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A Divergent Enantioselective Synthesis of 9-J_1-Phytoprostane and 9-A_1-Phytoprostane Methyl Ester

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The first syntheses of 9-J_1-phytoprostane and 9-A_1-phytoprostane methyl ester were achieved enantioselectively using a divergent approach from a common intermediate sulfone **4**. The divergence was accomplished using a sigmatropic rearrangement (swap protocol) to give sulfone **5** in 47 % overall yield. The two upper side-chains, with a stereodefined *E* double bond, were installed using consolidated Julia–Lythgoe olefination reactions of sulfones **4** and **5**, with the same enantiopure α-protected aldehyde **6**.

Introduction

Phytoprostanes (PhytoPs) are prostaglandin-like compounds produced in plants by nonenzymatic free-radical peroxidation of membrane-bound α-linolenic acid.[1] The main differences between most PhytoPs chiefly and the prostaglandins are in the lengths and the thermodynamically less stable *cis* stereochemical relationship of the two side-chains on the five-membered ring. Another important feature of the nonenzymatic pathway to natural phytoprostanes is the absence of control of the absolute stereochemistry of the stereogenic centres of the cyclopentane ring and the allylic hydroxy group. There are seven classes of phytoprostanes, which, in analogy to the prostaglandin nomenclature system, have been named PPA_1, PPB_1, PPD_1, PPE_1, PPF_1, PPJ_1, and PPL_1, with the latter being the regioisomer of PPB_1.[2a] (Figure 1).

It should be pointed out that the compounds of each of the classes of phytoprostanes have two possible regioisomers, i.e., the 9 and 16 regioisomers, each of which comprises several stereoisomers due to the stereocentres of the prostanoid ring. Accordingly to the more recent proposed phytoprostane nomenclature system, our synthetic targets were 9-J_1-PhytoP (**1**) and 9-A_1-PhytoP (**2**),[2a,2b] which correspond to PPA_1-II and PPJ_1-II, respectively, in an older nomenclature system.[2c] Phytoprostane 9-J_1-PhytoP (**1**) has been detected in tobacco cell cultures after an induced oxi-

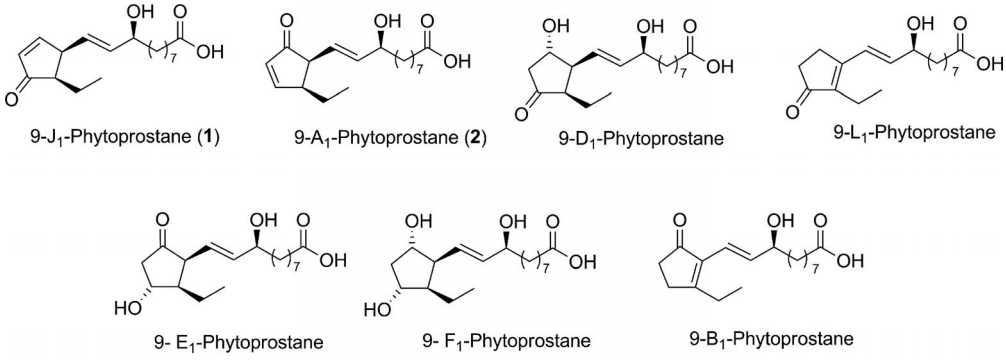

Figure 1. Representative phytoprostanes of the A_1, B_1, D_1, E_1, F_1, J_1, and L_1 classes.

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dative stress, and also, in very low quantities, in tomato plants infected with the necrotrophic fungus *Botrytis cinerea*.[3] The isolation and characterization of 9-J_1-PhytoP, has also been claimed, but in fact, the reported spectroscopic data correspond to the respective dehydration product. On the other hand, 9-A_1-PhytoP (**2**) is too elusive to have been isolated and characterized.[2a,4] A few biological activities have been attributed to cyclopentenone 9-J_1-phytoprostane (**1**) both in plants and in humans. For example, In plants, 9-J_1-PhytoP significantly activated the mitogen-activated protein kinase in cell suspension of tomato cultures, and induced a high expression of the orthologous gene in tobacco. Moreover, **1** induced glutathione-S-transferase 1 expression in *Arabidopsis*; this enzyme plays a key role in the detoxification of reactive electrophiles, thus triggering an adaptive response in plants and partially preventing cell death.[5] In humans, J_1-phytoprostanes show significant anti-inflammatory activity in HEK 293 cells and RAW 264.7 macrophages, through the down-regulation of the NF-κB signalling pathway and the inhibition of nitric oxide synthesis, respectively. In addition, 9-J_1-PhytoP shows antitumor activity by inducing the apoptosis of leukaemia Jukart T cells.[6] Considering that J_1-phytoprostanes have been detected in edible oils,[6] it is of paramount importance to clarify their physiological activity, as has been done for prostanoids and isoprostanes in animals.[1c] This is especially true for the elusive 9-A_1-phytoprostane, whose biological activity is unknown. A detailed evaluation of the biological activities of 9-J_1-PhytoP and 9-A_1-PhytoP has been prevented so far by the poor availability of the pure compounds.

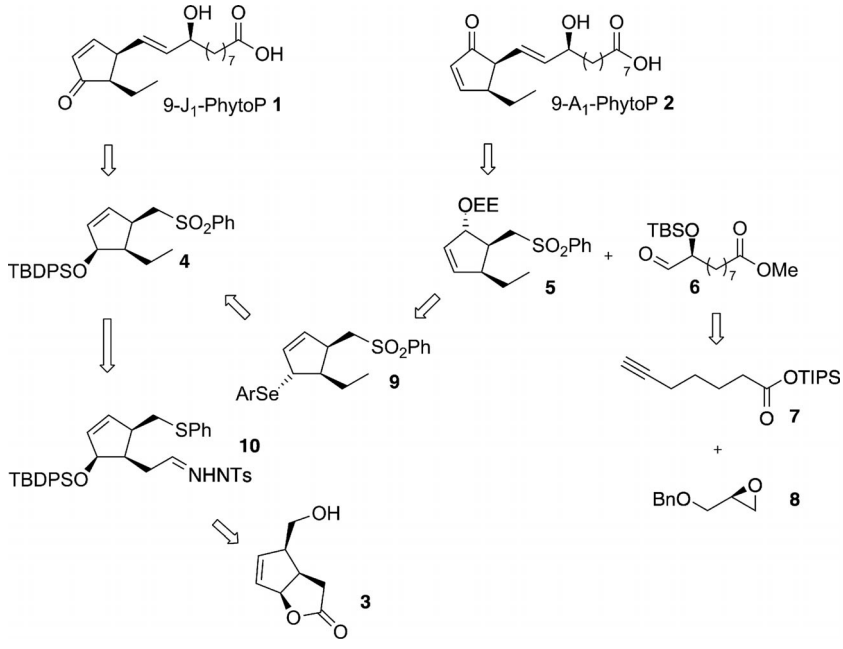
Thus, the chemical synthesis of 9-J_1-PhytoP and 9-A_1-PhytoP is not only a highly challenging goal, but it is the only way to prepare enough material for biological studies. However, no synthesis of 9-J_1-PhytoP or 9-A_1-PhytoP has been reported in the literature to date.

Results and Discussion

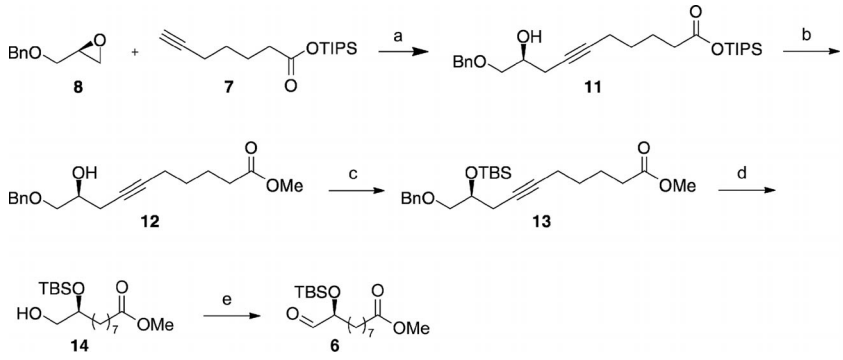
In this paper, we describe the first enantioselective divergent synthesis of cyclopentenone phytoprostane **1** and the methyl ester of **2**, starting from a common chiral building block, namely the enantiopure hydroxymethyl γ-lactone (–)-(3a*S*,4*S*,6a*R*)-**3**, which is available on a multigram scale.[7] According to our retrosynthetic strategy (Scheme 1), the upper side-chains (α side-chains) of phytoprostanes **1** and **2**, with a stereodefined *E* double bond, were installed by consolidated Julia–Lythgoe olefination reactions of sulfones **4** and **5**, respectively, with enantiopure α-protected aldehyde **6**.

The *S* absolute stereochemistry of the alcohol in the α side-chain precursor **6** was secured by a regio- and stereocontrolled nucleophilic oxirane ring-opening of (*S*)-glycidyl benzyl ether **8** by hept-6-ynoic acid TIPS ester **7**. Sulfone **5** converged to sulfone **4** via cyclopentenyl aryl selenoether intermediate **9** using our swap protocol.[8] The ethyl group of the ω side-chain of **1** and the methyl ester of **2** was obtained from the reduction of tosylhydrazone **10** with $(Ph_3P)_2CuBH_4$ to give the corresponding hydrocarbon.[9] Retrosynthetically, simple functional group manipulations indicated that lactone **3** was the ideal precursor.

The enantioselective synthesis of phytoprostanes **1** and the methyl ester of **2** thus began with the preparation of enantiopure *O*-TBS-protected α-hydroxyaldehyde **6** (Scheme 2). In the event, nucleophilic addition of the alkynide anion of hept-6-ynoic acid TIPS ester **7** to commercially available enantiopure (*S*)-glycidyl benzyl ether **8** under



Scheme 1. Retrosynthesis of 9-J_1- and 9-A_1-phytoprostanes; Ts = 4-tolylsulfonyl, EE = ethoxyethyl, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl, Ar = 2-nitrophenyl.



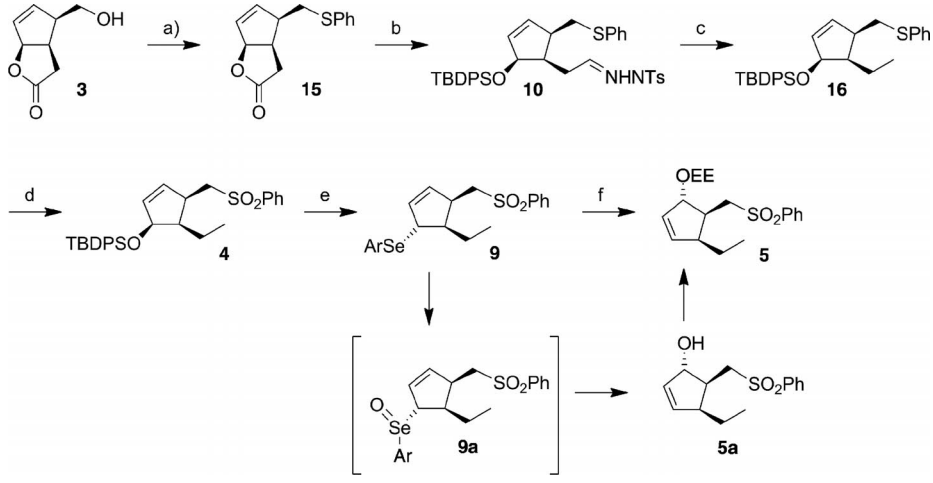
Scheme 2. Synthesis of α side-chain precursor **6**. Reagents and conditions: a) **7**, BuLi, –78 °C, 1 h, then $BF_3{\cdot}Et_2O$, 10 min. then **8**, –78 °C, 2 h; b) i. K_2CO_3, THF/H_2O (1:1), room temp., 4 d; ii. CAL-B lipase, MTBE/MeOH (9:1), room temp., 30 h, 70%; c) TBSCl, imidazole, CH_2Cl_2, room temp., 36 h, quant.; d) Pd/C (10%), H_2, EtOAc/MeOH (9:1), room temp., 7 d, 86%; e) DMP, CH_2Cl_2, room temp., 1 h, 75%. DMP = Dess–Martin periodinane, MTBE = methyl *tert*-butyl ether, CAL-B = *Candida antarctica* lipase B, TBSCl = *tert*-butyldimethylsilyl chloride.

Yamaguchi conditions[10] (BuLi, –78 °C, followed by $BF_3{\cdot}Et_2O$, and then epoxide **8**) gave alcohol **11** as a single regioisomer, which was used in the next step without purification.

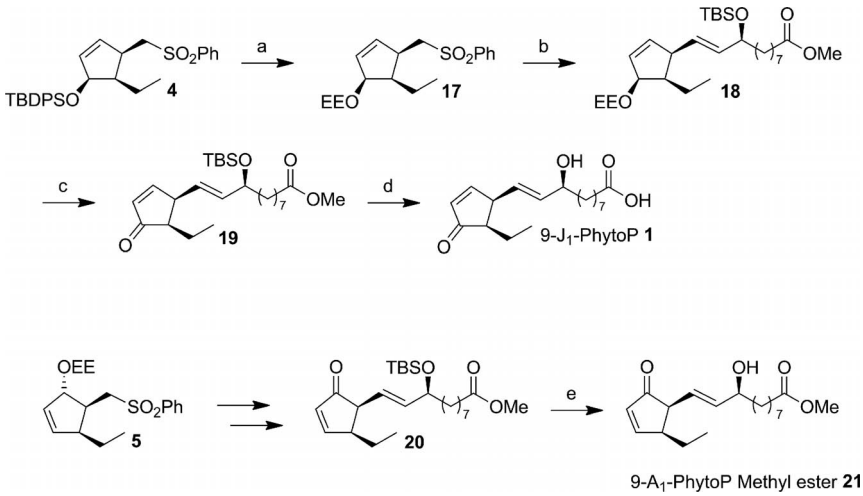
Transesterification of TIPS ester **11**, in the presence of the free C-9 hydroxy group, was accomplished in a biocatalytic approach using *Candida antarctica* lipase B (CAL-B) in the presence of MeOH at room temp. The corresponding methyl ester (i.e., **12**) was thus obtained in a satisfactory 70% isolated yield over three steps. Subsequently, alcohol **12** was protected as its TBS ether **13**, and then the triple bond was fully reduced [Pd on carbon (10%), H_2 (1 atm), EtOAc/MeOH, 9:1] with concomitant benzyl ether cleavage, to give saturated primary alcohol **14** in 86% overall yield. Dess–Martin periodinane oxidation[11] of alcohol **14** smoothly delivered aldehyde **6**, $[a]_D^{20}$ = –22.1 (*c* = 1.55, CH_2Cl_2), in 75% isolated yield.

Having established an efficient route to key intermediate **6**, we then turned our attention to the enantioselective synthesis of the two phytoprostane cores **4** and **5**, and this was achieved by the reaction sequences shown in Scheme 3.

Enantiopure hydroxymethyl lactone **3**[7] was converted into sulfide **15** in 88% yield with PhSSPh in the presence of nBu_3P and pyridine at room temp. Tosylhydrazone **10** was then obtained in three steps in 63% overall yield. DIBAL-H reduction of **15** at –78 °C gave the corresponding lactol, which was then treated with tosylhydrazine in dry THF at room temp., followed by protection of the allylic alcohol with TBDPSCl in the presence of imidazole in CH_2Cl_2 at room temp. After some experiments, the crucial reduction of **10** to give ethyl derivative **16** was achieved with $(Ph_3P)_2CuBH_4$ in refluxing dry $CHCl_3$ for 3 h;[9] compound **16** was thus obtained in 55% isolated yield, $[a]_D^{20}$ = 39.1 (*c* = 0.35, CH_2Cl_2). Subsequently, sulfone **4**, a key building



Scheme 3. Synthesis of key sulfones **4** and **5**. Reagents and conditions: a) PhSSPh, THF, 0 °C to room temp. 88%; b) i. DIBAL-H, CH_2Cl_2, –78 °C, 1 h, 95%; ii. $TsNHNH_2$, THF, room temp., 18 h, 99%; iii. TBDPSCl, CH_2Cl_2, imidazole, room temp., 2 d, 70%; c) $(Ph_3P)_2CuBH_4$, $CHCl_3$, 70 °C, 3 h, 55%; d) H_2O_2 (50% v/v solution), $(NH_4)MoO_4$ (cat.), room temp., 2 d, 50%; e) i. TBAF (1 M in THF), THF, room temp., 2 d, 70%; ii. 2-nitrophenyl selenocyanate, nBu_3P, THF, room temp., 1 h, 90%; f) i. H_2O_2 (35% v/v solution), pyridine, 0 °C to 4 °C, 18 h, 60%; ii. Ethyl vinyl ether, CH_2Cl_2, PPTS, room temp., 4 h, 87%; PPTS = pyridinium *p*-toluenesulfonate, Ts = *p*-tolylsulfonyl, TBDPSCl = *tert*-butyldiphenylsilyl chloride, TBAF = tetrabutylammonium fluoride, DIBAL-H = diisobutylaluminium hydride.



Scheme 4. Finale of the total synthesis of phytoprostanes **1** and **21**. Reagents and conditions: a) i. TBAF (1 M in THF), THF, room temp., 5 d, 70%; ii. Ethyl vinyl ether, CH_2Cl_2, PPTS, room temp., 4 h, 80%; b) i. **17**, BuLi (2.5 M in hexane), THF, –78 °C, 40 min, then **6** in THF, –78 °C, 4 h; ii. Na_2HPO_4, MeOH, –40 °C, then Na (20% Hg), –40 °C to –20 °C, 2 h, 61%; c) i. PPTS, EtOH/CH_2Cl_2 (3:1), room temp., 4 h, 91%; ii. DMP, CH_2Cl_2, room temp., 1.5 h, 95%; d) i. HF (48% aq. v/v), MeCN, room temp., 4 h, 93%; ii. CAL-B, H_2O, MTBE, room temp., 1 d, 90%; e) NH_4F, MeOH, room temp., 4 h, 65%.

block for the synthesis of phytoprostane **1** and the divergent synthesis of phytoprostane **2** was easily prepared by chemoselective oxidation of **16** with H_2O_2 in the presence of a catalytic amount of $(NH_4)_2MoO_4$ in methanol at room temp.[12] A divergent route to **2** from sulfone **4** was accomplished after cleavage of the TBDPS group, using our "swap" strategy,[8] via 2-nitrophenyl selenyl ether **9**, which was prepared in 90% yield using 2-nitrophenyl selenocyanate in the presence of nBu_3P in THF at room temp. Hydrogen peroxide [H_2O_2 (30%), pyridine, THF, 7 °C] smoothly triggered the [2,3]-sigmatropic rearrangement of the corresponding secondary allylic selenoxide **9a** to give the desired alcohol (i.e., **5a**) in 60% isolated yield. This alcohol was subsequently protected as its ethoxyethyl ether **5** (ethyl vinyl ether, CH_2Cl_2, pyridinium *p*-toluenesulfonate, 87% yield).

With the two key sulfones **4** and **5** in hand, the synthesis was expected to proceed readily to give target phytoprostanes **1** and **21**, respectively (Scheme 4), using the same olefination strategy for both compounds to introduce the unsaturated side-chains. In the event, simple functional group manipulation in **4** gave EE-protected sulfone **17**, which was condensed with aldehyde **6** under our modified Julia–Lythgoe olefination conditions[13] to give olefin **18** as a single *E* stereoisomer (^{13}C NMR spectroscopy) in 61% isolated yield over two steps. Removal of the labile EE protecting group [abs. EtOH/CH_2Cl_2 (3:1), pyridinium *p*-toluenesulfonate, room temp., 91% yield], followed by Dess–Martin periodinane oxidation, gave the corresponding enone (i.e., **19**) in 95% isolated yield. Finally, two consecutive deprotection steps, namely *O*-TBS ether cleavage with aq. HF, and methyl ester hydrolysis under our "buffer-free" conditions,[14] delivered the expected 9-J_1-PhytoP (**1**), $[\alpha]_D^{20}$ = –170.4 (*c* = 0.55, CH_2Cl_2), in 84% yield over two steps. Following the same synthetic sequence used for the transformation of **4** into enone **19**, sulfone **5** gave the expected enone (i.e., **20**; see Supporting Information), from which the *O*-TBS ether was detached using NH_4F in MeOH instead of aq. HF, in order to prevent a biomimetic dehydration[2a,4] (Scheme 4) of the corresponding free alcohol. Under these conditions, the elusive 9-A_1-PhytoP (**2**) was obtained as its methyl ester (i.e., **21**) in 65% isolated yield, $[\alpha]_D^{20}$ = 67.5 (*c* = 0.12, CH_2Cl_2). The extreme instability of the 9-A_1-phytoprostane structure is reflected in both the yield of the crucial Dess–Martin oxidation (31%) en route to **20**, and the extensive decomposition of 9-A_1-PhytoP methyl ester **21** that was observed during an attempted hydrolysis under extremely mild CAL-B mediated conditions.[15]

Conclusions

In summary, the first enantioselective divergent synthesis of the elusive cyclopentenone 9-J_1-phytoprostane **1** and of 9-A_1-phytoprostane methyl ester **21** has been accomplished starting from the common chiral building block **3**, which is available in multigram amounts in enantiopure form. Further studies aiming for the total synthesis of the other two regioisomeric A_1 and J_1 cyclopentenone phytoprostanes, 16-J_1-PhytoP and 16-A_1-PhytoP, are in progress in our laboratory, and the results will be reported in due course.

Experimental Section

General Information: THF was distilled from sodium with benzophenone ketyl radical as indicator. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2. All moisture-sensitive reactions were carried out under O_2-free Ar using oven-dried glassware and a vacuum line. Flash column chromatography was carried out using Merck SiO_2 60 (230–400 mesh), and TLC was carried out using commercially available Merck F254 precoated sheets. Visualization of reaction components was achieved under UV light at a wavelength of 254 nm, or by staining by exposure to vanillin (0.5% solution in H_2SO_4/EtOH) followed by gentle heating. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 instrument. Chemical

shifts are given in ppm, and are referenced using the residual signals of the solvent as internal standard (^{1}H: $CHCl_3$, δ = 7.26 ppm; [D_5]acetone, δ = 2.05 ppm. ^{13}C: $CDCl_3$, δ = 77.0 ppm). IR spectra were recorded with a Perkin–Elmer Paragon 100 PC spectrometer. Mass spectra were recorded with a Thermo LTQ-XL mass spectrometer (H-ESI) or a Finnigan MAT-90 mass spectrometer. Melting points were determined using an OptiMelt MPA100 device from Stanford Research Systems.

(*E*)-*N*′-(2-{(1*R*,2*S*,5*R*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-5-[(phenylthio)methyl]cyclopent-3-en-1-yl}ethylidene)-4-methylbenzenesulfonohydrazide (10): A stirred solution of sulfide **15** (260 mg, 1.057 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 °C, and DIBAL-H (1 M in hexane; 1.3 mL, 1.2 equiv.) was added dropwise. Stirring was continued for an additional 1 h, and then a saturated solution of NH_4Cl (10 mL) was added at –78 °C. The mixture was gradually warmed to room temp., then it was diluted with CH_2Cl_2 (30 mL), and acidified with concentrated HCl. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic phases were washed with H_2O and brine, and dried with $MgSO_4$. The volatiles were evaporated in vacuo to give the desired lactol (256 mg, 98%), a 9:1 mixture of diastereomeric hemiacetals, as a white solid, m.p. 107–110 °C. Spectroscopic data are in agreement with the literature.[13]

$TsNHNH_2$ (284 mg, 1.3 mmol, 1.2 equiv.) was added portionwise to a stirred solution of the sulfide lactol (276 mg, 1.1 mmol) in dry THF (11 mL) at room temperature. Stirring was continued for 18 h, and then the volatiles were removed under reduced pressure. Imidazole (6 equiv., 332 mg) and TBDPS chloride (2.5 equiv., 0.53 mL) were added to a stirred solution of the crude hydrazone (0.34 g, 0.815 mmol) in dry CH_2Cl_2 (8 mL) under an Ar atmosphere. After 40 h, H_2O (15 mL) was added, and the layers were separated. The aqueous phase was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with *n*-hexane/Et_2O (7:3) gave silyl ether **10** (361 mg, 70%) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3204.1, 3061, 2929, 2857, 1587, 1480, 1471, 1428, 1360, 1320, 1186, 1166, 1111, 1055, 885, 814, 739 cm^{-1}. ^{1}H NMR (300 MHz. $CDCl_3$): δ = 7.88–7.19 (m, 21 H), 6.90 (s, 1 H), 6.11 (dd, *J* = 5.8, 2.6 Hz, 1 H), 5.68 (d, *J* = 5.8 Hz, 1 H), 4.51 (dd, *J* = 5.6, 2.3 Hz, 1 H), 3.13 (dd, *J* = 12.2, 5.2 Hz, 1 H), 2.93–2.24 (m, 8 H), 1.03 (d, *J* = 13.1 Hz, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.8 (d), 149.7 (s), 144.1 (s), 138.5 (d), 137.7 (s), 136.8 (s), 136.0 (d), 135.9 (d), 135.8 (d), 135.2 (s), 134.0 (s), 133.8 (s), 133.6 (d), 133.3 (s), 130.0 (s), 129.8 (d), 129.7 (s), 129.6 (d), 129.5 (s), 129.0 (d), 128.9 (d), 128.8 (d), 128.0 (d), 127.8 (d), 127.5 (d), 126.2 (d), 125.8 (d), 77.1 (d), 45.2 (d), 45.0 (d), 44.4 (d), 43.8 (d), 36.4 (t), 36.2 (t), 28.5 (t), 27.0 (q), 23.4 (t), 21.6 (q), 19.2 (s), 19.1 (s) ppm. MS (ESI): *m*/*z* (%) = 662 (100) [M + Na]$^+$, 639 (20). HRMS: calcd. for $C_{38}H_{42}N_2O_3S_2$ 638.2637; found 638.2629.

***tert*-Butyl({(1*S*,4*R*,5*R*)-5-ethyl-4-[(phenylthio)methyl]cyclopent-2-en-1-yl}oxy)diphenylsilane (16):** $(PPh_3)_2CuBH_4$ (285 mg, 0.474 mmol, 1.1 equiv.) was added to a stirred solution of hydrazone **10** (282 mg, 0.43 mmol) in dry $CHCl_3$ (4 mL). The reaction mixture was heated at reflux for 3 h, and then it was filtered through short Celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel. Elution with *n*-hexane/Et_2O (97:3) gave **16** (112 mg, 55%) as a colourless oil. $[\alpha]_D^{20}$ = +39.1 (*c* = 3.5, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3071, 2932, 2862, 1450, 1422, 1301, 1148, 1110, 1060, 1022, 874, 830 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (m, 4 H), 7.3 (m, 11 H), 6.25 (dd, *J* = 2.77, 5.8 Hz, 1 H), 5.66 (dd, *J* = 1.4, 5.7 Hz, 1 H), 4.5 (dd, *J* = 2.5, 5.3 Hz, 1 H), 3.36 (dd, *J* = 4.4, 12.2 Hz, 1 H), 3.02 (t, *J* = 11.4 Hz, 1 H), 2.73 (m, 1 H), 1.78 (m, 4 H), 1.08 (s, 9 H), 0.96 (t *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.3 (d), 137.3 (s), 136.2 (d), 136.1 (d), 135.5 (d), 134.7 (d), 134.2 (d), 133.8 (s), 129.7 (d), 129.4 (d), 128.9 (d), 127.6 (d), 127.4 (d), 125.7 (d), 49.4 (d), 45.4 (d), 37.2 (t), 27.0 (s), 19.3 (d), 18.5 (t), 12.8 (d) ppm. MS (ESI): *m*/*z* (%) = 479 (100) [M + Na]$^+$. HRMS: calcd. for $C_{31}H_{36}OS$ 456.2487; found 456.2496.

***tert*-Butyl({(1*S*,4*R*,5*R*)-5-ethyl-4-[(phenylsulfonyl)methyl]cyclopent-2-en-1-yl}oxy)diphenylsilane (4):** Sulfide **16** (40 mg, 0.085 mmol) was dissolved in MeOH (8 mL), and the resulting solution was cooled to 0 °C. Solid $(NH_4)_2MoO_4$ (6 mg) and H_2O_2 (50%; 180 μL, 96 equiv.) were added. The temperature was allowed to reach room temp., and stirring was continued for 3 h. Further H_2O_2 (50%; 70 μL) and $(NH_4)_2MoO_4$ (4 mg) were added, and the resulting yellow slurry was stirred for an additional 14 h. The reaction was quenched by adding solid Na_2SO_3. The mixture was stirred for 40 min at room temp., then the MeOH was removed by evaporation in vacuo, and the residue was partitioned between a saturated solution of NH_4Cl (6 mL) and CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layers were washed with brine, and dried with Na_2SO_4. The residue obtained from evaporation of the volatiles was purified on silica gel (8 g; *n*-hexane/EtOAc, 9:1) to give sulfone **4** (21 mg, 50%) as a pale yellow viscous oil. $[\alpha]_D^{20}$ = +39.5 (*c* = 0.4, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3070, 2931, 2857, 1447, 1428, 1306, 1147, 1112, 1075, 1040, 1021, 865, 822 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (m, 2 H), 7.62 (m, 7 H), 7.45 (m, 6 H), 6.20 (dd, *J* = 2.83, 5.80 Hz, 1 H), 5.6 (dd, *J* = 2.02, 5.61 Hz, 1 H), 4.46 (dd, *J* = 2.52, 5.09 Hz, 1 H), 3.4 (m, 2 H), 2.92 (m, 1 H), 1.9 (m, 1 H), 1.65 (m, 1 H), 1.45 (m, 1 H), 1.12 (s, 9 H), 0.85 (t, *J* = 7.34 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.0 (s), 138.1 (d), 136.0 (d), 135.9 (d), 134.6 (d), 134.2 (s), 133.5 (d), 133.4 (s), 129.7 (d), 129.2 (d), 127.8 (d), 127.5 (d), 127.4 (d), 76.3 (d), 59.5 (t), 49.2 (t), 40.0 (d), 26.9 (q), 19.2 (s), 18.5 (t), 12.1 (d) ppm. MS (ESI): *m*/*z* (%) = 489 (100) [M + H]$^+$. HRMS: calcd. for $C_{31}H_{36}O_3S$ 488.2385; found 488.2376.

({[(1*R*,4*S*,5*R*)-4-(1-Ethoxyethoxy)-5-ethylcyclopent-2-en-1-yl]-methyl}sulfonyl)benzene (17): TBAF (418 μL, 0.12 mmol, 4 equiv.) was added to a solution of **4** (60 mg, 0.1203 mmol) in dry THF (1.2 mL) under Ar. The reaction mixture was stirred at room temp. until complete conversion was reached. The reaction was quenched with saturated aq. NH_4Cl (2 mL), and the mixture was diluted with Et_2O (2 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 6:4) to give the free alcohol (22.4 mg, 70%). $[\alpha]_D^{20}$ = –50.0 (*c* = 0.5, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3435, 3073, 2933, 2864, 1451, 1426, 1316, 1147, 1045, 1030, 1022, 870 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (m, 2 H), 7.6 (m, 3 H), 6.33 (dd, *J* = 2.12, 5.79 Hz, 1 H), 6.00 (dd, *J* = 2.66, 5.45 Hz, 1 H), 3.30 (m, 1 H), 3.10 (m, 2 H), 2.04 (m, 1 H), 1.54 (m, 2 H), 1.36 (m, 1 H), 0.97 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9 (s), 139.4 (d), 133.8 (d), 133.7 (d), 129.3 (d), 127.9 (d), 74.8 (d), 59.5 (t), 47.8 (d), 40.0 (d), 18.2 (t), 12.3 (d) ppm. MS (ESI): *m*/*z* (%) = 289 (100) [M + Na]$^+$. HRMS: calcd. for $C_{14}H_{18}O_3S$ 266.0977; found 266.0983.

The above cyclopentenol (22.4 mg, 0.084 mmol) was dissolved in CH_2Cl_2/ethyl vinyl ether (7:1; 1 mL), and PPTS (cat.) was added. The resulting mixture was stirred for 4 h, then excess solid $NaHCO_3$ was added, followed by a saturated solution of $NaHCO_3$

(5 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 15 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with *n*-hexane/EtOAc (8:2) gave acetal **17** (22.6 mg, 80%, 1:1 mixture of anomers) as a colourless oil. IR (neat): $\tilde{\nu}$ = 2972, 1446, 1306, 1386, 1306, 1147, 1086, 997, 863, 691 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ = 7.98 (m, 2 H), 7.71 (m, 3 H), 6.24 (m, 1 H), 6.11 (m, 1 H), 4.72 (m, 1 H), 4.35 (dm 1 H), 3.50 (m, 3 H), 3.01 (m, 2 H), 2.10 (m, 1 H), 1.50 (m, 2 H), 1.18 (m, 6 H), 0.89 (m, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 141.3 (s), 140.3 (d), 139.3 (d), 134.4 (d), 133.7 (d), 130.2 (d), 128.7 (d), 101.0 (d), 98.7 (d), 81.8 (d), 77.4 (d), 61.2 (t), 60.0 (t), 49.4 (d), 41.5 (d), 21.2 (d), 20.6 (d), 18.9 (t), 15.6 (d), 12.5 (d) ppm. MS (ESI): *m*/*z* (%) = 339 (100) $[M + H]^+$. HRMS: calcd. for $C_{18}H_{26}O_4S$ 338.1552; found 338.1562.

{(1*R*,4*R*,5*R*)-5-Ethyl-4-[(phenylsulfonyl)methyl]cyclopent-2-en-1-yl}(2-nitrophenyl)selane (9): Solid, freshly sublimed (*o*-nitrophenyl)-selenocyanate (136.8 mg, 0.6 mmol, 1.5 equiv.) was added to the cyclopentenol prepared from **4** (see above; 106.6 mg, 0.4 mmol) in dry THF (5 mL) under an argon atmosphere, and then nBu$_3$P (0.158 mL, 0.64 mmol, 1.6 equiv.) was added dropwise by cannula at room temperature. Stirring was continued for an additional 1 h. The reaction mixture was then diluted with EtOAc, and the organic layer was separated and washed with a saturated solution of $NaHCO_3$ and then with brine. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The oily, brown-orange residue was purified on silica gel. Elution with hexanes/EtOAc (8:2) gave selenide **9** (151 mg, 90%) as a brown-yellow oil. IR (neat): $\tilde{\nu}$ = 3063, 2964, 2932, 2876, 2255, 1710, 1654, 1590, 1566, 1510, 1448, 1332, 1305, 1148, 1086, 1037, 911, 852, 783, 732, 688 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.3 (dd, *J* = 1.18, 8.25 Hz, 1 H), 7.9 (m, 2 H), 7.6 (m, 5 H), 7.3 (t, *J* = 7.14 Hz, 1 H), 6.0 (m, 2 H), 4.2 (m, 1 H), 3.4 (m, 1 H), 3.35 (dd, *J* = 4.52, 13.84 Hz, 1 H), 3.15 (dd, *J* = 10.0, 13.81 Hz, 1 H), 2.35 (m, 1 H), 1.5 (m, 2 H), 0.97 (t, *J* = 7.27 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3 (s), 139.2 (s), 135.4 (d), 133.8 (d), 133.6 (s), 133.3 (d), 131.6 (d), 130.0 (d), 129.4 (d), 128.0 (d), 126.3 (d), 125.7 (d), 56.5 (t), 49.3 (d), 48.8 (d), 40.6 (d), 21.6 (t), 12.3 (q) ppm. MS (ESI): *m*/*z* (%) = 452 (100) $[M + H]^+$. HRMS: calcd. for $C_{20}H_{21}O_4SSe$ 451.0357; found 451.0361.

({[(1*S*,2*S*,5*S*)-2-(1-Ethoxyethoxy)-5-ethylcyclopent-3-en-1-yl]methyl}sulfonyl)benzene (5): Pyridine (126 mg, 1.568 mmol, 4 equiv.) was added by syringe to a stirred solution of selenide **9** (164 mg, 0.392 mmol) in THF (10 mL) at room temperature. The mixture was cooled to 0 °C, and hydrogen peroxide (30% v/v; 532 μL, 15.7 mmol, 14 equiv.) was added dropwise. Stirring was continued at +7 °C for an additional 18 h. The reaction was then quenched with water and diluted with EtOAc. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with a saturated solution of $NaHCO_3$ and with brine, dried with $MgSO_4$, and filtered, and the solvents were evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc, 7:3) to give pure cyclopentenol **5a** (54 mg, 60%). IR (neat): $\tilde{\nu}$ = 3504, 3060, 2964, 2929, 2876, 1448, 1304, 1146, 1085, 742, 689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.95 (m, 2 H), 7.75 (m, 1 H), 7.65 (m, 2 H), 6.00 (m, 1 H), 5.8 (m, 1 H), 4.77 (m, 1 H), 3.30 (m, 3 H), 3.20 (s 1 H), 2.70 (m, 1 H), 2.45 (m, 1 H), 1.50 (m, 2 H), 1.05 (m, 1 H), 0.85 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9 (s), 136.9 (d), 134.7 (d), 134.2 (d), 130.2 (d), 128.8 (d), 81.7 (d), 57.6 (t), 49.3 (d), 46.4 (d), 24.9 (t), 12.5 (q) ppm. MS (ESI): *m*/*z* (%) = 267 (100) $[M + H]^+$. HRMS: calcd. for $C_{14}H_{18}O_3S$ 266.0977; found 266.0981.

Cyclopentenol **5a** (33.6 mg, 0.084 mmol) was dissolved in CH_2Cl_2/ethyl vinyl ether (7:1; 1.5 mL), and PPTS (cat.) was added. The resulting mixture was stirred for 4 h, then excess solid $NaHCO_3$ was added, followed by a saturated solution of $NaHCO_3$ (5 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 15 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with *n*-hexane/EtOAc (8:2) gave acetal **5** (33.8 mg, 87%, 1:1 mixture of anomers) as a colourless oil. IR (neat): $\tilde{\nu}$ = 2973, 1450, 1310, 1389, 1309, 1150, 1087, 999, 861, 692 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ = 7.90 (m, 2 H), 7.70 (m, 3 H), 6.00 (m, 1 H), 5.8 (m, 1 H), 4.75 (m, 1 H), 4.45 (m, 1 H), 3.30 (m, 3 H), 2.70 (m, 1 H), 2.50 (m, 1 H), 1.65 (m, 1 H), 1.27 (m, 3 H), 1.18 (m, 3 H), 1.06 (m, 1 H), 0.85 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 141.3 (s), 140.3 (d), 139.3 (d), 134.4 (d), 133.7 (d), 130.2 (d), 128.7 (d), 101.0 (d), 98.7 (d), 81.8 (d), 77.4 (d), 61.2 (t), 60.0 (t), 49.4 (d), 41.5 (d), 21.2 (d), 20.6 (d), 18.9 (t), 15.8 (d), 12.5 (q) ppm. MS (ESI): *m*/*z* (%) = 339 (100) $[M + H]^+$. HRMS: calcd. for $C_{18}H_{26}O_4S$ 338.1552; found 338.1561.

Triisopropylsilyl Hept-6-ynoate (7): Imidazole (621 mg, 9.13 mmol, 1.3 equiv.) and then TIPSCl (1.6 mL, 7.37 mmol, 1.05 equiv.) were added to a solution of hept-6-ynoic acid (886 mg, 7.02 mmol) in dry CH_2Cl_2 (14 mL). The reaction mixture was stirred for 3 h at room temperature, then it was quenched with water (5 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 15 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with *n*-hexane/MTBE (98:2) gave ester **7** (1.87 g, 99%) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3313, 2946, 2869, 1718, 1465, 1213 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.39 (t, *J* = 7.3 Hz, 2 H), 2.24 (td, *J* = 7.0, 2.6 Hz, 2 H), 1.96 (t, *J* = 2.7 Hz, 1 H), 1.77 (dd, *J* = 8.4, 7.3 Hz, 2 H), 1.62–1.57 (m, 2 H), 1.30 (td, *J* = 7.9, 6.1 Hz, 3 H), 1.09 (d, *J* = 7.3 Hz, 19 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5 (s), 83.9 (s), 68.5 (d), 35.3 (t), 27.8 (t), 24.2 (t), 18.2 (t), 17.8 (q), 11.9 (d) ppm. MS (ESI): *m*/*z* (%) = 305 (100) $[M + Na]^+$. HRMS: calcd. for $C_{16}H_{30}O_2Si$ 282.2015; found 282.2020.

(*S*)-Methyl 10-(Benzyloxy)-9-hydroxydec-6-ynoate (12): nBuLi (0.49 mL, 1.24 mmol, 2 equiv.) was added dropwise to a solution of **7** (0.33 g, 1.23 mmol, 2 equiv.) in dry THF (6 mL) under Ar at –78 °C. After 1 h, $BF_3{\cdot}Et_2O$ (0.155 mL, 1.24 mmol, 2 equiv.) was added, and after 10 min, **8** (0.101 g, 0.62 mmol) in dry THF (2 mL) was added. The reaction was monitored by TLC (hexane/EtOAc, 8:2), and after 2 h at –78 °C was quenched with saturated aq. NH_4Cl (10 mL) and CH_2Cl_2 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (4× 7 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was filtered through short pad of silica gel (hexane/EtOAc, 9:1) to give compound **11** (0.495 g, 90%) as a pale yellow oil, which was used immediately in the next step.

H_2O (2 mL) and K_2CO_3 (0.14 g, 1.01 mmol, 1.01 equiv.) were added to a magnetically stirred solution of **11** (0.45 g, 1.0 mmol) in THF (2 mL) at room temp. After 16 h of stirring at room temp., the reaction was quenched with saturated aq. $NaHSO_4$ (2 mL), H_2O (2 mL), and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (4× 6 mL), and the combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated under vacuum.

The crude acid was dissolved in HPLC-grade MTBE (4 mL), and HPLC-grade MeOH (0.50 mL) was added. Solid-supported CAL-

B (80 mg) was added to the stirred solution, and the resulting suspension was gently stirred at 35 °C for 18 h. The enzyme was removed by filtration through a sintered glass funnel, and the solid was carefully washed with MeCN/MTBE (1:1, 4 × 2 mL). The filtrates were combined, and the solvents were evaporated under vacuum (***CAUTION:*** without heating). The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc, 7:3) to give pure ester **12** (213 mg, 70%). $[\alpha]_D^{20}$ = +9.45 (*c* = 0.85, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3462, 2931, 1736, 1454, 1208, 1118, 739, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5 H), 4.58 (s, 2 H), 3.93 (dd, *J* = 3.4, 3.2 Hz, 1 H), 3.67 (s, 3 H), 3.60 (dd, *J* = 9.5, 4.0 Hz, 1 H), 3.50 (dd, *J* = 9.5, 6.6 Hz, 1 H), 2.61 (d, *J* = 3.8 Hz, 1 H), 2.42 (dt, *J* = 6.1, 2.5 Hz, 2 H), 2.33 (t, *J* = 7.4 Hz, 2 H), 2.18 (tt, *J* = 6.9, 2.4 Hz, 2 H), 1.72 (dt, *J* = 15.2, 7.5 Hz, 2 H), 1.51 (quint, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8 (s), 137.9 (s), 128.3 (d), 127.6 (d), 81.9 (s), 76.0 (s), 73.3 (t), 72.9 (t), 69.1 (d), 51.4 (q), 33.4 (t), 28.2 (t), 24.0 (t), 23.8 (t), 18.3 (t) ppm. MS (ESI): *m*/*z* (%) = 305 (100) $[M + H]^+$. HRMS: calcd. for $C_{18}H_{24}O_4$ 304.1675; found 304.1679.

Methyl (*S*)-10-(Benzyloxy)-9-[(*tert*-butyldimethylsilyl)oxy]dec-6-ynoate (13): Imidazole (272 mg, 4 mmol, 2 equiv.) and TBSCl (361 mg, 2.4 mmol, 1.2 equiv.) were added to a solution of **12** (0.608 g, 2 mmol) in dry CH_2Cl_2 (6 mL) under Ar. The reaction was complete after 2 h, and it was quenched with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried on $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel column (*n*-hexane/EtOAc, 95:5) to give compound **13** (0.827 g, 99%) as a slightly yellow oil. $[\alpha]_D^{20}$ = +2.96 (*c* = 2.2, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2929, 2857, 1741, 1436, 1362, 1255, 1123, 1006, 837, 778, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5 H), 4.58 (s, 2 H), 3.93 (dd, *J* = 3.4, 3.2 Hz, 1 H), 3.67 (s, 3 H), 3.60 (dd, *J* = 9.5, 4.0 Hz, 1 H), 3.50 (dd, *J* = 9.5, 6.6 Hz, 1 H), 2.61 (d, *J* = 3.8 Hz, 1 H), 2.42 (dt, *J* = 6.1, 2.5 Hz, 2 H), 2.33 (t, *J* = 7.4 Hz, 2 H), 2.18 (tt, *J* = 6.9, 2.4 Hz, 2 H), 1.72 (dt, *J* = 15.2, 7.5 Hz, 2 H), 1.51 (quint, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9 (s), 1384 (s), 128.5 (d), 127.5 (d), 127.4 (d), 81.0 (s), 77.3 (s), 73.8 (t), 73.3 (t), 70.8 (d), 51.4 (q), 33.6 (t), 28.3 (t), 25.8 (q), 25.0 (t), 24.1 (t), 18.5 (t), 18.1 (s), –4.6 (q), 4.8 (q) ppm. MS (ESI): *m*/*z* (%) = 441 (100) $[M + Na]^+$. HRMS: calcd. for $C_{24}H_{38}O_4Si$ 418.2539; found 418.2546.

Methyl (*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-10-hydroxydecanoate (14): Palladium on charcoal (10% Pd w/w; 80 mg) was added to a solution of **13** (0.766 mg, 1.88 mmol) in EtOAc/MeOH (9:1; 19 mL). The suspension was stirred at room temp. under a hydrogen atmosphere for 7 d. The suspension was filtered, and the solvent was removed from the filtrate under vacuum. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc, 95:5) to give compound **14** (0.537 g, 86%) as a colourless oil. $[\alpha]_D^{20}$ = +7.19 (*c* = 1.2, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3468, 2930, 2857, 1742, 1464, 1362, 1255, 1116, 837, 776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.73–3.39 (m, 6 H), 2.29 (t, *J* = 7.5 Hz, 2 H), 1.97 (t, *J* = 6.0 Hz, 1 H), 1.63–1.56 (m, 2 H), 1.48–1.44 (m, 2 H), 1.29–1.23 (m, 8 H), 0.92 (s, 9 H), 0.07 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2 (s), 72.8 (d), 66.2 (t), 51.4 (q), 34.0 (t), 33.9 (t), 29.5 (t), 29.1 (t), 29.0 (t), 25.8 (q), 25.2 (t), 24.8 (t), 18.0 (s), –4.5 (q), –4.6 (q) ppm. MS (ESI): *m*/*z* (%) = 333 (100) $[M + H]^+$. HRMS: calcd. for $C_{17}H_{36}O_4Si$ 332.2383; found 332.2379.

Methyl (*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-10-oxodecanoate (6): Dess–Martin periodinane (DMP; 0.158 g, 0.37 mmol, 1.1 equiv.) was added to a solution of alcohol **14** (0.113 g, 0.34 mmol) in dry CH_2Cl_2 (4 mL). The reaction was complete after 2 h, and was quenched with H_2O (8 mL), MTBE (9 mL), saturated aq. $NaHCO_3$ (5 mL), and saturated aq. $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with MTBE/*n*-hexane, 9:1. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under vacuum. The residue was filtered through silica gel (hexane/EtOAc, 9:1) to give compound **6** (85 mg, 75%) as a colourless oil, which was used in the next step without further purification. $[\alpha]_D^{20}$ = –22.12 (*c* = 1.55, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2930, 2857, 1739, 1464, 1437, 1362, 1253, 1170, 1118, 1006, 838, 779, 666 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.4 (d, *J* = 1.6 Hz, 1 H), 3.9 (m, 1 H), 3.6 (s, 3 H), 2.3 (t, *J* = 7.5 Hz, 2 H), 1.6 (m, 5 H), 1.3 (s, 9 H), 0.9 (m, 10 H), 0.1 (m, 6 H) ppm. MS (ESI): *m*/*z* (%) = 331 (100) $[M + H]^+$.

Methyl (9*S*,*E*)-9-[(*tert*-Butyldimethylsilyl)oxy]-11-[(1*S*,4*S*,5*R*)-4-(1-ethoxyethoxy)-5-ethylcyclopent-2-en-1-yl]undec-10-enoate (18): Sulfone **17** (22.5 mg, 0.067 mmol) was dissolved in dry THF (1.2 mL), and the solution was cooled to –78 °C. The solution was stirred for 10 min, and then *n*BuLi (2.5 M in hexane; 0.030 mL, 1.11 equiv.) was added dropwise. The mixture was stirred for 45 min at the same temperature, then the deep orange solution was slowly added by cannula to a solution of aldehyde **6** (25.3 mg, 0.077 mmol, 1.16 equiv.) in dry THF (0.4 mL). The solution was stirred at the same temperature for an additional 2 h, then a saturated solution of NH_4Cl (5 mL) was added at –78 °C, and the temperature was allowed to reach room temp. The two layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, and evaporated under reduced pressure. The crude product was filtered through a short pad of silica gel using *n*-hexane/EtOAc (8:2) as eluent. The crude hydroxysulfone was immediately used in the next step.

Crude hydroxysulfone (20 mg, 0.03 mmol) was dissolved in dry MeOH (2 mL) under an argon atmosphere. Na_2HPO_4 (190 mg) was added , and the slurry was cooled to –40 °C. The mixture was stirred vigorously for 10 min, then sodium amalgam (20% Na; 60 mg) was slowly added portionwise in such a way as to keep the temperature below –40 °C. At the end of the addition, the temperature was allowed to reach –20 °C, and stirring was continued for an additional 1.5 h. The mixture was warmed to room temp. and filtered through filter paper. Evaporation of volatiles in vacuo under 40 °C gave a residue, which was partitioned between CH_2Cl_2 (5 mL) and a saturated aqueous solution of $NaHCO_3$. The two phases were separated, and the aqueous layer was reextracted with CH_2Cl_2 (3 × 3 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (10 g). Elution with *n*-hexane/EtOAc (94:6) gave compound **18** as a colourless oil (13.7 mg, 61%). IR (neat): $\tilde{\nu}$ = 2929, 2360, 1736, 1466, 1273, 1123, 1074, 992, 836, 775, 668 cm^{-1}. ^1H NMR [300 MHz, $(CD_3)_2CO$]: δ = 6.05 (dddd, *J* = 14.2, 5.8, 2.3, 1.2 Hz, 1 H), 5.91 (ddd, *J* = 17.0, 5.8, 2.9 Hz, 1 H), 5.50–5.37 (m, 2 H), 4.76 (qd, *J* = 5.9, 5.3 Hz, 1 H), 4.47 (dd, *J* = 6.2, 2.3 Hz, 0.5 H), 4.33 (dd, *J* = 6.2, 2.4 Hz, 0.5 H), 4.15–4.08 (m, 1 H), 3.69–3.40 (m, 5 H), 3.17–3.08 (m, 1 H), 2.81–2.77 (m, 1 H), 2.30 (t, *J* = 7.4 Hz, 2 H), 2.10–1.97 (m, 2 H), 1.64–0.86 (m, 35 H), 0.12–0.09 (m, 6 H) ppm. ^{13}C NMR [75 MHz, $(CD_3)_2CO$]: δ = 174.8 (s), 148.0 (s), 141.3 (d), 141.1 (d), 140.3 (d), 136.2 (d), 136.1 (d), 134.1 (d), 133.6 (d), 133.3 (d), 133.0 (d), 132.8 (d), 132.6 (d), 101.8 (d), 99.4 (d), 83.1 (d), 79.4 (d), 74.9 (d), 74.9 (d), 61.7 (t), 60.5 (t), 52.2 (q), 52.1 (q), 51.9 (d), 50.3 (d), 50.3 (d), 40.1 (t), 35.1 (t), 27.1 (t), 26.9 (t), 26.7 (q), 26.4 (t), 22.0 (q), 21.4 (q), 20.7 (t), 20.6 (t), 19.5 (s), 16.5 (q), 13.8 (q), –3.2 (q), –3.8 (q) ppm. MS (ESI): *m*/*z* (%) = 534 (20) [M

+ Na – H_2O]$^+$, 515 (80) [M + Na – H_2O]$^+$. HRMS: calcd. for $C_{29}H_{54}O_5Si$ 510.3741; found 510.3746.

Methyl (*S*,*E*)-9-[(*tert*-Butyldimethylsilyl)oxy]-11-[(1*R*,5*R*)-5-ethyl-4-oxocyclopent-2-en-1-yl]undec-10-enoate (19): PPTS (cat.) was added to a stirred solution of acetal **18** (30 mg, 0.059 mmol) in EtOH/CH_2Cl_2 (3:1; 2 mL), and the resulting mixture was stirred for 4 h. An excess of solid $NaHCO_3$ was added, and the resulting mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. Elution with *n*-hexane/EtOAc (90:10) gave the desired alcohol (18.8 mg, 90%) as a colourless oil. $[\alpha]_D^{20}$ = –77.0 (*c* = 1.16, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3502, 2931, 1713, 1472, 1358, 1360, 1254, 1077, 986, 840, 776 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.08–5.98 (m, 2 H), 5.43 (t, *J* = 5.8 Hz, 2 H), 4.52–4.49 (m, 1 H), 4.04 (q, *J* = 5.9 Hz, 1 H), 3.68 (s, 3 H), 3.21–3.10 (m, 1 H), 2.31 (t, *J* = 7.5 Hz, 2 H), 1.99 (quint, *J* = 7.0 Hz, 1 H), 1.65–1.22 (m, 18 H), 1.02 (t, *J* = 7.3 Hz, 3 H), 0.94–0.91 (m, 11 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3 (s), 139.6 (d), 135.2 (d), 133.3 (d), 131.6 (d), 76.5 (d), 73.4 (d), 51.4 (d), 49.3 (q), 48.7 (d), 38.5 (t), 34.1 (t), 29.7 (t), 29.3 (t), 29.2 (t), 29.1 (t), 25.9 (q), 25.2 (t), 24.9 (t), 19.0 (t), 18.2 (t), 12.7 (q), –4.3 (q), –4.8 (q) ppm. MS (ESI): *m*/*z* (%) = 421 (100) [M – H_2O]$^+$, 515 (80) [M + Na – H_2O]$^+$. HRMS: calcd. for $C_{25}H_{46}O_4Si$ 438.3165; found 438.3151.

DMP (23.7 mg, 0.056 mmol, 1.2 equiv.) was added to a stirred solution of the alcohol prepared as described above (20.4 mg, 0.047 mmol) in dry CH_2Cl_2 (1 mL). After 30 min, Et_2O (6 mL) was added, and the resulting mixture was filtered through a short pad of silica gel, which was thoroughly washed with *n*-hexane/Et_2O (9:1; 70 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. Elution with *n*-hexane/EtOAc (9:1) gave compound **19** (19.3 mg, 95%) as a colourless oil. $[\alpha]_D^{20}$ = –129.5 (*c* = 0.42, EtOAc). IR (neat): $\tilde{\nu}$ = 3734, 2929, 2856, 2360, 1741, 1712, 1587, 1462, 1251, 1778, 1250, 1073, 836, 776, 668 cm^{-1}. ^{1}H NMR (300 MHz, CD_3CN): δ = 7.55 (dd, *J* = 5.7, 2.9 Hz, 1 H), 6.13 (dd, *J* = 5.7, 1.7 Hz, 1 H), 5.58 (dd, *J* = 15.4, 6.0 Hz, 1 H), 5.40 (dd, *J* = 15.5, 8.8 Hz, 1 H), 4.17 (q, *J* = 6.1 Hz, 1 H), 3.74–3.73 (m, 1 H), 3.62 (s, 3 H), 2.34–2.27 (m), 1.97 (dtd, *J* = 4.9, 2.5, 0.5 Hz, 1 H), 1.61–1.25 (m, 14 H), 0.99 (t, *J* = 7.4 Hz, 3 H), 0.92–0.86 (m, 11 H), 0.07–0.00 (m, 6 H) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 211.3 (s), 174.6 (s), 166.2 (d), 138.2 (d), 132.8 (d), 127.7 (d), 73.5 (d), 51.8 (d), 51.6 (q), 48.0 (d), 38.8 (t), 34.3 (t), 29.8 (t), 29.7 (t), 29.5 (t), 26.0 (q), 25.6 (t), 25.5 (t), 20.2 (t), 18.6 (s), 12.8 (q), –4.4 (q), –4.8 (q) ppm. MS (ESI): *m*/*z* (%) = 459 (100) [M + Na]$^+$. HRMS: calcd. for $C_{25}H_{44}O_4Si$ 436.3009; found 436.3013.

(*S*,*E*)-11-[(1*R*,5*R*)-5-ethyl-4-oxocyclopent-2-en-1-yl]-9-hydroxyundec-10-enoic Acid (9-J$_1$-PhytoP; 1): Aqueous HF (48%; 0.063 mL) was added to a stirred solution of silyl ether **19** (17.1 mg, 0.0392 mmol) in HPLC-grade CH_3CN (4 mL) in a PE (polyethylene) test tube. After 4 h, a phosphate buffer (pH 6.8, 5 mL) was added. The layers were separated, and the aqueous phase was extracted with EtOAc (4 × 5 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with *n*-hexane/EtOAc (6:4) gave pure 9-J$_1$-PhytoP-Me-Ester (13.9 mg, 93%) as a pale yellow oil. $[\alpha]_D^{20}$ = –170.4 (*c* = 0.55, EtOAc). IR (neat): $\tilde{\nu}$ = 3445, 2929, 1738, 1713, 1699, 1694, 1559, 1456 cm^{-1}. ^{1}H NMR (300 MHz, CD_3CN): δ = 7.57 (dd, *J* = 5.7, 2.9 Hz, 1 H), 6.14 (dd, *J* = 5.7, 1.8 Hz, 1 H), 5.59 (ddd, *J* = 15.4, 6.2, 0.6 Hz, 1 H), 5.42 (ddd, *J* = 15.4, 8.7, 1.0 Hz, 1 H), 4.00 (quint, *J* = 5.6 Hz, 1 H), 3.74–3.73 (m, 1 H), 3.61 (s, 3 H), 2.75 (d, *J* = 4.7 Hz, 1 H), 2.30 (t, *J* = 7.5 Hz, 3 H), 1.96 (dt, *J* = 4.9, 2.5 Hz, 1 H), 1.68–1.25 (m, 14 H), 1.00 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 211.4 (s), 174.6 (s), 166.2 (d), 138.4 (d), 132.9 (d), 127.7 (d), 72.2 (d), 51.7 (d), 51.6 (q), 48.0 (d), 38.0 (t), 34.3 (t), 29.8 (t), 29.7 (t), 29.5 (t), 25.9 (t), 25.4 (t), 20.3 (t), 12.6 (q) ppm. MS (ESI): *m*/*z* (%) = 355 (100) [M + Na]$^+$. HRMS: calcd. for $C_{19}H_{30}O_4$ 332.2144; found 332.2133.

The methyl ester prepared as described above (11.1 mg, 0.034 mmol) was dissolved in HPLC-grade MTBE (0.4 mL), and HPLC-grade H_2O (0.043 mL, 2.4 mmol, 70 equiv.) was added. Solid-supported CAL-B (2 mg) was added to the resulting stirred solution, and the suspension was gently stirred at room temperature for 18 h. The enzyme was removed by filtration through a sintered glass funnel, and the solid was carefully washed with MeCN/MTBE (1:1; 4 × 2 mL). The filtrates were combined, and the solvents were evaporated under vacuum (***CAUTION:*** without heating). The residue was purified by silica gel column chromatography (hexane/EtOAc, 1:1, with 0.5% AcOH) to give pure acid **1** (6.7 mg, 90%) as a pale yellow oil. $[\alpha]_D^{20}$ = –129.1 (*c* = 0.11, EtOAc). IR (neat): $\tilde{\nu}$ = 3313, 2928, 1705, 1581, 1240, 968 cm^{-1}. ^{1}H NMR (300 MHz, CD_3CN): δ = 7.57 (dd, *J* = 5.7, 2.8 Hz, 1 H), 6.15 (dd, *J* = 5.7, 1.8 Hz, 1 H), 5.56 (ddd, *J* = 15.4, 6.0, 0.6 Hz, 1 H), 5.39 (ddd, *J* = 15.4, 8.8, 1.0 Hz, 1 H), 4.00 (quint, *J* = 5.4 Hz, 1 H), 3.8–3.7 (m, 2 H), 2.48–1.94 (m, 9 H), 1.75–1.15 (m, 10 H), 1.04 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 211.4 (s), 174.9 (s), 166.2 (d), 138.4 (d), 132.9 (d), 127.8 (d), 72.2 (d), 51.6 (q), 48.0 (d), 38.0 (t), 34.0 (t), 29.9 (t), 29.7 (t), 29.5 (t), 25.8 (t), 25.4 (t), 20.3 (t), 12.6 (q) ppm. MS (ESI): *m*/*z* (%) = 309 (100) [M + H]$^+$. HRMS: calcd. for $C_{18}H_{28}O_4$ 308.1988; found 308.1992.

Methyl (*S*,*E*)-9-[(*tert*-Butyldimethylsilyl)oxy]-11-[(1*S*,2*S*)-2-ethyl-5-oxocyclopent-3-en-1-yl]undec-10-enoate (20)

Julia–Lythgoe Olefination: Following the same procedure used for compound **18**, sulfone **5** (39.4 mg, 0.117 mmol) underwent the Julia–Lythgoe olefination reaction to give compound **S1** (23.6 mg, 60%) as a colourless oil. IR (neat): $\tilde{\nu}$ = 2929, 2360, 1736, 1461, 1273, 1123, 1074, 992, 836, 775, 668 cm^{-1}. ^{1}H NMR (300 MHz, CD_3CN): δ = 5.98 (m, 1 H), 5.77 (m, 1 H), 5.65–5.45 (m, 2 H), 4.76 (qd, *J* = 5.9, 5.3 Hz, 1 H), 4.47 (dd, *J* = 6.2, 2.3 Hz, 1 H), 4.33 (dd, *J* = 6.2, 2.4 Hz, 1 H), 4.15–4.08 (m, 1 H), 3.69–3.40 (m, 4 H), 3.17–3.08 (m, 1 H), 2.78–2.66 (m, 1 H), 2.30 (t, *J* = 7.4 Hz, 2 H), 2.10–1.97 (m, 2 H), 1.64–0.86 (m, 34 H), 0.12–0.09 (m, 6 H) ppm. ^{13}C NMR [75 MHz, $(CD_3)_2CO$]: δ = 173.8 (s), 138.0 (s), 137.6 (d), 135.6 (d), 135.6 (d), 131.8 (d), 130.9 (d), 129.2 (d), 129.0 (d), 133.3 (d), 133.0 (d), 132.8 (d), 132.6 (d), 101.8 (d), 99.4 (d), 83.1 (d), 79.4 (d), 74.9 (d), 74.9 (d), 60.5 (t), 60.1 (t), 52.2 (q), 51.8 (q), 50.8 (d), 49.2 (d), 49.1 (d), 38.2 (t), 33.5 (t), 29.1 (t), 28.9 (t), 28.9 (q), 28.7 (t), 22.0 (q), 21.4 (q), 20.7 (t), 20.6 (t), 19.5 (s), 16.5 (q), 13.8 (q), –5.0 (q), –5.4 (q) ppm. MS (ESI): *m*/*z* (%) = 534 (20) [M + Na]$^+$. HRMS: calcd. for $C_{29}H_{54}O_5Si$ 510.3741; found 510.3749.

EE Deprotection: Following the same procedure used for compound **18**, EE-protected cyclopentenol **S1** (39.4 mg, 0.077 mmol) gave free cyclopentenol **S2** (24.6 mg, 91%) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3502, 2931, 1713, 1472, 1358, 1360, 1254, 1077, 986, 840, 776 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.98–5.96 (m, 1 H), 5.78–5.76 (m, 1 H), 5.65–5.45 (m, 2 H), 4.52–4.49 (m, 1 H), 4.04 (q, *J* = 5.9 Hz, 1 H), 3.68 (s, 3 H), 2.77–2.51 (m, 3 H), 2.31 (t, *J* = 7.5 Hz, 2 H), 1.99 (m, 1 H), 1.65–1.22 (m, 14 H), 1.00–0.65 (m, 10 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3 (s), 139.6 (d), 135.2 (d), 133.3 (d), 131.6 (d), 76.5 (d), 73.4 (d), 51.4 (d), 49.3 (q), 48.7 (d), 38.5 (t), 34.1 (t), 29.7 (t), 29.3 (t), 29.2 (t), 29.1 (t), 25.9 (q), 25.2 (t), 24.9 (t), 19.0 (t), 18.2 (t), 12.7 (q), –4.3 (q), –4.8 (q) ppm. MS (ESI): *m*/*z* (%) = 421 (100)

$[M + H]^+$. HRMS: calcd. for $C_{25}H_{46}O_4Si$ 438.3165; found 438.3153.

DMP Oxidation: DMP (28.4 mg, 0.067 mmol, 1.2 equiv.) was added to a stirred solution of cyclopentenol ester **S2** (24.5 mg, 0.056 mmol) in dry CH_2Cl_2 (1.5 mL). After 30 min, Et_2O (6 mL) was added, and the resulting mixture was filtered through a short pad of silica gel, which was then thoroughly washed with *n*-hexane/Et_2O (9:1, 70 mL). The resulting mixture was concentrated under reduced pressure WITHOUT HEATING! The residue was purified by flash chromatography on silica gel. Elution with *n*-hexane/EtOAc (9:1) gave compound **20** (7.2 mg, 31%) as a pale yellow oil. $[a]_D^{20}$ = 23.6 (*c* = 0.275, EtOAc). IR (neat): $\tilde{\nu}$ = 3734, 2929, 2856, 2360, 1741, 1712, 1587, 1462, 1251, 1778, 1250, 1073, 836, 776, 668 cm^{-1}. ^1H NMR (300 MHz, CD_3CN): δ = 7.55 (dd, *J* = 5.7, 2.9 Hz, 1 H), 6.13 (dd, *J* = 5.7, 1.7 Hz, 1 H), 5.70–5.30 (m, 2 H), 4.17 (m, 1 H), 3.62 (s, 3 H), 3.2–2.9 (m, 2 H), 2.5–1.9 (m, 10 H), 1.75–1.3 (m, 9 H), 0.95 (t, *J* = 7.4 Hz, 3 H), 0.92–0.86 (m, 6 H), 0.07–0.00 (m, 6 H) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 211.3 (s), 174.6 (s), 166.2 (d), 138.2 (d), 132.8 (d), 127.7 (d), 73.5 (d), 51.8 (d), 51.6 (q), 48.0 (d), 38.8 (t), 34.3 (t), 29.8 (t), 29.7 (t), 29.5 (t), 26.0 (q), 25.6 (t), 25.5 (t), 20.2 (t), 18.6 (s), 12.8 (q), –4.4 (q), –4.8 (q) ppm. MS (ESI): *m*/*z* (%) = 437 (100) $[M + H]^+$. HRMS: calcd. for $C_{25}H_{44}O_4Si$ 436.3009; found 436.3015.

Methyl (*S*,*E*)-11-[(1*S*,2*S*)-2-ethyl-5-oxocyclopent-3-en-1-yl]-9-hydroxyundec-10-enoate (9-A_1-PhytoP-Me-Ester; 21): NH_4F (7 M aq.; 0.057 mL, 10 equiv.) was added to a stirred solution of silyl ether **20** (6.9 mg, 0.0196 mmol) in HPLC-grade CH_3OH (2 mL) in a PE test tube. After 4 h, a phosphate buffer (pH 6.8, 3 mL) was added. The layers were separated, and the aqueous phase was extracted with EtOAc (4 × 3 mL). The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure WITHOUT HEATING! The residue was purified by flash chromatography on silica gel. Elution with *n*-hexane/EtOAc (6:4) gave pure 9-A_1-PhytoP-Me-Ester **21** (1.4 mg, 31%) as a pale yellow oil. $[a]_D^{20}$ = 67.5 (*c* = 0.12, MeCN). IR (neat): $\tilde{\nu}$ = 3448, 2930, 1739, 1715, 1700, 1693, 1555, 1453 cm^{-1}. ^1H NMR (400 MHz, CD_3CN): δ = 7.57 (dd, *J* = 5.7, 2.3 Hz, 1 H), 6.10 (dd, *J* = 5.7, 2.0 Hz, 1 H), 5.63 (dd, *J* = 15.5, 6.2 Hz, 1 H), 5.52 (dd, *J* = 15.6, 7.7 Hz, 1 H), 3.98 (quint, *J* = 5.6 Hz, 1 H), 3.61 (s, 3 H), 2.75–2.55 (m, 3 H), 2.30 (t, *J* = 7.5 Hz, 2 H), 1.78–1.25 (m, 14 H), 1.00 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3CN): δ = 209.74 (s), 174.92 (s), 168.2 (d), 138.0 (d), 132.9 (d), 127.7 (d), 72.6 (d), 55.7 (d), 51.9 (q), 50.7 (d), 38.3 (t), 34.6 (t), 30.0 (t), 29.8 (t), 27.5 (t), 26.2 (t), 25.7 (t), 14.5 (t), 12.2 (q) ppm. MS (ESI): *m*/*z* (%) = 355 (100) $[M + Na]^+$. HRMS: calcd. for $C_{19}H_{30}O_4$ 332.2144; found 332.2135.

Supporting Information (see footnote on the first page of this article): Synthetic sequence for the conversion of **5** into **20**. Copies of the ^1H, ^{13}C, and DEPT NMR spectra are provided.

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[15] It should be emphasized that in all the phytoprostane syntheses reported to date, instead of the naturally occurring free acids, the corresponding methyl esters, are prepared. See ref.[1c], and references cited therein. See also: A. Vázquez-Romero, L. Cárdenas, E. Blasi, X. Verdaguer, A. Riera, *Org. Lett.* **2009**, *11*, 3104–3107 and W. Perlikowska, M. Mikolajczyk, *Tetrahedron: Asymmetry* **2011**, 22, 1767–1771.

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