JOC The Journal of Organic Chemistry

Article

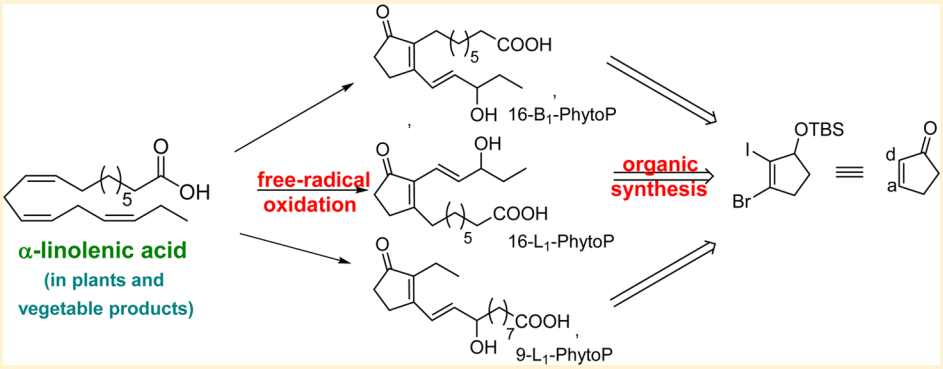
pubs.acs.org/joc

General Strategy for the Synthesis of B_1 and L_1 Prostanoids: Synthesis of Phytoprostanes (*RS*)-9-L_1-PhytoP, (*R*)-9-L_1-PhytoP, (*RS*)-16-B_1-PhytoP, and (*RS*)-16-L_1-PhytoP

Ruggero Beretta, Mirko Giambelli Gallotti, Umberto Pennè, Alessio Porta, Juan Fernando Gil Romero, Giuseppe Zanoni, and Giovanni Vidari*

Sezione di Chimica Organica, Dipartimento di Chimica, Università di Pavia, Via Taramelli 12, 27100 Pavia, Italy

Supporting Information



ABSTRACT: In this paper we describe a novel general synthetic approach to B_1- and L_1-type phytoprostanes, which are formed in vivo from free-radical-catalyzed nonenzymatic peroxidation of α-linolenic acid (**1**). The synthesis of phytoprostanes (*RS*)-9-L_1-PhytoP (**5**), (*R*)-9-L_1-PhytoP (**5a**), (*RS*)-16-B_1-PhytoP (**6**), and (*RS*)-16-L_1-PhytoP (**7**) exemplifies this strategy. The common starting compound **8** has been proved to be synthetically equivalent to a cyclopent-2-en-1-one synthon having opposite donor and acceptor properties at carbons α and β, respectively. Key steps include the chemoselective lithiation of a 1-iodo-2-bromoolefin, the introduction of the side chains by transition-metal catalysis following Heck- or Suzuki-type protocols, the construction of an enone moiety by a mild Au(I)-catalyzed Meyer Schuster rearrangement, and a lipase-mediated hydrolysis of methyl esters to deliver the phytoprostanes as free carboxylic acids.

INTRODUCTION

Cyclopentanoid phytoprostanes (PhytoPs) represent a novel group of bioactive compounds that are produced from α-linolenic acid (ALA, **1**) in a free-radical-catalyzed nonenzymatic peroxidation process.[1] **1** is a major component of leaf lipids and especially of the photosynthetic apparatus of algae and higher plants.[2] The reaction cascade[1] giving rise to phytoprostanes (Figure 1) closely resembles the oxidation of arachidonic acid (AA), leading to mammalian prostaglandins, and for this reason, a similar nomenclature system is used for the different A, B, D, E, ... classes.[3] However, in the absence of an enzymatic control, end products are produced as racemic mixtures of all possible regio- and diastereomers. For example, in the case of **1**, the initial hydrogen radical abstraction may occur at either of the two bisallylic positions 11 and 14, thus giving rise to the regioisomeric 13-hydroperoxy (**2**) and 12-hydroperoxy (**3**) radicals, respectively. The primarily formed G_1 phytoprostanes are labile and readily give rise to reduction, rearrangements, H_2O elimination, and double bond isomerization reactions, resulting in a large array of structurally and functionally different phytoprostanes.[1] The B_1-PhytoPs **4** and **6** and L_1-PhytoPs **5** and **7** are among the most representative examples of stable end products of **1** peroxidation and transformation sequence (Figure 1).

Phytoprostanes are continuously generated at a low background level as part of the cell signaling machinery in healthy organisms, but their concentration increases significantly in leaves wounded or attacked by pathogens and parasites.[4] In fact, one function of A_1- and B_1-PhytoPs is the gene upregulation of xenobiotic detoxification and cytoprotective responses, including accumulation of antimicrobial phytoalexins.[4] More specifically, ALA radical peroxidation occurs by the action of reactive oxygen species (ROS) and free radicals, which are massively produced in plants under severe biotic and abiotic stress conditions.[5] In addition, autoxidative processes may become significantly important in plants and plant-derived products,[6] especially vegetable oils, during drying/cooking and storage postmortem in the absence of antioxidative defense systems and metabolism. Humans can thus be exposed to

Received: November 6, 2014
Published: January 9, 2015

DOI: 10.1021/jo502538b
J. Org. Chem. 2015, 80, 1601−1609

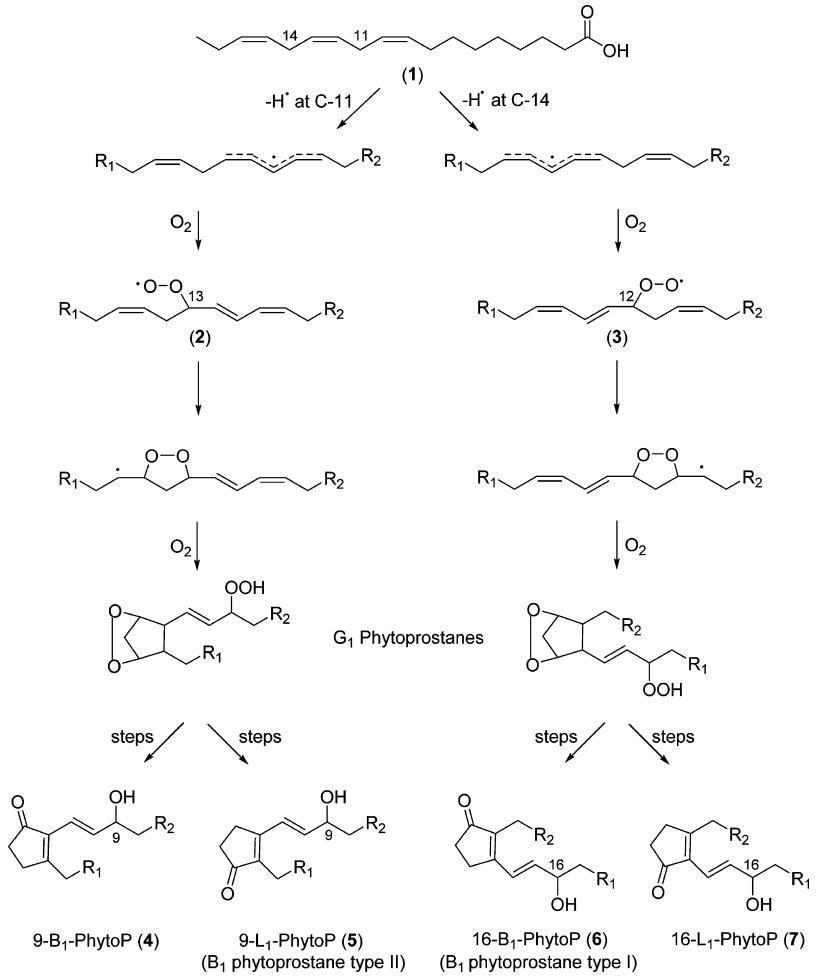


Figure 1. Free-radical-catalyzed oxidation of α-linolenic acid (**1**) to B_1 and L_1 phytoprostanes. R_1 = Me, and R_2 = $(CH_2)_6COOH$.

PhytoPs through oral consumption of plant products or even though inhalation of pollen, which is rich in both ALA and PhytoPs.[7] This aspect cannot be underestimated, since PhytoPs have already been demonstrated to be bioactive lipids not only in plants, but also in animal systems. Biological activities of some PhytoPs in humans include immunomodulatory activity on dendritic cells and anti-inflammatory and apoptotic properties. Recently, B_1- and L_1-PhytoPs have been found to protect immature human neurons against oxidant injury and to promote oligodendrocyte progenitor differentiation through peroxisome proliferator-activated receptor γ (PPAR-γ) activation.[7]

A few syntheses of B_1 and L_1 phytoprostanes have already been published:[8] however, the construction of compounds such as **4** and **7** having a 1-alken-3-ol unit near the carbonyl group was not addressed in previous approaches.[8]

The interesting biological properties in plants and animals and structural features of phytoprostanes prompted us to develop a novel efficient approach to phytoprostanes of the B_1 and L_1 classes, including one (**7**) with a 1-alken-3-ol unit near the carbonyl group. More ambitiously, our plan was to find a general synthetic route, which, in principle, could be extended to other congener prostanoids having two different substituents attached to carbons 2 and 3 of a cyclopent-2-enol or cyclopentenone ring.[1a]

Moreover, we planned to deliver the final products in the form of free carboxylic acids instead of the corresponding methyl or ethyl esters obtained in the previous syntheses.[8] In fact, phytoprostanes are mainly present as free acids in cell cytoplasm after release from membrane lipids. Our novel strategy is exemplified by the syntheses of phytoprostanes (*RS*)-9-L_1-PhytoP (B_1 phytoprostane type II)[3d] (**5**), (*R*)-9-L_1-PhytoP (**5a**), and (*RS*)-16-B_1-PhytoP (B_1 phytoprostane type I)[3d] (**6**) and by the first synthesis of (*RS*)-16-L_1-PhytoP (**7**).

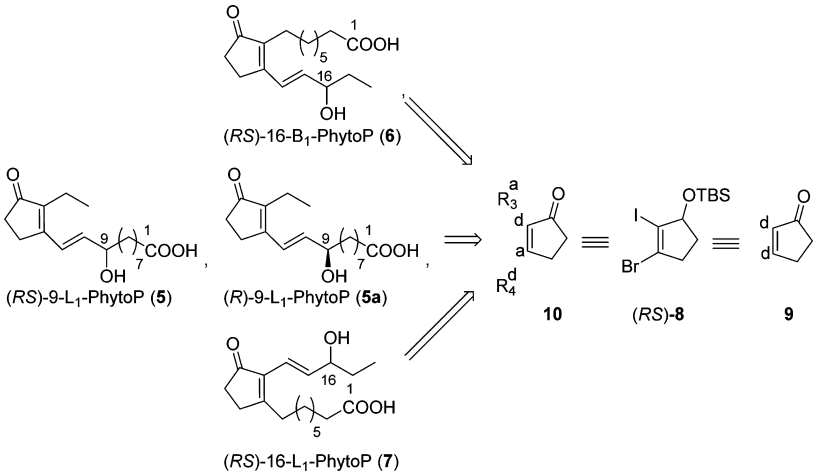
RESULTS AND DISCUSSION

We envisioned completing the syntheses of the four phytoprostanes **5**–**7** and **5a** in a divergent fashion from *O*-TBS-protected 2-iodo-3-bromocyclopentenol (*RS*)-**8** as the common starting material. In a previous study, this compound, which is readily available in four steps from cyclopentane-1,3-dione on a gram scale,[9a] was demonstrated to be synthetically equivalent to the cyclopentene bisdonor synthon **9**. By exploiting this reactivity, different 2,3-disubstituted cyclopentenol and cyclopentenone derivatives were synthesized through two consecutive regioselective reactions with electrophiles.[9a] In this study, further extending its synthetic versatility, we show that compound **8** is also synthetically equivalent to the cyclopent-2-enone synthon **10**, having opposed donor and acceptor properties at carbons α and β, respectively (Scheme 1),

According to our retrosynthetic strategy (Scheme 1), we envisioned that chemoselective monolithiation at C-2 of compound **8**,[9a] followed by addition of an electrophilic species

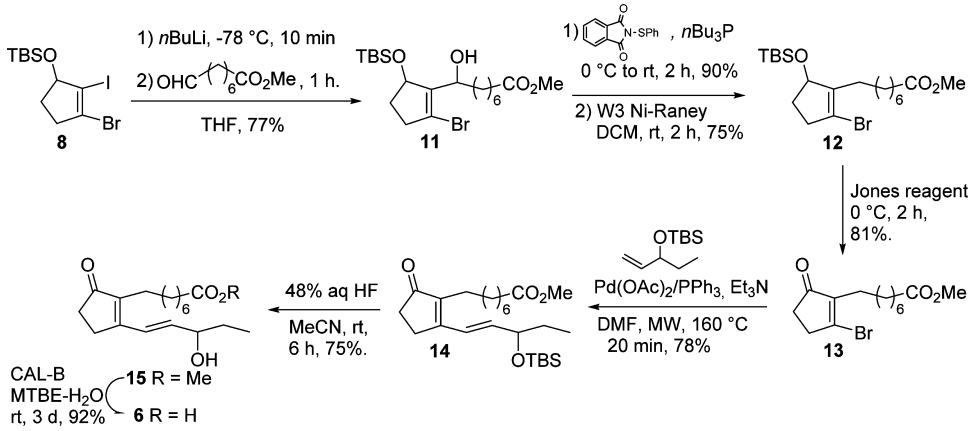
DOI: 10.1021/jo502538b
J. Org. Chem. 2015, 80, 1601−1609

Scheme 1. Retrosynthesis of Phytoprostanes (*RS*)-9-L$_1$-PhytoP (5), (*R*)-9-L$_1$-PhytoP (5a), (*RS*)-16-B$_1$-PhytoP (6), and 16-L$_1$-PhytoP (7)[a]



[a]The letters a and d denote synthon acceptor and donor characteristics.

Scheme 2. Synthesis of Phytoprostane (*RS*)-16-B$_1$-PhytoP (6)



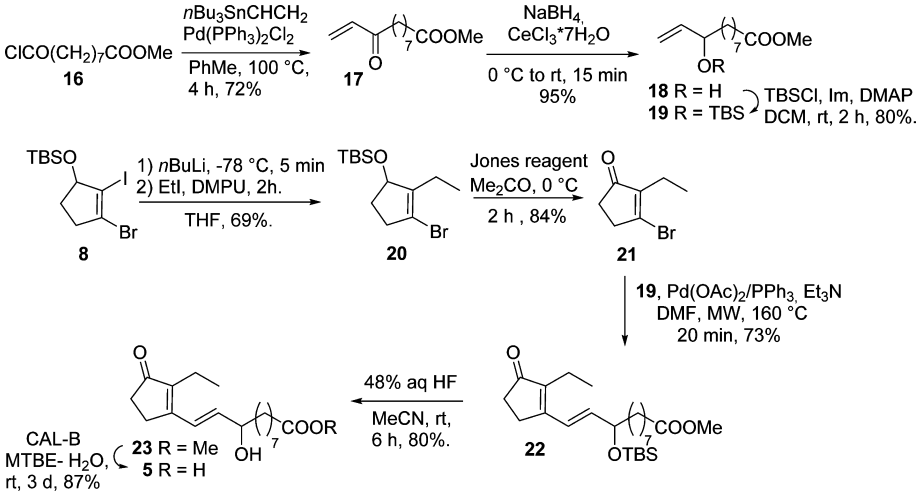
R_3, would allow the construction of the α-substituent of target phytoprostanes; subsequently, Pd-mediated coupling of the olefinic bromine with an organometallic species R_4 would allow the introduction of the ω-chain.

The synthesis of (*RS*)-16-B$_1$-PhytoP (**6**) commenced with the regioselective I/Li exchange in (*RS*)-**8**,[9a] followed by addition of methyl 7-formylheptanoate[10] to the resulting lithium salt to give allylic alcohol **11** in 77% yield (Scheme 2). Deoxygenation of the carbinol function was achieved by conversion of **11** to the corresponding sulfide under Mitsunobu conditions, followed by Raney Ni desulfurization to afford **12** in 68% overall yield. Exposure of silyl ether **12** to the Jones reagent[11] readily produced unveiling of the free allylic alcohol, followed by oxidation to cyclopentenone **13** in 81% yield. The lower side chain of phytoprostane **6** was then introduced in 78% yield by a microwave-assisted Heck reaction of the vinyl bromide **13** with *O*-TBS-protected (*RS*)-pent-1-en-3-ol,[12] by using a 2.4:1 mixture of PPh_3 and $Pd(OAc)_2$ as the catalyst in the presence of Et_3N (Scheme 2). Adduct **14**[8d,f] was delivered in 78% yield and with ≥95% *E*-diastereoselectivity (NMR). After cleavage of the TBS group under standard conditions, the resulting known methyl ester **15**[8a−d,f] was then cleaved by using the "buffer-free" enzymatic protocol developed by us, which is based on the hydrolase activity of lipase B from *Candida antartica* (CAL-B).[13] The free carboxylic acid **6** was thus smoothly produced in 69% overall yield from **14**.

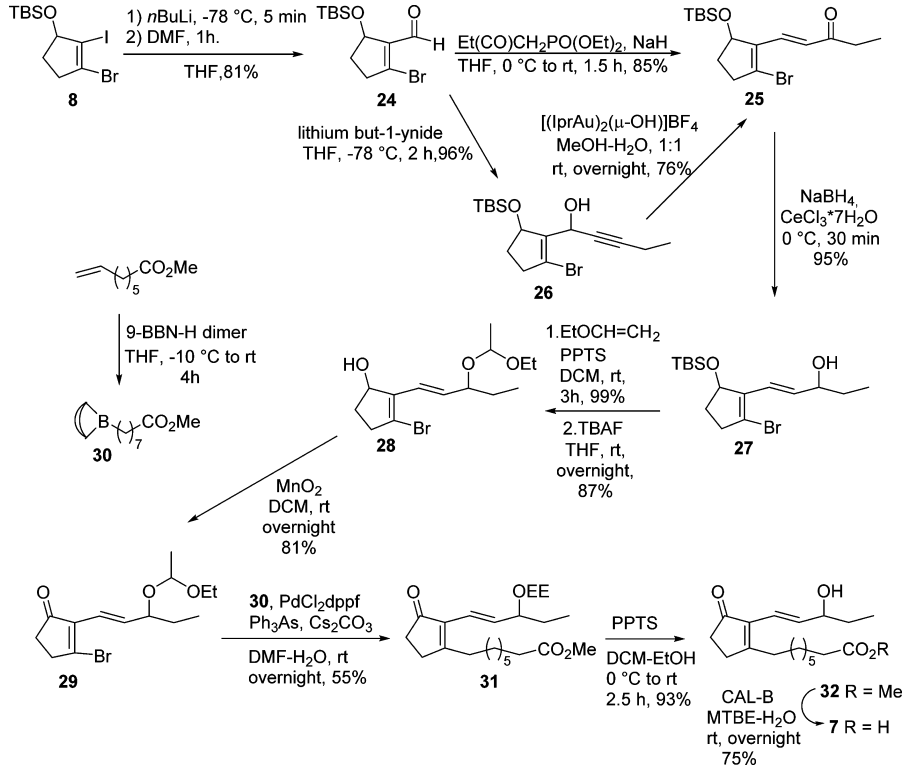
The synthesis of (*RS*)-9-L$_1$-PhytoP (**5**) was accomplished by using the same key reactions leading to phytoprostane **6**. The lower alkyl chain (*RS*)-**19**[8e] was readily prepared from commercially available methyl 9-chloro-9-oxononanoate (**16**). In the event, Stille cross-coupling of **16** with vinyltributylstannane afforded the known enone **17**,[14] which by $NaBH_4$ reduction of the carbonyl group, followed by protection of the resulting allylic alcohol **18**[8e] as an *O*-TBS ether under standard conditions, afforded (*RS*)-**19**.[8e] On the other hand, ethyl group addition to the lithium salt chemoselectively generated from (*RS*)-**8**[9a] readily delivered **20**, which was directly oxidized to enone **21** by the Jones reagent[11] (Scheme 3). Under optimized conditions, microwave-assisted Heck reaction of compounds **19** and **21** produced adduct **22**[8e] in 73% yield and with ≥95% *E*-diastereoselectivity (NMR). Deprotection of the allylic alcohol, followed by lipase-mediated hydrolysis[13] of the resulting methyl ester **23**,[8a,b,d−f] afforded **5**, as a free carboxylic acid, uneventfully.[15] Stille- and Suzuki-like reactions of bromide **21** with, respectively, 1-alkenyltributylstannane or catechol 1-alkenylboronate ester, corresponding to olefin **19**, gave the coupling product **22** in yields comparable to that of the Heck reaction of **21** with alkene **19**.

DOI: 10.1021/jo502538b
J. Org. Chem. 2015, 80, 1601−1609

Scheme 3. Synthesis of Phytoprostane (*RS*)-9-L$_1$-PhytoP (5)



Scheme 4. Synthesis of Phytoprostane (*RS*)-16-L$_1$-PhytoP (7)



The first synthesis of (*RS*)-16-L$_1$-PhytoP (7) differs significantly from those of **5** and **6** in the strategy used to construct the unsaturated chain on the cyclopentene core and to attach the sp^3 alkyl substituent. In fact, the upper unsaturated substituent was built stepwise instead of introducing the entire preformed alkenyl chain by a Pd-catalyzed coupling. On the other hand, introduction of the lower alkyl chain took place through a Suzuki coupling of a vinyl bromide with a functionalized organoborane instead of the electrophilic addition of an alkyl group to a lithium salt (Scheme 4). However, the order by which the two side chains were appended to the cyclopentenone core remained the same as in the syntheses of phytoprostanes **5** and **6**. At first, the upper 3-hydroxypent-1-enyl appendage was introduced by formylation of the 2-lithium derivative of (*RS*)-**8**[9a] with dimethylformamide to give aldehyde **24**, which was submitted to the Wadsworth–Horner–Emmons reaction with commercial diethyl (2-oxobutyl)phosphonate to yield (*E*)-enone **25** in excellent yield and with ≥95% *E*-diastereoselectivity (NMR). We then explored an alternative route to avoid the organophosphorus reagent. In fact, a few years ago, we found that the NHC–Au(I)-catalyzed (NHC = *N*-heterocyclic carbene) Meyer–Schuster rearrangement of a propargylic ester or alcohol to the corresponding enone[16] constitutes an attractive and efficient entry to the allylic alcohol moiety characteristic of the lower side chain of prostaglandins,[16d] which are structurally related to compound **7**.

According to this methodology, propargylic alcohol **26**, the immediate precursor of enone **25**, was readily prepared by addition of lithium but-1-ynide to aldehyde **24**. This two-step

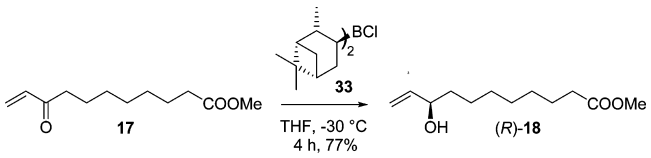
DOI: 10.1021/jo502538b
J. Org. Chem. 2015, 80, 1601−1609

sequence from compound **8** was more practical than the direct addition of pent-2-ynal to the 2-lithium derivative of iodide **8**, owing to difficulties in preparing and handling this very volatile aldehyde.

Subsequently, upon exposure to Nolan's Au(I) dinuclear catalyst $[(IPrAu)_2(\mu\text{-}OH)]BF_4$ in MeOH−H_2O, 1:1,[17] the propargylic alcohol **26** smoothly rearranged to enone **25** in 76% isolated yield and with ≥95% *E*-diastereoselectivity (NMR). Due to the Lewis acidity of the Au(I) species, a small amount of the corresponding deprotected cyclopentenol derivative was also obtained, which was reprotected in the standard manner to raise the total yield of **25** to 82%. Subsequently, the enone **25** was converted through four standard reactions, in 66% overall yield, to vinyl bromide **29**, ready for the successive Suzuki−Miyaura reaction. Hydroboration of known methyl oct-7-enoate[18] with 9-BBN−H dimer (1.1 equiv),[19] smoothly afforded the sp^3 partner of the coupling, namely, organoborane **30**. Crude **30** was then brought to react with bromide **29** under Johnson conditions,[19] to deliver adduct **31** in a satisfactory 55% yield. The synthesis of (*RS*)-16-L_1-PhytoP (**7**) was then completed uneventfully from **31** by deprotection of the allylic alcohol upon exposure to EtOH and cat PPTS, followed by hydrolysis of the resulting carboxylic acid methyl ester **32** by using our reliable biocatalytic method.[13]

Although the syntheses described above afforded phytoprostanes **5**−**7** as racemic mixtures, namely, in the form they are formed in nature by a nonstereoselective free-radical-catalyzed peroxidation process (Figure 1), our strategy is also readily suitable to the synthesis of enantioenriched compounds. Thus, the routes depicted in Schemes 2 and 3 would afford phytoprostanes **6** and **5** in an enantioselective manner by simply switching from racemic to known enantioenriched pent-1-en-3-ol[20] and methyl 9-hydroxyundec-10-enoate (**19**),[8e] respectively, in the key Heck couplings with compounds **13** and **21**, respectively. Moreover, the allylic alcohol moiety present in **5**−**7** could, in principle, be obtained with the desired absolute configuration by Brown's DIP-Cl-mediated asymmetric reduction of the corresponding enone precursor.[16d,21] As an indicative example, enone **17**[14] was converted in 77% yield to (*R*)-**18**,[8e] er = 98:2, by using 3.4 equiv of (+)-DIP-Cl (diisopinocampheylchloroborane) (**33**) in THF at −30 °C.[16d,21] (Scheme 5). The alcohol (*R*)-**18** was then submitted

Scheme 5. DIP-Cl Enantioselective Reduction of Enone 17



to the same reaction sequence leading to (*RS*)-**5** from (*RS*)-**18** (Scheme 3). In the event, the phytoprostane (*R*)-9-L_1-PhytoP (**5a**) was obtained with the same efficiency as the racemic compound.

In our opinion, the synthetic pathways described in this paper are flexible enough to allow the preparation of other analogues of **5**−**7**, including **4**-type compounds (Figure 1). In fact, building blocks containing the corresponding R_1 and R_2 groups are commercially available or can readily be synthesized by routes similar to those described for the synthetic precursors of phytoprostanes **5**−**7**. Then the two side chains would be attached to the cyclopentene core **8**[9a] by exploiting its synthetic equivalence with either synthon **9** or synthon **10**. Indeed, given its modular reactivity, we consider compound **8** as an ideal starting material for the synthesis of a large array of disubstituted cyclopentenol and cyclopentenone derivatives.

With phytoprostanes **5**−**7** in hand, we are planning to execute different biological tests in vitro as well as in vivo. In addition, since 16-L_1-PhytoP (**7**) has not yet been identified in nature, the use of a synthetic reference sample should facilitate the search for evidence confirming or excluding its formation from oxidation of α-linolenic acid (**1**). Details on our findings will be reported in due course.

EXPERIMENTAL SECTION

Methyl (*RS*)-8-((*RS*)-2-Bromo-5-((*tert*-butyldimethylsilyl)oxy)cyclopent-1-en-1-yl)-8-hydroxyoctanoate (11). *n*-BuLi (1.6 M in hexane, 250 μL, 0.41 mmol, 1.1 equiv) was added to a solution of compd (*RS*)-**8**[9a] (0.150 g, 0.37 mmol, 1 equiv) in dry THF (3.7 mL) at −78 °C, and the resulting solution was stirred for 12 min. Methyl 7-formylheptanoate[10] (76 mg, 0.44 mmol, 1.2 equiv) was then added, and the reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched by addition of Et_2O and satd aq NH_4Cl. The aq layer was extracted with Et_2O, and the organic layer was washed with brine, dried on $MgSO_4$, filtered, and concd. The residue was separated by chromatography on silica gel. Elution with hexane−EtOAc, 95:5, yielded **11** (127.6 mg, 77%), a mixture of diastereomers, as a colorless oil. A sample enriched in the more abundant diastereomer was used for NMR analysis. TLC: R_f = 0.23 (hexane−EtOAc, 95:5). IR (cm^{-1}): ν 3510 (OH), 1741 (ester C═O), 1654 (C═C). ^1H NMR (more abundant diastereomer) (300 MHz, $CDCl_3$): δ 0.14 (s, 3H), 0.17 (s, 3H), 0.93 (s, 3 × 3H), 1.19−1.74 (m's, 11H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.25−2.40 (m,1H), 2.50−2.62 (m, 1H), 2.65−2.80 (m,1H), 3.40 (d, *J* = 7.8 Hz, OH, 1H), 3.68 (s, 3H), 4.52 (distorted q, *J* = 6.6 Hz, 1H), 5.0 (br t, *J* = 7.3 Hz, 1H). ^{13}C NMR (more abundant diastereomer) (75 MHz, $CDCl_3$): δ −5.0 (Me), −3.9 (Me), 17.7 (C), 24.8 (CH_2), 25.3 (CH_2), 25.7 (3 × Me), 29.1 (CH_2), 29.2 (CH_2), 33.9 (CH_2), 34.1 (CH_2), 35.6 (CH_2), 37.7 (CH_2), 51.4 (Me), 70.4 (CH), 77.5 (CH), 122.8 (C), 141.7 (C), 174.2 (C). ESI-MS (ion trap, positive ion): *m*/*z* 471.2 $[M + Na]^+$ (^{79}Br) and 473.2 $[M + Na]^+$ (^{81}Br). Anal. Calcd for $C_{20}H_{37}BrO_4Si$: C, 53.44; H, 8.30. Found: C, 53.55; H, 8.42.

Methyl (*RS*)-8-(2-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-cyclopent-1-en-1-yl)octanoate (12). To a stirred solution of compd **11** (103.5 mg, 0.23 mmol, 1 equiv) in dry THF (1 mL) under an argon atmosphere was added solid thiophene-yl phthalimide (176.3 mg, 0.69 mmol, 3 equiv), the mixture was cooled to 0 °C in an ice bath, and then nBu_3P (170 μL, 0.23 mmol, 3 equiv) was added dropwise. The ice bath was removed, and the solution was stirred at rt for 2 h. Satd aq $NaHCO_3$ (3 mL) and DCM were then added to the reaction mixture, and the aq layer was extracted with DCM (3 × 10 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. Elution with hexane−EtOAc, 9:1, gave the expected sulfide as a pale yellow oil (112 mg, 90%). TLC: R_f = 0.28 (hexane−EtOAc, 9:1). ^1H NMR (mixture of diastereomers) (300 MHz, $CDCl_3$): δ 0.1 (s, 3H), 0.19 (s, 3H), 0.91 (s, 3 × 3H), 1.21−1.84 (m's, 10H), 1.91−2.14 (m's, 2H), 2.28−2.42 (m, 1H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.66−2.77 (m, 1H), 3.66 (s, 3H), 4.33 (t, *J* = 7.0 Hz, 1H), 4.97 (br t, 1H), 7.12−7.33 (m, 5H). Excess Raney nickel (25 mL of an aq suspension) was decanted and the solid washed with EtOH (3 × 1.5 mL). CH_2Cl_2 (3 mL) and EtOH (200 μL) were then added. Under Ar, a solution of freshly prepared sulfide (200 mg, 0.37 mmol) in CH_2Cl_2 (1 mL) was added, and the mixture was stirred at rt for 1 h, monitoring the reaction by TLC (hexane−EtOAc, 6:4). The mixture was diluted with CH_2Cl_2 and filtered. Solvent was evaporated, and the residue was separated by column chromatography on silica gel. Elution with hexane−EtOAc, 1:1, yielded ester **12** (119.5 mg, 75%), as a colorless oil. TLC: R_f = 0.29 (hexane−EtOAc, 1:1). IR (cm^{-1}): ν 1743 (ester C═O), 1697

DOI: 10.1021/jo502538b
J. Org. Chem. 2015, 80, 1601−1609

(C═C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 3 × 3H), 1.28−1.50 (m, 8H), 1.50−1.88 (m, 3H), 2.07−2.25 (m, 2H), 2.25−2.40 (m, 1H), 2.32 (t, J = 7.5 Hz, 2H), 2.45−2.60 (m, 1H), 2.63−2.77 (m, 1H), 3.66 (s, 3H), 4.68−4.75 (br t, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9 (Me), −4.4 (Me), 18.1 (C), 24.9 (CH_2), 25.8 (3 × Me), 27.0 (CH_2), 27.1 (CH_2), 29.1 (2× CH_2), 29.4 (CH_2), 33.5 (CH_2), 34.1 (CH_2), 37.4 (CH_2), 51.4 (Me), 79.1 (CH), 120.1 (C), 143.4 (C), 174.3 (C). ESI-MS (ion trap, positive ion): m/z 455.17 $[M + Na]^+$ (^{79}Br) and 457.2 $[M + Na]^+$ (^{81}Br). Anal. Calcd for $C_{20}H_{37}BrO_3Si$: C, 55.41; H, 8.60. Found: C, 55.53; H, 8.69.

Methyl 8-(2-Bromo-5-oxocyclopent-1-en-1-yl)octanoate (13). The Jones reagent[11] was prepared by carefully adding 0.5 mL of concd H_2SO_4 to 2.5 mL of a 2 M (200 g/L) solution of CrO_3 (MW = 100) in H_2O cooled at 0 °C. A fraction of the resulting red solution was dropped over a stirred solution of compd **12** (57 mg, 0.133 mmol, 1 equiv) in Me_2CO (1 mL) at 0 °C. After 2 h the reaction TLC analysis showed that **12** was consumed; the oxidant was then quenched by the addition of *i*PrOH (0.5 mL). The mixture was diluted with water and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine, dried on $MgSO_4$, filtered, and concd. The residue was separated by chromatography on silica gel. Elution with hexane−EtOAc, 6:1, afforded enone **13** (34 mg, 81%) as a colorless oil. TLC: R_f = 0.27 (hexane−EtOAc, 6:1). IR (cm^{-1}): ν 1738 (ester C═O), 1708 (ketone C═O), 1629 (C═C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25−1.40 (m, 6H), 1.40−1.50 (m, 2H), 1.57−1.7 (m, 2H), 2.21−2.37 (two overlapped triplets, J = 7.5 Hz, 4H), 2.45−2.55 (m, 2H), 2.90−3.0 (m, 2H), 3.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7 (CH_2), 24.9 (CH_2), 27.0 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 34.1 (CH_2), 35.1 (CH_2), 35.9 (CH_2), 51.4 (Me), 145.2 (C), 155.9 (C), 174.3 (C), 203.8 (C). ESI-MS (ion trap, positive ion): m/z 339.08 $[M + Na]^+$ (^{79}Br) and 341.1 $[M + Na]^+$ (^{81}Br). Anal. Calcd for $C_{14}H_{21}BrO_3$: C, 53.01; H, 6.67. Found: C, 53.13; H, 6.74.

Methyl (*RS*,*E*)-8-(2-(3-((*tert*-Butyldimethylsilyl)oxy)pent-1-en-1-yl)-5-oxocyclopent-1-en-1-yl)octanoate (14). After standard cycles of evacuation and backfilling with dry and pure argon, an oven-dried microwave vial equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 0.07 equiv), PPh_3 (3.3 mg, 0.012 mmol, 0.17 equiv), bromide **13** (22.8 mg, 0.072 mmol, 1 equiv), and *O*-TBS-protected pent-1-en-3-ol[12] (27.3 mg, 0,136 mmol, 1.9 equiv) followed by Et_3N (30 μL, 0.129 mmol, 1.8 equiv). The vial was evacuated under vacuum and backfilled with argon (this procedure was repeated three times). The vial was sealed, and the mixture was allowed to stir under argon at 160 °C (internal probe) for 22 min in a microwave oven. The mixture was diluted with Et_2O−H_2O and poured through a short pad of Celite into a separator funnel. The aq layer was extracted with Et_2O−hexane, 1:1 (3 × 10 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 chromatography on silica gel. Elution with hexane−EtOAc, 95:5, gave product **14** as a pale yellow oil (24 mg, 78%). TLC: R_f = 0.18 (hexane−EtOAc, 95:5). The spectroscopic data were in nice agreement with the literature.[8d,f]

Methyl (*RS*,*E*)-8-(2-(3-Hydroxypent-1-en-1-yl)-5-oxocyclopent-1-en-1-yl)octanoate (15). Excess 48% aq HF (73 μL, 2.015 mmol, 40 equiv) was added to compd **14** (22 mg, 0.0504 mmol) dissolved in MeCN (2.3 mL). After 4 h of stirring at rt, a pH 6.8 phosphate buffer (2 mL) and EtOAc (6 mL) were added, and the two layers were separated. The aq phase was extracted with EtOAc (4 × 3 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concd in vacuo. The residue was purified by flash column chromatography on silica gel. Elution with hexane−EtOAc, 4:1, gave free alcohol **15** (12 mg, 75%) as a pale yellow oil. TLC: R_f = 0.41 (hexane−EtOAc, 4:1). The spectroscopic data were in complete agreement with the literature.[8a−d,f]

(*RS*,*E*)-8-(2-(3-Hydroxypent-1-en-1-yl)-5-oxocyclopent-1-en-1-yl)octanoic Acid [(*RS*)-16-B$_1$-PhytoP, 6]. Methyl ester **15** (186.8 mg, 0.58 mmol) was dissolved in HPLC-grade MTBE (40 mL), and HPLC-grade H_2O (0.53 mL, 29 mmol) was added. To the resulting stirred solution was added CAL-B,[13] (40 mg), and the suspension was gently stirred at 35 °C for 18 h. The enzyme was filtered off over a sintered glass funnel, and the solid was carefully washed with MeCN−MTBE (1:1, 4 × 15 mL). The filtrates were collected and evaporated under vacuum (*caution: without heating*). The residue was purified by silica gel column chromatography on silica gel. Elution with hexane−EtOAc, 3:2, afforded acid **6** (164 mg, 92%) as a colorless oil. TLC: R_f = 0.2 (hexane−EtOAc, 3:2). The spectroscopic data were in nice agreement with the literature.[13]

Methyl (*RS*)-9-Hydroxyundec-10-enoate [(*RS*)-18]. Enone **17**[14] (50 mg, 0.24 mmol, 1 equiv) and $CeCl_3{\cdot}7H_2O$ (9 mg, 0.024 mmol, 0.1 equiv) were dissolved in MeOH, and the obtained solution was cooled to 0 °C. After 10 min, $NaBH_4$ (7.2 mg, 0.19 mmol, 0.8 equiv) was added to the solution in three portions. After 15 min of stirring at rt, the reduction was completed (TLC). Excess solid $NaHCO_3$ was then added, and the resulting mixture was filtered and dried under vacuum. The residue was then dissolved in H_2O (20 mL) and extracted with Et_2O (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concd under vacuum. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane−DCM, 9:1, afforded alcohol (*RS*)-**18** (48.5 mg, 95%) as a colorless oil. NMR data were identical with those of the (*R*)-enantiomer.[8e]

Methyl (*R*)-9-Hydroxyundec-10-enoate [(−)-(*R*)-18] and Methyl (*R*)-9-((*tert*-Butyldimethylsilyl)oxy)undec-10-enoate [(−)-(*R*)-19]. (+)-DIP-Cl (1.8 M in THF, 0.912 mL, 1.64 mmol, 3.4 equiv) was slowly added dropwise to a stirred solution of ketone **17**[14] (100 mg, 0.48 mmol, 1 equiv) in dry THF (3.2 mL) at −30 °C.[21] Stirring was continued for 4 h, then the reaction was quenched by the addition of MeOH (0.62 mL), and the mixture was warmed to rt. Volatiles were evaporated under vacuum, the residue was dissolved in DCM (20 mL), and the resulting solution was washed with H_2O (20 mL), followed by satd aq NH_4Cl (20 mL). After drying over Na_2SO_4, the organic phase was evaporated, and the residue was chromatographed over silica gel. Elution with a gradient of DCM in hexane (from 100% hexane to hexane−DCM, 9:1) afforded known (*R*)-**18**[8e] (80 mg, 77%) as a colorless oil. TLC: R_f = 0.28 (hexane−DCM, 9:1). $[\alpha]_D^{20}$ −5.5 (c = 1, $CHCl_3$) [lit.[8e] $[\alpha]_D^{20}$ −5.8 (c = 1.1, $CHCl_3$)]. The er = 98:2 was measured on an HPLC (150 × 2.1 mm × 5 μm) analytical column: eluent heptane−*i*PrOH, 97.5:2.5; t_R[(*R*)-**18**] = 13.4 min; t_R[(*S*)-**18**] = 14.2 min.

Silylation of alcohol (−)-(*R*)-**18** to compd (−)-(*R*)-**19** [colorless oil; TLC R_f = 0.31 (hexane−EtOAc, 9:1); $[\alpha]_D^{20}$ −5.9 (c = 1.5, $CHCl_3$) [lit.[8e] $[\alpha]_D^{20}$ −6.15 (c = 2.77, $CHCl_3$)]] was executed in 82% yield according to the same procedure described in the literature.[8e,22] The spectroscopic data of compounds **18** and **19** were in nice agreement with the literature.[8e]

(*RS*)-((3-Bromo-2-ethylcyclopent-2-en-1-yl)oxy)*tert*-butyldimethylsilane (20). *n*BuLi (1.6 M in hexane, 341 μL, 0.546 mmol, 1.1 equiv) was added to a solution of compd (*RS*)-**8**[9a] (207 mg, 0.496 mmol, 1 equiv) in dry THF (4.5 mL) at −78 °C, and the resulting pale yellow solution was stirred for 12 min. EtI (200 μL, 3.44 mmol, 6.9 equiv) was added followed by freshly distilled DMPU (300 μL, 0.37 mmol), and the reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched by dilution with Et_2O and satd aq NH_4Cl. The aq layer was extracted with Et_2O (3 × 30 mL), and the combined organic layers were washed with brine, dried on $MgSO_4$, filtered, and concd. The residue was separated by chromatography on silica gel. Elution with hexane yielded compd **20** (108.0 mg, 69%) as a colorless oil. TLC: R_f = 0.21 (hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.10 (s, 3H), 0.11 (s, 3H), 0.91 (s, 3 × 3H), 0.98 (t, J = 7.5 Hz, 3H), 1.62−1.80 (m, 1H), 2.05−2.35 (m, 2H), 2.45−2.55 (m, 1H), 2.60−2.75 (m, 1H), 4.73 (br t, J = 5.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9 (Me), −4.4 (Me), 11.6 (Me), 18.0 (C), 20.4 (CH_2), 25.8 (3 × Me), 33.4 (CH_2), 37.4 (CH_2), 76.5 (CH, 1H), 119.5 (C), 144.6 (C). ESI-MS (ion trap, positive ion): m/z 485.2 $[M + Na]^+$ (^{79}Br) and 487.2 $[M + Na]^+$ (^{81}Br). Anal. Calcd for $C_{13}H_{25}BrOSi$: C, 51.14; H, 8.25. Found: C, 51.26; H, 8.33.

3-Bromo-2-ethylcyclopent-2-en-1-one (21). Silyl ether (*RS*)-**20** (103.8 mg, 0.337 mmol, 1 equiv) was directly oxidized to ketone **21** by the Jones reagent,[11] according to the same procedure described above for the oxidation of compd **12** to **13**. After the usual workup and

DOI: 10.1021/jo502538b
J. Org. Chem. 2015, 80, 1601−1609

evaporation of volatiles, the residue was separated by chromatography on silica gel to yield the desired cyclopentenone **21** (52 mg, 84%) as a pale yellow oil. TLC: R_f = 0.29 (hexane−EtOAc, 9:1). IR (cm^{-1}): ν 1710 (ketone C═O), 1635 (C═C). ^1H NMR (300 MHz, $CDCl_3$): δ 1.05 (t, J = 7.5 Hz, 3H), 2.31 (q, J = 7.5 Hz, 2H), 2.50−2.58 (m, 2H), 2.87−2.95 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6 (Me), 18.1 (CH_2), 35.1 (CH_2), 36.0 (CH_2), 146.4 (C), 155.4 (C), 203.7 (C). ESI-MS (ion trap, positive ion): m/z 211 $[M + Na]^+$ (^{79}Br) and 213 $[M + Na]^+$ (^{81}Br). Anal. Calcd for C_7H_9BrO: C, 44.47; H, 4.80. Found: C, 44.50; H, 4.90.

Methyl (*R*,*E*)-9-((*tert*-Butyldimethylsilyl)oxy)-11-(2-ethyl-3-oxocyclopent-1-en-1-yl)undec-10-enoate [(+)-(*R*,*E*)-22]. After standard cycles of evacuation and backfilling with dry and pure argon, an oven-dried microwave vial equipped with a magnetic stirring bar was charged with $Pd(OAc)_2$ (2.9 mg, 0.013 mmol, 0.05 equiv), PPh_3 (6.8 mg, 0.03 mmol, 0.1 equiv), bromide **21** (49.4 mg, 0.264 mmol, 1 equiv), and (−)-(*R*)-**19** (150.6 mg, 0,459 mmol, 1.7 equiv), followed by Et_3N (67 μL, 0.481 mmol, 1.8 equiv). The vial was evacuated and backfilled with argon (this procedure was repeated three times), then it was sealed, and the mixture was allowed to stir under argon at 160 °C (probe temperature) for 22 min in a microwave oven. The mixture was diluted with Et_2O−H_2O and filtered on a short pad of Celite into a separator funnel. The aq layer was extracted with Et_2O−hexane, 1:1 (3 × 10 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. Elution with hexane−EtOAc, 95:5, gave product (*R*,*E*)-**22** as a pale yellow oil (84 mg, 73%). TLC: R_f = 0.22 (hexane−EtOAc, 95:5). $[\alpha]_D^{20}$ +2.0 (c = 0.8, $CHCl_3$) [lit.[8e] $[\alpha]_D^{20}$ +2.2 (c = 1.73, CH_2Cl_2)]. The spectroscopic data were in complete agreement with the literature.[8e]

Methyl (*R*,*E*)-11-(2-Ethyl-3-oxocyclopent-1-en-1-yl)-9-hydroxyundec-10-enoate [(−)-(*R*)-23]. Excess 48% aq HF (0.088 mL) was added to compd **22** (20 mg, 0.050 mmol) dissolved in MeCN (3 mL). After 4 h of stirring at rt, a pH 6.8 phosphate buffer (5 mL) and EtOAc (10 mL) were added, and the two layers were separated. The aq phase was extracted with EtOAc (4 × 5 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concd in vacuo. The residue was purified by flash column chromatography on silica gel. Elution with hexane−EtOAc, 4:1, gave the free alcohol (*R*)-**23** (11 mg, 79%) as a pale yellow oil. TLC: R_f = 0.22 hexane−EtOAc, 4:1. $[\alpha]_D^{20}$ −23.5 (c = 0.5, MeOH) [lit.[8e] $[\alpha]_D^{20}$ −24.1 (c = 2.07, MeOH)]. The spectroscopic data were in nice agreement with the literature.[8a,b,d−f]

(*R*,*E*)-11-(2-Ethyl-3-oxocyclopent-1-en-1-yl)-9-hydroxyundec-10-enoic Acid [(*R*)-9-L$_1$-PhytoP, (−)-(*R*)-5a]. Methyl ester (*R*)-**23** (61.4 mg, 0.191 mmol) was dissolved in HPLC-grade MTBE (40 mL), and HPLC-grade H_2O (0.175 mL, 9.6 mmol) was added. To the resulting stirred solution was added CAL-B (14 mg),[13] and the suspension was gently stirred at 35 °C for 18 h. The enzyme was filtered off over a sintered glass funnel, and the solid was carefully washed with MeCN−MTBE (1:1, 4 × 5 mL). The filtrates were collected and evaporated under vacuum (*caution: without heating*). Silica gel column chromatography of the residue afforded, by elution with hexane−EtOAc, 1:1, **5a** (52 mg, 88%) as an amorphous colorless solid. TLC: R_f = 0.26 (hexane−EtOAc, 1:1). $[\alpha]_D^{20}$ −18.5 (c = 1.0, EtOAc) [lit.[13] $[\alpha]_D^{20}$ +16.7 (c = 0.054, EtOAc) for the enantiomer (*S*)-9-L$_1$-PhytoP acid]. The spectroscopic data were in nice agreement with the literature.[13]

(*RS*)-2-Bromo-5-((*tert*-butyldimethylsilyl)oxy)cyclopent-1-ene-1-carbaldehyde (24). Cyclopentene (*RS*)-**8**[9a] (180 mg, 0.45 mmol, 1 equiv) was dissolved in dry THF (3 mL), and the solution was cooled to −78 °C. *n*-BuLi (2.5 M in hexane, 214 μL, 0.54 mmol, 1.2 equiv) was added, and the reaction mixture was stirred at −78 °C for 15 min. Dry DMF (62 μL, 0.80 mmol, 1.8 equiv) was then added dropwise to the solution. After 1 h the reaction was quenched with satd aq NH_4Cl−MTBE, 1:1. The aq layer was extracted with MTBE (3 × 10 mL), and the collected organic layers were dried over Na_2SO_4, filtered, and concd under vacuum. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane−MTBE, 95:5, gave aldehyde **24** (111 mg, 81%) as a colorless oil. TLC: R_f = 0.22 (hexane−MTBE, 95:5). IR (cm^{-1}): ν 1715 (C═O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 3H), 0.17 (s, 3H), 0,89 (s, 3 × 3H), 1.78−1.89 (m, 1H), 2.17−2.35 (m, 1H), 2.74 (ddd, J = 12.7, 9.1, 3.6 Hz, 1H), 3.12 (ddd, 12.7, 6.2, 2.0 Hz, 1H), 5.05 (dt, J = 7.1, 2,1 Hz, 1H), 9.89 (s,1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.1 (Me), −4.9 (Me), 18.2 (C), 25.8 (3 × Me), 33.4 (CH_2), 40.2 (CH_2), 73.4 (CH), 141.4 (C), 145.3 (C), 188.4 (CH). ESI-MS (ion trap, positive ion): $[M + Na]^+$ m/z 327 (^{79}Br) and m/z 329 (^{81}Br). Anal. Calcd for $C_{12}H_{21}BrO_2Si$: C, 47.21; H, 6.93. Found: C, 47.32; H, 7.02.

(*RS*,*E*)-1-(2-Bromo-5-((*tert*-butyldimethylsilyl)oxy)cyclopent-1-en-1-yl)pent-1-en-3-one (25). *Method a. Wadsworth−Horner−Emmons Reaction of Aldehyde **24**.* To a suspension of NaH (18 mg, 60% dispersion in mineral oil, 0.45 mmol, 1.1 equiv) in anhydrous THF (2 mL) cooled to 0 °C under argon was added commercial diethyl (2-oxobutyl)phosphonate (93.6 mg, 0.45 mmol, 1.1 equiv). After the mixture was stirred for 30 min, aldehyde **24** (125 mg, 0.41 mmol, 1 equiv) was added, and the reaction mixture was allowed to warm to rt and stirred for an additional 1.5 h. The mixture was then diluted with Et_2O (15 mL). The organic layer was washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and evaporated to give an oily residue which was purified by flash column chromatography on silica gel. Elution with hexane−MTBE, 95:5, gave enone (*RS*,*E*)-**25** (133 mg, 85%) as a pale yellow oil. The physical and spectroscopic data of this sample were identical with those of enone **25** obtained by method b.

*Method b. Meyer−Schuster Reaction of Propargylic Alcohol **26**.* Propargylic alcohol **26** (20 mg, 0.066 mmol, 1 equiv) was dissolved in 1 mL of MeOH−H_2O, 1:1. Catalyst $[(IPrAu)_2OH]BF_4$ was added (5.1 mg, MW = 1274.92, 0.004 mmol, 0.06 equiv) to the solution, which was then stirred overnight. Subsequently, the reaction mixture was evaporated under vacuum, and the resulting residue was purified by flash column chromatography on silica gel. Elution with hexane−MTBE, 95:5, gave enone (*RS*,*E*)-**25** (18 mg, 76%) as a pale yellow oil. TLC: R_f = 0.21 (hexane−MTBE, 95:5). IR (cm^{-1}): ν 1690 (C═O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 3H), 0.18 (s,3H), 0.92 (s, 3 × 3H), 1.15 (t, J = 7.3 Hz, 3H), 1.82−1.92 (m, 1H), 2.25−2.38 (m,1H), 2.60 (q, J = 7.3 Hz, 2H) 2.70−2.75 (m, 1H), 2.9−3.02 (m,1H), 4.99−5.03 (m,1H), 6.50 (d, J = 16.2 Hz, 1H), 7.35 (d, J = 16.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.7 (Me), −3.8 (Me), 8.1 (Me), 17.9 (C), 25.7 (3 × Me), 33.5 (CH_2), 33.9 (CH_2), 39.0 (CH_2), 75.4 (CH), 128.7 (CH), 134.0 (CH), 134.4 (C), 139.1 (C), 201.1 (C). ESI-MS (ion trap, positive ion): $[M + Na]^+$ m/z 381.1 (^{79}Br) and 383.1 (^{81}Br). Anal. Calcd for $C_{16}H_{27}BrO_2Si$: C, 53.47; H, 7.57. Found: C, 53.57; H, 7.61.

(*RS*)-1-(2-Bromo-5-((*RS*)-(*tert*-butyldimethylsilyl)oxy)-cyclopent-1-en-1-yl)pent-2-yn-1-ol (26). 1-Butyne gas was condensed in a flask cooled at −30 °C under an Ar atmosphere, and dry THF was added to give a 0.25 M solution. A 4.0 mL volume of this solution (1.0 mmol of 1-butyne) was then transferred to another flask cooled at −78 °C. *n*-BuLi (2.2 M in hexane, 0.5 mL, 1.1 mmol, 1.1 equiv vs 1-butyne) was added, and the solution was stirred at −30 °C for 30 min. Subsequently, the solution was cooled to −78 °C, and aldehyde **24** (332 mg, 0.98 mmol, 1 equiv) in dry THF (1,5 mL) was added. After 2 h of stirring, Et_2O (5 mL) and satd aq NH_4Cl (10 mL) were added; the two layers were separated, and the aq phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. The resulting residue was purified by flash column chromatography on silica gel. Elution with hexane−EtOAc, 95:5, gave compd **26** as a diastereomeric mixture (339 mg, 96%) and a colorless oil. TLC: R_f = 0.28 (hexane−EtOAc, 95:5). IR (cm^{-1}): ν 3350 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 3H), 0.15 (s, 3H), 0.94 (s, 3 × 3H), 1.15 (t, J = 7.5 Hz, 3H), 1.27 (br s, 1H), 1.78−1.90 (m, 1H), 2.24 (br q, J = 7.5 Hz, 2H), 2.25−2.32 (m, 1H), 2.40 (br d, J = 7.5 Hz, 1H, OH), 2.51−2.65 (m, 1H), 2.70−2.85 (m, 1H), 4.98 (br t, 1H), 5.25 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9 (Me), −4.2 (Me), 12.6 (CH_2), 13.6 (Me), 18.0 (C), 25.8 (3 × Me), 33.6 (CH_2), 38.3 (CH_2), 60.0 (CH), 76.3 (CH), 77.9 (C), 87.4 (C), 121.3 (C), 141.3 (C). ESI-MS (ion trap, positive ion):

DOI: 10.1021/jo502538b
J. Org. Chem. 2015, 80, 1601−1609

$[M + Na]^+$ m/z 381.1 (^{79}Br) and 383.1 (^{81}Br). Anal. Calcd for $C_{16}H_{27}BrO_2Si$: C, 53.47; H, 7.57. Found: C, 53.55; H, 7.62.

(*RS*,*E*)-1-((*RS*)-2-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-cyclopent-1-en-1-yl)pent-1-en-3-ol (27). Enone (*RS*)-**25** (60 mg, 0.16 mmol, 1 equiv) and $CeCl_3{\cdot}7H_2O$ (6.2 mg, 0.016 mmol, 0.1 equiv) were dissolved in MeOH, and the obtained solution was cooled to 0 °C. After 10 min, $NaBH_4$ (4.9 mg, 0.13 mmol, 0.8 equiv) was added to the solution in three portions. After 30 min the reduction was completed; excess solid $NaHCO_3$ was added, and the resulting mixture was filtered and dried under vacuum. The residue was then dissolved in H_2O (20 mL) and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and concd under vacuum. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane−EtOAc, 4:1, afforded alcohol **27** (58 mg, 95%), a mixture of diastereomers, as a colorless oil. TLC: R_f = 0.32 (hexane−EtOAc, 4:1). IR (cm^{-1}): ν 3350 (O−H). ^1H NMR (300 MHz, $CDCl_3$): δ 0.11 (s, 3H), 0.14 (s, 3H), 0.88 (s, 3 × 3H), 0.95 (t, J = 7.5, 3H), 1.54−1.68 (m, 2H), 1.70 (br s, 1H, OH), 1.78−1.92 (m,1H), 2.25−2.37 (m, 1H), 2.58 (ddd, J = 16.9, 8.7, 4.7 Hz,1H), 2.78−2.98 (m,1H), 4.12 (distorted quintuplet, J = 7.0 Hz,1H), 5.10−4.90 (m,1H), 6.05 (td, J = 15.0, 6.5, 1H), 6.39 (dd, J = 15.9, 2.2 Hz,1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.6 (Me), −3.9 (Me), 9.7 (Me), 9.8 (Me), 17.9 (C), 25.8 (3 × Me), 29.9 (CH_2), 30.1 (CH_2), 33.5 (CH_2), 38.2 (CH_2), 74.3 (CH), 74.7 (CH), 75.7 (CH), 75.8 (CH), 122.9 (CH), 123.4 (CH), 125.1 (C), 125.3 (C), 135.9 (CH), 136.1 (CH), 139.0 (C), 139.1 (Cs). ESI-MS (ion trap, positive ion): $[M + Na]^+$ m/z 383.1 (^{79}Br) and 385.1 (^{81}Br). Anal. Calcd for $C_{16}H_{29}BrO_2Si$: C, 53.18; H, 8.09. Found: C, 53.27; H, 8.16.

(*RS*)-3-Bromo-2-((*RS*,*E*)-3-(1-ethoxyethoxy)pent-1-en-1-yl)-cyclopent-2-en-1-ol (28). Allylic alcohol **27** (50 mg, 0.14 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (1.4 mL). PPTS (3.5 mg, 0.014 mmol, 0.1 equiv) was added to the solution, followed by freshly distilled ethyl vinyl ether (402 μL, 4.2 mmol, 30 equiv). The reaction went to completion in 3 h and was quenched with satd aq $NaHCO_3$. The aq layer was extracted with DCM (3 × 5 mL), and the collected organic layers were dried over Na_2SO_4, filtered, and concd under vacuum. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane−Et_2O, 9:1, gave the 1-ethoxyethyl ether of alcohol **27** (60 mg, 99%), mixture of diastereomers, as a colorless oil. TLC: R_f = 0.26 (hexane−Et_2O, 9:1). To this compound (60 mg, 0.14 mmol, 1 equiv), dissolved in dry THF (1.4 mL), was added dropwise TBAF (1 M in THF, 277 μL, 0.28 mmol, 2 equiv), and the solution was stirred overnight. The reaction was then quenched with satd aq NH_4Cl, and the aq layer was extracted with EtOAc (3 × 5 mL). The collected organic layers were dried over Na_2SO_4, filtered, and concd under vacuum to give compd **28** (39 mg, 87%), a mixture of diastereomers, as a colorless oil. TLC: R_f = 0.26 (hexane−EtOAc, 4:1). IR (cm^{-1}): ν 3345 (O−H). ^1H NMR (300 MHz, Me_2CO-d_6): δ 0.93 (t, J = 7.4 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H), 1.20−1.25 (m, 3H), 1.45−1.70 (m, 2H), 2.25−2.40 (m, 1H), 2.50−2.65 (m, 1H), 2.80−2.95 (m, 1H), 3.30−3.70 (m, 2H), 3.88−4.10 (m, 1H), 4.62−4.75 (m, 1H), 4.80−4.95 (m, 1H), 6.07 (dd, J = 16.0, 7.6, 1H), 6.35 (d, J = 16.0, 1H). ^{13}C NMR (75 MHz, Me_2CO-d_6): δ 10.5 (Me), 16.2 (Me), 21.3 (Me), 29.7 (CH_2), 30.8 (CH_2), 34.3 (CH_2), 39.2 (CH_2), 60.4 (CH_2), 75.6 (CH), 79.0 (CH), 79.4 (CH), 98.5 (CH), 99.8 (C), 125.3 (CH), 125.4 (CH), 136.3 (CH), 136.4 (CH), 137.2 (C), 141.4 (C). ESI-MS (ion trap, positive ion): $[M + Na]^+$ m/z 341.1 (^{79}Br) and 343.1 (^{81}Br). Anal. Calcd for $C_{14}H_{23}BrO_3$: C, 52.67; H, 7.26. Found: C, 52.77; H, 7.34.

(*RS*,*E*)-3-Bromo-2-(3-(1-ethoxyethoxy)pent-1-en-1-yl)-cyclopent-2-en-1-one (29). MnO_2 (339.1 mg, 3.9 mmol, 30 equiv) was added to compd **28** (37 mg, 0.12 mmol, 1 equiv) dissolved in dry DCM (1.3 mL), and the reaction mixture was then stirred at rt overnight. Subsequently, the suspension was filtered under vacuum on a Celite pad, and the resulting solution was evaporated under vacuum. The residue was purified by flash chromatography on silica gel. Elution with hexane−EtOAc, 4:1, afforded enone (*RS*)-**29** (31 mg, 81%), a mixture of diastereomers, as a colorless oil. TLC: R_f = 0.38 (hexane−EtOAc, 4:1). IR (cm^{-1}): ν 1690 (C═O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.85−1.0 (two overlapped triplets, J = 7.4 Hz, totally 3H), 1,17 and 1.21 (two triplets, J = 7.1 Hz, totally 3H), 1.33 (d, J = 6.3 Hz, 3H), 1.52−1.75 (m, 2H), 2.51−2.65 (m, 2H), 2.95−3.05 (m, 2H), 3.40−3.75 (m, 2H), 4.07 and 4.13 (two quartets, J = 6.8 Hz, totally 1H),4.65−4.77 (two overlapped quartets, J = 6.0 Hz, 1H), 6.26 and 6.30 (two doublets, J = 16.0, Hz, totally 1H), 6.91 and 7.01 (dd, J = 16.0, 7.4 Hz, totally 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.5 (Me), 9.9 (Me), 15.2 (Me), 15.4 (Me), 20.4 (Me), 20.5 (Me), 28.4 (CH_2), 28.7 (CH_2), 35.2 (CH_2), 36.5 (CH_2), 59.4 (CH_2), 61.0 (CH_2), 78.1 (CH), 78.4 (CH), 97.5 (CH), 98.9 (CH), 119.0 (CH), 119.9 (CH), 137.7 (C), 137.8 (C), 138.3 (CH), 138.9 (CH), 155.7 (C), 156.0 (C), 202.4 (C). ESI-MS (ion trap, positive ion): $[M + Na]^+$ m/z 339 (^{79}Br) and 341 (^{81}Br). Anal. Calcd for $C_{14}H_{21}BrO_3$: C, 53.01; H, 6.67. Found: C, 53.13; H, 6.78.

Methyl (*RS*,*E*)-8-(2-(3-(1-Ethoxyethoxy)pent-1-en-1-yl)-3-oxocyclopent-1-en-1-yl)octanoate (31). Methyl oct-7-enoate[18] (56 mg, 0.36 mmol, 1 equiv) was dissolved in dry THF (3.6 mL) in a flame-dried round-bottom flask. The solution was cooled to −10 °C, and a THF solution of 9-BBN−H dimer[19] (684 μL, 0.39 mmol, 1.1 equiv) was added dropwise over 5 min. The solution was then warmed to rt and stirred for an additional 4 h. The resulting crude organoborane **30** was used directly in the following step without purification. Bromo enone (*RS*)-**29** (28 mg, 0.09 mmol, 1 equiv) was added to a mixture of Cs_2CO_3 (52 mg, 0.16 mmol, 1.8 equiv), $PdCl_2$(dppf) (1.9 mg, 2.67×10^{-3} mmol, 0.03 equiv), Ph_3As (2.6 mg, 8.9×10^{-3} mmol, 0.1 equiv), and DMF (1 mL). Deoxygenated H_2O (18 μL, 1.07 mmol, 12 equiv) was then added, followed by the addition of the freshly prepared trialkylborane **30** (1 mL). The reaction mixture was stirred overnight and then quenched by adding a phosphate buffer (pH 7.0, 10 mL). The aq layer was extracted with Et_2O (3 × 7 mL), and the collected organic layers were dried over $MgSO_4$, filtered, and concd under vacuum. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane−EtOAc, 4:1, gave adduct (*RS*)-**31** (19.5 mg, 55%), a mixture of diastereomers, as a colorless oil. TLC: R_f = 0.29 (hexane−EtOAc, 4:1). IR (cm^{-1}): ν 1730 (ester C═O), 1690 (ketone C═O). ^1H NMR (300 MHz, CD_2Cl_2): δ 0.85−1.0 (two overlapped triplets, J = 7.3 Hz, totally 3H), 1,12−1.25 (two overlapped triplets, J = 7.1 Hz, totally 3H), 1.25−1.28 (two overlapped doublets, J = 6.3 Hz, totally 3H), 1.32−1.52 (m, 6H), 1.50−2.0 (m, 6H), 2.32 (t, J = 7.5 Hz, 3H), 2.30−2.50 (m, 2H), 2.50−2.75 (m, 4H), 3.38−3.70 (m, 2H), 3.66 (s, 3H), 4.70−4.80 (m, 1H), 6.20 and 6.25 (two doublets, J = 16.0, Hz, totally 1H), 6.59 and 6.70 (dd, J = 16.0, 7.5 Hz, totally 1H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 10.7 (Me), 10.9 (Me), 16.4 (Me), 16.6 (Me), 21.7 (Me), 21.8 (Me), 26.2 (CH_2), 28.9 (CH_2), 30.0 (CH_2), 30.3 (CH_2), 30.4 (CH_2), 30.8 (CH_2), 32.5 (CH_2), 35.3 (CH_2), 36.2 (CH_2), 52.6 (Me), 60.8 (CH_2), 62.4 (CH_2), 80.2 (CH), 80.3 (CH), 98.7 (CH), 100.1 (CH), 120.8 (CH), 121.8 (CH), 135.4 (C), 135.9 (CH), 136.6 (CH), 175.2 (C), 176.6 (C), 176.9 (C), 209.3 (C). ESI-MS (ion trap, positive ion): $[M + H]^+$ m/z 395. Anal. Calcd for $C_{23}H_{38}O_5$: C, 70.02; H, 9.71. Found: C, 70.18; H, 9.81.

Methyl (*RS*,*E*)-8-(2-(3-Hydroxypent-1-en-1-yl)-3-oxocyclopent-1-en-1-yl)octanoate (32). PPTS (3 mg, 0.01 mmol, 0.2 equiv) was added to compd **31** (16 mg, 0.04 mmol, 1 equiv) dissolved in dry DCM−EtOH, 1:1 (200 μL:200 μL), at 0 °C. The resulting solution was then warmed to rt. The reaction was completed in 2.5 h and was quenched with satd aq $NaHCO_3$. The resulting suspension was filtered through a short pad of Celite, dried under vacuum, and evaporated. The residue was purified by flash chromatography on silica gel. Elution with hexane−EtOAc, 7:3, afforded ester (*RS*)-**32** (12 mg, 93%) as a colorless oil. TLC: R_f = 0.23 (hexane−EtOAc, 7:3). IR (cm^{-1}): ν 3400 (O−H), 1730 (ester C═O), 1690 (ketone C═O). ^1H NMR (300 MHz, CD_2Cl_2): δ 0.95 (t, J = 7.4 Hz, 3H), 1.25−1.45 (m, 6H), 1.50−1.65 (m, 6H), 1.75 (br, 1H, OH), 2.32 (t, J = 7.4 Hz, 2H), 2.38−2.42 (m, 2H), 2.51−2.62 (m, 4H), 3.66 (s, 3H), 4.11 (q, J = 6.3 Hz,1H), 6.30 (br d, J = 15.5, 1H), 6.80 (dd, J = 15.9, 6.4 Hz, 1H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 10.9 (Me), 26.2 (CH_2), 28.8 (CH_2), 30.3 (CH_2), 30.3 (CH_2), 30.4 (CH_2), 30.7 (CH_2), 31.7 (CH_2), 32.4 (CH_2), 35.3 (CH_2), 36.2 (CH_2), 52.7 (Me), 75.9 (CH), 119.9 (CH), 135.3 (C), 137.8 (CH), 175.3 (C), 177.1 (C), 209.5 (C). ESI-

DOI: 10.1021/jo502538b
J. Org. Chem. 2015, 80, 1601−1609

MS (ion trap, positive ion): $[M + H]^+$ m/z 323. Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.83; H, 9.48.

(*RS*,*E*)-8-(2-(3-Hydroxypent-1-en-1-yl)-3-oxocyclopent-1-en-1-yl)octanoic Acid [(*RS*)-16-L$_1$-PhytoP, 7]. CAL-B (17 mg) was added to ester **32** (17 mg, 0.06 mmol, 1 equiv) dissolved in 1.1 mL of MTBE−H_2O, 10:1, and the suspension was stirred overnight. After enzyme removal by filtration, the solution was evaporated under vacuum. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane−*i*PrOH, 4:1, gave **7** (12 mg, 75%) as a colorless oil. TLC: R_f = 0.27 (hexane−*i*PrOH, 4:1). IR (cm^{-1}): ν 3400−2700 (br, O−H), 1710 (acid C═O), 1690 (ketone C═O). ^{1}H NMR (300 MHz, CD_3CN): δ 0.91 (t, J = 7.5 Hz, 3H), 1.25−1.50 (m, 6H), 1.50−1.62 (m, 6H), 2.28 (t, J = 7.4 Hz, 2H), 2.30−2.42 (m, 2H), 2.50−2.60 (m, 4H), 4.03 (q, J = 6.4 Hz, 1H), 6.29 (d, J = 15.9 Hz, 1H), 6.73 (dd, J = 15.9, 6.2 Hz, 1H). ^{13}C NMR (75 MHz, CD_3CN): δ 9.2 (Me), 24.5 (CH_2), 27.1 (CH_2), 28.5 (CH_2), 28.6 (CH_2), 28.7 (CH_2), 28.9 (CH_2), 30.2 (CH_2), 30.6 (CH_2), 33.2 (CH_2), 34.5 (CH_2), 73.6 (CH), 118.1 (CH), 133.6 (C), 136.6 (CH), 174.3 (C), 176.0 (C), 208.1 (C). ESI-MS (ion trap, negative ion): $[M - H]^-$ m/z 307. Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.19; H, 9.21.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra of new compounds and ^{1}H NMR spectra of the known compounds for confirmation. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +39-0382098322. Fax: +39-0382987323. E-mail: vidari@unipv.it.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Italian Ministry of Education, University and Research (MIUR) (funds PRIN 2011). We thank Prof. Mariella Mella for recording the NMR spectra.

■ REFERENCES

(1) (a) Jahn, U.; Galano, J.-M.; Durand, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5894−5955. (b) Durand, T.; Bultel-Poncé, V.; Guy, A.; Berger, S.; Mueller, M. J.; Galano, J.-M. *Lipids* **2009**, *44*, 875−888.

(2) Thoma, L.; Krischke, M.; Loeffler, C.; Mueller, M. J. *Chem. Phys. Lipids* **2004**, *128*, 135−148.

(3) In this paper we have followed the nomenclature system recently revised by Jahn et al.: (a) Jahn, U.; Galano, J.-M.; Durand, T. *Prostaglandins, Leukotrienes Essent. Fatty Acids* **2010**, *82*, 83−86. Other terminology systems were previously proposed: (b) Taber, D. F.; Morrow, J. D.; Robers, L. J., II. *Prostaglandins* **1997**, *53*, 63−67. (c) Rokach (Rokach, J.; Khanapure, S. P.; Hwang, S. W.; Adiyaman, M.; Lawson, J. A.; FritzGerald, G. A. *Prostaglandins* **1997**, *54*, 853−873. (d) Mueller, M. J. *Prostaglandins, Leukotrienes Essent. Fatty Acids* **2010**, *82*, 71−81.

(4) (a) Mueller, M. J. *Curr. Opin. Plant Biol.* **2004**, *7*, 441−448. (b) Loeffler, C.; Berger, S.; Guy, A.; Durand, T.; Bringmann, G.; Dreyer, M.; von Rad, U.; Durner, J.; Mueller, M. J. *Plant Physiol.* **2005**, *137*, 328−340. (c) Durand, T.; Bultel-Poncé, V.; Guy, A.; El Fangour, S.; Rossi, J. C.; Galano, J.-M. *Biochimie* **2011**, *93*, 52−60.

(5) Thoma, L.; Krischke, M.; Loeffler, C.; Mueller, M. J. *Chem. Phys. Lipids* **2004**, *128*, 135−148.

(6) Karg, K.; Dirsch, V. M.; Vollmar, A. M.; Cracowski, J.-L.; Laporte, F.; Mueller, M. J. *Free Radical Res.* **2007**, *41*, 25−37.

(7) Minghetti, L.; Salvi, R.; Salvatori, M. L.; Ajmone-Cat, M. A.; De Nuccio, C.; Visentin, S.; Bultel-Poncé, V.; Oger, C.; Guy, A.; Galano, J.-M.; Greco, A.; Bernardo, A.; Durand, T. *Free Radical Biol. Med.* **2014**, *73*, 41−50.

(8) 16-B$_1$-PhytoP and 9-L$_1$-PhytoP: (a) El Fangour, S.; Guy, A.; Vidal, J.-P.; Rossi, J.-C.; Durand, T. *J. Org. Chem.* **2005**, *70*, 989−997. (b) Schmidt, A.; Boland, W. *J. Org. Chem.* **2007**, *72*, 1699−1706. (c) Perlikowska, W.; Mikolajczyk, M. *Synthesis* **2009**, *16*, 2715−2718. (d) Vázquez-Romero, A.; Cardenas, L.; Blasi, E.; Verdaguer, X.; Riera, A. *Org. Lett.* **2009**, *11*, 3104−3107. (e) Perlikowska, W.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **2011**, *22*, 1767−1771. (f) Vázquez-Romero, A.; Verdaguer, X.; Riera, A. *Eur. J. Org. Chem.* **2013**, 1716−1725.

(9) (a) Luparia, M.; Vadalà, A.; Zanoni, G.; Vidari, G. *Org. Lett.* **2006**, *8*, 2147−2150. For related studies on a single Br/Mg exchange of symmetrical 1,2-dibromocyclopentene derivatives, see: (b) Despotopoulou, C.; Bauer, R. C.; Krasovskiy, A.; Mayer, P.; Stryker, J. M.; Knochel, P. *Chem.—Eur. J.* **2008**, *14*, 2499−2506.

(10) Duffy, M. G.; Grayson, D. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1555−1563.

(11) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39−45.

(12) Prepared in 95% yield from commercially available pent-1-en-3-ol upon exposure to (TBS)Cl, imidazole, and DMAP in DCM at rt.

(13) Zanoni, G.; Valli, M.; Bendjeddou, L.; Porta, A.; Bruno, P.; Vidari, G. *J. Org. Chem.* **2010**, *75*, 8311−8314.

(14) Trost, B. M.; Pinkerton, A. B. *Org. Lett.* **2000**, *2*, 1601−1603.

(15) The synthesis of (*RS*)-9-L$_1$-PhytoP (**5**) from bromocyclopentenone **21** and alcohol (*RS*)-**18**, shown in Scheme 3, was repeated in an enantioselective fashion starting from enantioenriched alcohol (*R*)-**18** to afford (*R*)-9-L$_1$-PhytoP (**5a**). Similar yields were observed in the different steps. Therefore, for the sake of simplicity, in the Experimental Section, the reactions of compounds **18**, **19**, **21**, **22**, and **23**, and the spectroscopic data of the products, are reported only for the enantioenriched samples.

(16) (a) Marion, N.; Carlqvist, P.; Gealageas, R.; de Frémont, P.; Maseras, F.; Nolan, S. P. *Chem.—Eur. J.* **2007**, *13*, 6437−6451. (b) Ramon, R. S.; Marion, N.; Nolan, S. P. *Tetrahedron* **2009**, *65*, 1767−1773. (c) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149−4158. (d) Zanoni, G.; D'Alfonso, A.; Porta, A.; Feliciani, L.; Nolan, S. P.; Vidari, G. *Tetrahedron* **2010**, *66*, 7472−7478.

(17) Gaillard, S.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 2742−2744.

(18) Yamamoto, N.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2011**, *76*, 2937−2941.

(19) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014−11015.

(20) Hayashi, M.; Kaneko, T.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1991**, 25−28.

(21) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Org. Chem.* **1986**, *51*, 3394−3396.

(22) Miura, A.; Kuwahara, S. *Tetrahedron* **2009**, *65*, 3364−3368.

DOI: 10.1021/jo502538b
J. Org. Chem. 2015, 80, 1601−1609