295.

Vinylation of Alkenyl Iodides 5a−c, General Procedure. Phytoprostane B_1 Type I. Methyl 8-(2-((*E*)-3-Hydroxypent-1-enyl)-5-oxocyclopent-1-enyl)octanoate (7a). A mixture of methyl 8-(2-iodo-5-oxocyclopent-1-enyl) octanoate **5a** (1.7 g, 4.7 mmol, 1 equiv), tetrahydro-2-(pent-1-en-3-yloxy)-2*H*-pyran (1.3 g, 7.8 mmol, 1.67 equiv)[17] (prepared according to literature and used without chromatographic purification), and triethylamine (1.3 mL, 9.3 mmol, 2 equiv) with 120 mg of the palladium catalyst (mixture

of palladium diacetate and triphenylphosphine, 1:2 molar ratio) was heated to 100 °C in a small flask for 24 h. Diethyl ether was added, and the insoluble compounds were filtered off. After evaporation, the residue was loaded onto a silica gel column using diethyl ether as eluent. For the protected alcohols the THP group was first cleaved off by dissolving the residue in 42 mL of a 4:2:1 mixture of acetic acid/THF/water and heating to 45 °C overnight (white solid, 0.94 g, 65% over two steps). Mp: 43−46 °C. IR ν (cm^{-1}): 3338 (OH), 1734 (C═O), 1673 (C═O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.98 (t, J = 7.46 Hz, 3H), 1.25−1.28 (m, 6H), 1.35−1.4 (m, 2H), 1.56−1.68 (m, 4H), 2.02 (1H, OH), 2.24−2.29 (m, 4H), 2.4−2.42 (m, 2H), 2.63−2.65 (m, 2H), 3.65 (s, 3H), 4.24−4.28 (m, 1H), 6.25 (dd, J = 5.93, 15.68 Hz, 1H), 6.78 (d, J = 15.87 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.8, 23.1, 24.9, 25.7, 28.8, 29.0, 29.1, 29.4, 30.3, 34.0, 34.2, 51.6, 73.7, 124.2, 140.1, 141.5, 163.3, 174.6, 209.8. EI-MS: $M^{+\bullet}$ 322 (28), 304 (12), 291 (9), 273 (16), 265 (51), 263 (50), 233 (100), 205 (28), 133 (26), 121 (29), 105 (21), 91 (32), 79 (28), 59 (21), 55 (42). HR-MS calcd for $C_{19}H_{30}O_4$ ($M^{+\bullet}$) 322.214410, found 322.212974.

Phytoprostane B_1 Type II. (10*E*)-Methyl 11-(2-Ethyl-3-oxocyclopent-1-enyl)-9-hydroxyundec-10-enoate (7b). Synthesized from 1 g (4.2 mmol) 2-ethyl-3-iodocyclopent-2-enone **5b**, 2.1 g (7.1 mmol) methyl 9-(tetrahydro-2*H*-pyran-2-yloxy)undec-10-enoate[17,20] (synthesized from methyl 9-hydroxy-undec-10-enoate according to literature in 93% yield; used without chromatographic purification), 1.2 mL (8.5 mmol) triethylamine, and 70 mg of the palladium catalyst (mixture of palladium diacetate and triphenylphosphine, 1:2 molar ratio), dissolved in 28 mL of a 4:2:1 mixture of acetic acid/THF/water. Yield: 0.94 g (69%), yellow oil. IR ν (cm^{-1}): 3430 (OH), 1737 (C═O), 1692 (C═O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.0 (t, J = 7.55 Hz, 3H), 1.31−1.45 (m, 8H), 1.56−1.64 (m, 4H), 1.84 (1H, OH), 2.27−2.31 (m, 4H), 2.4−2.42 (m, 2H), 2.62−2.64 (m, 2H), 3.65 (s, 3H), 4.3−4.34 (m, 1H), 6.25 (dd, J = 5.93, 15.68 Hz, 1H), 6.81 (d, J = 15.68 Hz; 1H) ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.6, 16.4, 25.0, 25.4, 25.7, 29.1, 29.3, 29.4, 34.0, 34.2, 37.4, 51.6, 72.5, 123.9, 140.2, 142.9, 162.8, 174.4, 209.6. EI-MS: $M^{+\bullet}$ 322 (0.25), 304 (100), 273 (13), 189 (55), 175 (23), 161 (25), 133 (18), 119 (10), 105 (18), 91 (20), 59 (4), 55 (10). HR-MS calcd for $C_{19}H_{30}O_4$ ($M^{+\bullet}$) 322.214410, found 322.214393.

Dinor Isoprostane B_1, Type III. Methyl 5-(2-((*E*)-3-Hydroxy-oct-1-enyl)-5-oxo-cyclopent-1-enyl)-pentanoate (7c). Synthesized from 0.5 g (1.6 mmol) methyl 5-(2-iodo-5-oxocyclopent-1-enyl) pentanoate **5c**, 0.6 g (2.6 mmol) tetrahydro-2-(oct-1-en-3-yloxy)-2*H*-pyran,[17] 0.4 mL (3.1 mmol) triethylamine, and 35 mg of the palladium catalyst (mixture of palladium diacetate and triphenylphosphine, 1:2 molar ratio), dissolved in 14 mL of a 4:2:1 mixture of acetic acid/THF/water. Yield: 0.26 g (52%), yellow oil. IR ν (cm^{-1}): 3435 (OH), 1736 (C═O), 1689 (C═O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.9 (t, J = 7.1 Hz, 3H), 1.29−1.38 (m, 4H), 1.4−1.47 (m, 4H), 1.57−1.64 (m, 4H), 1.91 (s, 1H, OH), 2.28−2.33 (m, 4H), 2.4−2.43 (m, 2H), 2.64−2.65 (m, 2H), 3.65 (s, 3H), 4.33−4.35 (m, 1H), 6.28 (dd, J = 15.68 Hz, 1H), 6.81 (d, J = 15.68 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.2, 22.6, 22.7, 24.8, 25.2, 25.8, 28.3, 31.9, 33.9 (2C), 37.3, 51.7, 72.5, 123.8, 140.7, 140.9, 163.7, 174.3, 209.6. EI-MS: $M^{+\bullet}$ 322 (0.4), 304 (100), 273 (40), 244 (70), 215 (44), 187 (64), 173 (46), 159 (33), 147 (48), 133 (70), 105 (49), 91 (54), 55 (14). HR-MS calcd for $C_{19}H_{30}O_4$ ($M^{+\bullet}$) 322.214410, found 322.213049.

Methyl 5-(2-((*R*,*E*)-(−)-3-Hydroxyoct-1-enyl)-5-oxocyclopent-1-enyl)-pentanoate. Synthesized from (*R*)-(−)-oct-1-en-3-ol-THP (obtained from (*R*)-(+)-oct-1-en-3-ol, Acros Organics). Yield: 57%. $[\alpha]^{25}_D$ = −24.5 (*c* 0.51, MeOH).

Methyl 8-(5-Oxo-2-((*E*)-pent-1-enyl)cyclopent-1-enyl)-octanoate (8a). Synthesized from 0.15 g (0.41 mmol) methyl 8-(2-iodo-5-oxocyclopent-1-enyl)octanoate **5a**, 4 × 90 μL (4 × 0.82 mmol) pent-1-ene, 115 μL (0.82 mmol) triethylamine, 12 mg of the palladium catalyst (mixture of palladium diacetate and triphenylphosphine, 1:2 molar ratio), 40 °C, 4 d. Yield: 122 mg (97%), yellow oil. IR ν (cm^{-1}): 1738 (C═O), 1693 (C═O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.95 (t, J = 7.35 Hz, 3H), 1.26−1.38 (m, 8H), 1.48−1.54 (m, 2H), 1.57−1.63 (m, 2H), 2.21−2.29 (m, 6H), 2.37−2.39 (m, 2H), 2.61−2.63 (m, 2H), 3.65 (s, 3H), 6.23−6.29 (m, 1H), 6.59 (d, J = 15.7 Hz), 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 22.3, 23.1, 25.1, 25.7, 29.0, 29.2 (2C), 29.6, 33.9, 34.2, 35.6, 51.5, 125.3, 139.4, 139.8, 164.3, 174.4, 209.7. EI-MS: $M^{+\bullet}$ 306 (32), 275 (24), 263 (65), 231 (100), 203 (20), 191 (15), 177 (9), 163 (7), 133 (20), 121 (55), 105 (16), 91 (18), 79 (15), 59 (3), 55 (10). HR-MS calcd for $C_{19}H_{30}O_3$ ($M^{+\bullet}$) 306.219495, found 306.220961.

(10*E*)-Methyl 11-(2-Ethyl-3-oxocyclopent-1-enyl)-undec-10-enoate (8b). Synthesized from 0.2 g (0.85 mmol) 2-ethyl-3-iodocyclopent-2-enone **5b**, 0.27 g (1.27 mmol) methyl undec-10-enoate, 0.24 mL (1.69 mmol) triethylamine, and 15 mg of the palladium catalyst (mixture of palladium diacetate and triphenylphosphine, 1:2 molar ratio). Yield: 159 mg (59%), yellow oil. IR ν (cm^{-1}): 1738 (C═O), 1704 (C═O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.0 (t, J = 7.56 Hz, 3H), 1.31 (m, 8H), 1.43−1.49 (m, 2H), 1.59−1.63 (m, 2H), 2.23−2.31 (m, 6H), 2.39−2.4 (m, 2H), 2.61−2.63 (m, 2H), 3.66 (s, 3H), 6.24−6.3 (m, 1H), 6.61 (d, J = 15.58 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.6, 16.4, 25.1, 25.7, 29.0, 29.2, 29.3 (2C), 29.4, 33.6, 34.0, 34.2, 51.6, 125.0, 139.6, 141.1, 164.0, 174.4, 209.6. EI-MS: $M^{+\bullet}$ 306 (18), 275 (8), 163 (26), 135 (100), 124 (10), 107 (8), 91 (10), 69 (1), 59 (2), 55 (6). HR-MS calcd for $C_{19}H_{30}O_3$ ($M^{+\bullet}$) 306.219495, found 306.218033.

Methyl 5-(2-((*E*)-Oct-1-enyl)-5-oxocyclopent-1-enyl)-pentanoate (8c). Synthesized from 0.2 g (0.62 mmol) methyl 5-(2-iodo-5-oxocyclopent-1-enyl)pentanoate **5c**, 0.12 g (1.04 mmol) oct-1-ene, 0.17 mL (1.24 mmol) triethylamine, and 15 mg of the palladium catalyst (mixture of palladium diacetate and triphenylphosphine, 1:2 molar ratio). Yield: 132 mg (70%), yellow oil. IR ν (cm^{-1}): 1739 (C═O), 1693 (C═O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.89 (t, J = 6.99 Hz, 3H), 1.26−1.35 (m, 6H), 1.39−1.49 (m, 4H), 1.58−1.64 (m, 2H), 2.22−2.32 (m, 6H), 2.38−2.4 (m, 2H), 2.62−2.64 (m, 2H), 3.65 (s, 3H), 6.25−6.31 (m, 1H), 6.58 (d, J = 15.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.2, 22.7, 22.8, 25.0, 25.8, 28.4, 29.0, 29.1, 31.8, 33.7, 33.9, 34.0, 51.6, 125.0, 139.1, 140.1, 164.7, 174.2, 209.6. EI-MS: $M^{+\bullet}$ 306 (38), 275 (23), 221 (97), 189 (100), 147 (29), 121 (25), 105 (17), 91 (23), 59 (4), 55 (11). HR-MS calcd for $C_{19}H_{30}O_3$ ($M^{+\bullet}$) 306.219495, found 306.220204.

Oxidation of Phytoprostanes 7a−c, General Procedure. Methyl 8-(5-Oxo-2-((*E*)-3-oxopent-1-enyl)cyclopent-1-enyl)- octanoate (9a). To a stirred solution of phytoprostane B_1 type I methyl ester **7a** (50 mg, 155 μmol, 1 equiv) in 3 mL of methylene chloride were added Bobbitt's reagent (4-acetylamino-2,2,6,6-tetra-methyl-piperidine-1-oxoammonium perchlorate) (51 mg, 163 μmol, 1.05 equiv) and 50 mg of silica gel to catalyze the oxidation. The yellow slurry was stirred until the color changed to white (∼ 5 h) and GC showed complete oxidation of the alcohol. The slurry was filtered, and the filter was washed with methylene chloride. After evaporation of the solvent, the residue was loaded onto a silica gel column using diethyl ether as eluent (yellow oil, 40 mg, 81%). IR ν (cm^{-1}): 1737 (C═O), 1698 (C═O). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.16 (t, J = 7.22 Hz, 3H), 1.27−1.29 (m, 6H), 1.39−1.42 (m, 2H), 1.58−1.6 (m, 2H), 2.29 (t, J = 7.45 Hz, 2H), 2.32−2.36 (m, 2H), 2.46−2.48 (m, 2H), 2.66−2.71 (m, 4H), 3.65 (s, 3H), 6.57 (d, J = 15.8 Hz, 1H), 7.64 (d, J = 15.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 8.1, 23.6, 25.0, 25.5, 29.1 (3C), 29.5, 34.0, 34.2, 34.9, 51.6, 130.4, 134.1, 148.0, 160.2, 174.4, 200.6, 209.0. EI-MS: $M^{+\bullet}$ 320 (17), 289 (18), 263 (96), 231 (100), 203 (27), 189 (9), 171 (8), 161 (10), 147 (11), 133 (19), 121 (21), 105 (14), 91 (18), 59 (7), 55 (16). HR-MS calcd for $C_{19}H_{28}O_4$ ($M^{+\bullet}$) 320.198760, found 320.199851.

(10*E*)-Methyl 11-(2-Ethyl-3-oxocyclopent-1-enyl)-9-oxoundec-10-enoate (9b). Synthesized from 100 mg (0.31 mmol) phytoprostane B_1 type II methyl ester **7b** in 5 mL methylene chloride, 102 mg (0.33 mmol) Bobbitt's reagent (4-acetylamino-2,2,6,6-tetra-

methylpiperidine-1-oxoammonium perchlorate), and 100 mg silica gel. Yield: 85 mg (86%), yellow oil. IR ν (cm^{-1}): 1737 (C═O), 1697 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.04 (t, J = 7.56 Hz, 3H), 1.32−1.35 (m, 6H), 1.58−1.68 (m, 4H), 2.29 (t, J = 7.56 Hz, 2H), 2.38 (q, J = 7.56 Hz, 2H), 2.46−2.48 (m, 2H), 2.62−2.68 (m, 4H), 3.65 (s, 3H), 6.56 (d, J = 16.04 Hz, 1H), 7.65 (d, J = 16.04 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 16.9, 24.1, 25.0, 25.5, 29.1 (2C), 29.2, 34.0, 34.2, 41.6, 51.6, 130.6, 134.1, 149.4, 159.7, 174.3, 200.2, 208.9. EI-MS: $M^{+\bullet}$ 320 (26), 289 (11), 178 (11), 163 (43), 135 (100), 121 (11), 107 (9), 91 (11), 59 (3), 55 (13). HR-MS calcd for $C_{19}H_{28}O_4$ ($M^{+\bullet}$) 320.198760, found 320.199601.

Methyl 5-(5-Oxo-2-((*E*)-3-oxooct-1-enyl)cyclopent-1-enyl)-pentanoate (9c). Synthesized from 50 mg (155 μmol) phytoprostane B_1 type III methyl ester **7c** in 3 mL methylene chloride, 51 mg (163 μmol) Bobbitt's reagent (4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perchlorate), and 50 mg silica gel. Yield: 39 mg (78%), yellow oil. IR ν (cm^{-1}): 1737 (C═O), 1697 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 0.9 (t, J = 7 Hz, 3H), 1.31−1.37 (m, 4H), 1.43−1.49 (m, 2H), 1.6−1.7 (m, 4H), 2.32 (t, J = 7.45 Hz, 2H), 2.38 (t, J = 7.68 Hz, 2H), 2.46−2.48 (m, 2H), 2.64−2.69 (m, 4H), 3.65 (s, 3H), 6.57 (d, J = 15.81 Hz, 1H), 7.59 (d, J = 16.04 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 22.6, 23.3, 23.9, 24.9, 25.6, 28.5, 31.5, 33.9, 34.0, 41.7, 51.7, 130.9, 134.0, 147.4, 160.6, 174.0, 200.4, 209.0. EI-MS: $M^{+\bullet}$ 320 (100), 289 (20), 221 (71), 189 (92), 161 (36), 147 (46), 133 (23), 105 (17), 91 (24), 59 (5), 55 (11). HR-MS calcd for $C_{19}H_{28}O_4$ ($M^{+\bullet}$) 320.198760, found 320.197166.

Alkynylation of Alkenyl Iodides 5a−c, General Procedure

Methyl 8-(2-(3-hydroxypent-1-ynyl)-5-oxocyclopent-1-enyl)-octanoate (10a). To a stirring solution of $PdCl_2(PPh_3)_2$ (40 mg, 0.06 mmol, 0.07 equiv) and CuI (24 mg, 0.12 mmol, 0.15 equiv) in 1 mL of anhydrous DMF were added successively pent-1-yn-3-ol (0.1 g, 1.24 mmol, 1.5 equiv) and a solution of methyl 8-(2-iodo-5-oxocyclopent-1-enyl)octanoate **5a** (0.3 g, 0.82 mmol, 1 equiv) in 4 mL of anhydrous DMF and triethylamine (0.14 mL, 0.99 mmol, 1.2 equiv). The mixture was stirred for 24 h at room temperature, and saturated NH_4Cl was added and extracted with diethyl ether. After washing with saturated NaCl and water and drying over Na_2SO_4, the ether was evaporated, and the crude residue was loaded onto a silica gel column using diethyl ether as eluent (yellow oil, 0.23 g, 88%). IR ν (cm^{-1}): 3424 (OH), 1738 (C═O), 1699 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.06 (t, J = 7.45 Hz, 3H), 1.26−1.31 (m, 6H), 1.42−1.48 (m, 2H), 1.57−1.63 (m, 2H), 1.77−1.85 (m, 2H), 2.27−2.31 (m, 4H), 2.4−2.42 (m, 2H), 2.61−2.63 (m, 2H), 3.66 (s, 3H), 4.6 (t, J = 6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.6, 24.6, 25.0, 27.7, 29.0, 29.1, 29.3, 30.3, 30.9, 34.2, 34.3, 51.7, 64.4, 80.7, 106.4, 149.1, 149.8, 174.6, 209.0. EI-MS: $M^{+\bullet}$ 320 (5), 302 (20), 271 (28), 261 (100), 231 (30), 203 (31), 191 (37), 187 (33), 161 (27), 147 (26), 133 (46), 121 (30), 105 (29), 91 (54), 59 (14), 55 (34). HR-MS calcd for $C_{19}H_{28}O_4$ ($M^{+\bullet}$) 320.198760, found 320.198096.

Methyl 11-(2-Ethyl-3-oxocyclopent-1-enyl)-9-hydroxyundec-10-ynoate (10b). Synthesized from 31 mg (0.04 mmol) $PdCl_2(PPh_3)_2$, 18 mg (0.09 mmol) CuI in 1 mL anhydrous DMF, 0.2 g (0.95 mmol) methyl 9-hydroxy-undec-10-ynoate[20] (synthesized from methyl undec-10-ynoate according to literature in 22% yield), 0.15 g (0.64 mmol) 2-ethyl-3-iodocyclopent-2-enone **5b** in 3 mL anhydrous DMF, and 0.11 mL (0.76 mmol) triethylamine. Yield: 185 mg (91%), brown oil. IR ν (cm^{-1}): 3423 (OH), 1738 (C═O), 1699 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.05 (t, J = 7.59 Hz, 3H), 1.31−1.38 (m, 6H), 1.46−1.52 (m, 2H), 1.59−1.65 (m, 2H), 1.74−1.83 (m, 2H), 2.08 (s, 1H, OH), 2.28−2.33 (m, 4H). 2.4−2.42 (m, 2H), 2.6−2.62 (m, 2H), 3.66 (s, 3H), 4.64 (t, J = 6.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.5, 18.0, 25.0, 25.2, 29.1 (2C), 29.3, 30.2, 34.2, 34.3, 37.7, 51.6, 63.1, 80.6, 106.5, 149.2, 150.4, 174.4, 208.9. EI-MS: $M^{+\bullet}$ 320 (3), 302 (49), 289 (10), 187 (24), 163 (54), 135 (100), 91 (56), 74 (36), 59 (17), 55 (53). HR-MS calcd for $C_{19}H_{28}O_4$ ($M^{+\bullet}$) 320.198760, found 320.199075.

Methyl 5-(2-(3-Hydroxyoct-1-ynyl)-5-oxocyclopent-1-enyl)-pentanoate (10c). Synthesized from 31 mg (0.04 mmol) $PdCl_2(PPh_3)_2$, 18 mg (0.09 mmol) CuI in 1 mL anhydrous DMF, 0.12 g (0.93 mmol) oct-1-yn-3-ol, 0.2 g (0.62 mmol, Acros Organics) methyl 5-(2-iodo-5-oxocyclopent-1-enyl)pentanoate **5c** in 3 mL anhydrous DMF, and 0.1 mL (0.75 mmol) triethylamine. Yield: 171 mg (86%), brown oil. IR ν (cm^{-1}): 3423 (OH), 1739 (C═O), 1699 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 0.9 (t, J = 7.1 Hz, 3H), 1.32−1.36 (m, 4H), 1.46−1.55 (m, 4H), 1.6−1.66 (m, 2H), 1.73−1.85 (m, 2H), 2.3−2.36 (m, 4H), 2.4−2.42 (m, 2H), 2.61−2.63 (m, 2H), 3.66 (s, 3H), 4.63 (q, J = 6.11 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 22.7, 23.9, 24.7, 25.0, 27.2, 30.2, 31.6, 33.8, 34.2, 37.6, 51.8, 63.0, 80.5, 107.5, 148.5, 150.4, 174.6, 208.8. EI-MS: $M^{+\bullet}$ 320 (1), 302 (100), 271 (22), 245 (16), 215 (56), 189 (34), 171 (37), 147 (31), 133 (27), 105 (19), 91 (39), 59 (8), 55 (22). HR-MS calcd for $C_{19}H_{28}O_4$ ($M^{+\bullet}$) 320.198760, found 320.197846.

(*R*)-(+)-Methyl 5-(2-(3-Hydroxyoct-1-ynyl)-5-oxocyclopent-1-enyl)pentanoate. Synthesized from (*R*)-(+)-oct-1-yn-3-ol-THP (obtained from (*R*)-(+)-oct-1-yn-3-ol, Acros Organics). Yield: 70%. $[\alpha]^{25}_D$ = 6.2 (*c* 0.50, MeOH).

Preparation of *O*-Alkyl Ethers from 4a−c, General Procedure. Methyl 8-(2-Butoxy-5-oxocyclopent-1-enyl)-octanoate (11a). To a stirring solution of methyl 8-(2-hydroxy-5-oxocyclopent-1-enyl)octanoate **4a** (0.5 g, 2 mmol, 1 equiv) in 10 mL DMSO was added 1-iodobutane (0.36 g, 2 mmol, 1 equiv). Sodium hydride (0.12 g, 3 mmol, 1.5 equiv) was added in portions, and the mixture was stirred for 24 h at room temperature. Water was added, and the product was extracted with diethyl ether. After washing with saturated $NaHCO_3$ and water, the organic phase was dried over Na_2SO_4 and evaporated. The residue was loaded onto a silica gel column using petrol ether/ethyl acetate (1:1) as eluent (yellow oil, 254 mg, 42%). IR ν (cm^{-1}): 1738 (C═O), 1687 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 0.96 (t. J = 7.5 Hz, 3H), 1.22−1.49 (m, 10H), 1.54−1.63 (m, 2H), 1.69−1.74 (m, 2H), 2.08−2.11 (m, 2H), 2.27 (t, J = 7.5 Hz, 2H), 2.41−2.42 (m, 2H), 2.61−2.63 (m, 2H), 3.64 (s, 3H), 4.12 (t, J = 6.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.8, 19.1, 21.3, 25.0, 25.1, 27.9, 29.1, 29.2, 29.4, 31.8, 33.6, 34.2, 51.5, 69.2, 120.9, 174.4, 184.6, 205.1. EI-MS: $M^{+\bullet}$ 310 (20), 279 (15), 237 (28), 223 (7), 195 (13), 181 (21), 168 (41), 153 (8), 139 (38), 125 (31), 112 (100), 96 (10), 55 (18). HR-MS calcd for $C_{18}H_{30}O_4$ ($M^{+\bullet}$) 310.214410, found 310.215523.

Methyl 10-(2-Ethyl-3-oxocyclopent-1-enyloxy)-decanoate (11b). Synthesized from 0.5 g (4 mmol) 2-ethylcyclopentane-1.3-dione **4b** in 10 mL DMSO, 1.1 g (4 mmol) methyl 10-bromodecanoate, and 0.24 g (6 mmol) sodium hydride. Yield: 0.91 g (74%), white solid. Mp: 43−44 °C. IR ν (cm^{-1}): 1739 (C═O), 1679 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 0.97 (t, J = 7.45 Hz, 3H), 1.3−1.43 (m, 10H), 1.58−1.62 (m, 2H), 1.7−1.75 (m, 2H), 2.14 (q, J = 7.48 Hz, 2H), 2.29 (t, J = 7.56 Hz, 2H), 2.39−2.41 (m, 2H), 2.6−2.62 (m, 2H), 3.65 (s, 3H), 4.12 (t, J = 6.53 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 12.7, 14.8, 25.0 (2C), 25.9, 29.2, 29.3 (2C), 29.4, 29.7, 33.7, 34.2, 51.5, 69.4, 122.2, 174.4, 184.1, 204.9. EI-MS: $M^{+\bullet}$ 310 (29), 279 (23), 237 (9), 185 (24), 153 (41), 135 (25), 127 (100), 126 (99), 11 (30), 83 (26), 69 (49), 59 (10), 55 (36). HR-MS calcd for $C_{18}H_{30}O_4$ ($M^{+\bullet}$) 310.214410, found 310.214056.

Methyl 5-(2-(Heptyloxy)-5-oxocyclopent-1-enyl)-pentanoate (11c). Synthesized from 0.2 g (0.94 mmol) methyl 5-(2-hydroxy-5-oxocyclopent-1-enyl)pentanoate **4c** in 5 mL DMSO, 0.21 g (0.94 mmol) 1-iodoheptane, 57 mg (1.42 mmol) sodium hydride. Yield: 0.14 g (48%), yellow oil. IR ν (cm^{-1}): 1738 (C═O), 1688 (C═O). ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (t, J = 7 Hz, 3H), 1.27−1.46 (m, 10H), 1.55−1.61 (m, 2H), 1.7−1.75 (m, 2H), 2.13 (t, J = 7.46 Hz, 2H), 2.29 (t, J = 7.74 Hz, 2H), 2.4−2.42 (m, 2H), 2.62−2.64 (m, 2H), 3.64 (s, 3H), 4.11 (t, J = 6.5 Hz, 2H). ^{13}C NMR

(125 MHz, $CDCl_3$) δ: 14.2, 20.9, 22.7, 24.8, 25.0, 25.8, 27.4, 29.0, 29.7, 31.8, 33.6, 34.0, 51.5, 69.5, 120.2, 174.4, 184.8, 205.0. EI-MS: $M^{+\bullet}$ 310 (32), 279 (25), 237 (66), 223 (22), 210 (19), 180 (48), 139 (100), 125 (46), 112 (86), 55 (23). HR-MS calcd for $C_{18}H_{30}O_4$ ($M^{+\bullet}$) 310.214410, found 310.213246.

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Supporting Information Available: IR spectra, EI-MS spectra, ^{1}H NMR and ^{13}C NMR spectra of compounds **2a,b**, **3a,b**, **4a,c**, **5a−c**, **7a−c**, **8a−c**, **9a−c**, **10a−c, 11a−c**, methyl 9-hydroxyundec-10-enoate, and methyl 9-hydroxyundec-10-ynoate. This material is available free of charge via the Internet at http://pubs.acs.org.

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