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SYNTHESIS OF 14,15-EPOXYISOPROSTANE A_2 PHOSPHORYLCHOLINE†

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Abstract – The product of the copper-promoted allylic substitution of the 4-hydroxycyclopent-2-enyl ester with TMS-C≡CCH_2MgBr was converted to the cyclopentenone with the PMBO$(CH_2)_4$CH=$CHCH_2$ side chain. Aldol reaction of the enone with the epoxy aldehyde derived from (*E*)-oct-2-en-1-ol through the Sharpless asymmetric epoxidation gave the full structure of the isoprostane. Dehydration, conversion of the PMBOCH_2 moiety to CO_2H, and condensation with lysophosphorylcholine produced the title molecule.

The cross-conjugated dienone core and a (*Z*)-allylic side chain are unique characteristics of the epoxy-isoprostane phosphorylcholines (**1a** and **2a**)[1,2] and several prostaglandins shown in Figure 1. To construct such a dienone structure, we developed an aldol strategy using enone and aldehyde, and its efficiency was demonstrated by the syntheses of methyl ester of Δ^7-PGA_2 (**5**).[3] Later, the approach has been applied to the dienones **1a**–**4a** possessing the allylic side chain and some of their acetylene analogues.[4–6] The allylic and propargylic side chains on the key enones **8** and **9** have been constructed through palladium-catalyzed allylation of the monoester of 4-cyclopentene-1,3-diol (**6**) with a malonate anion, which proceeds efficiently under the modified conditions[6] to produce **7** in good yield (Scheme 1).

Recently, we communicated a Hg-free preparation of the propargylic Grignard reagents including **11**,[7] which had been prepared by using a mercury salt as a catalyst. Furthermore, we found regio- and stereoselective allylic substitution of monoester **6** (R = Me, *t*-Bu) with the copper complex derived from

† This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

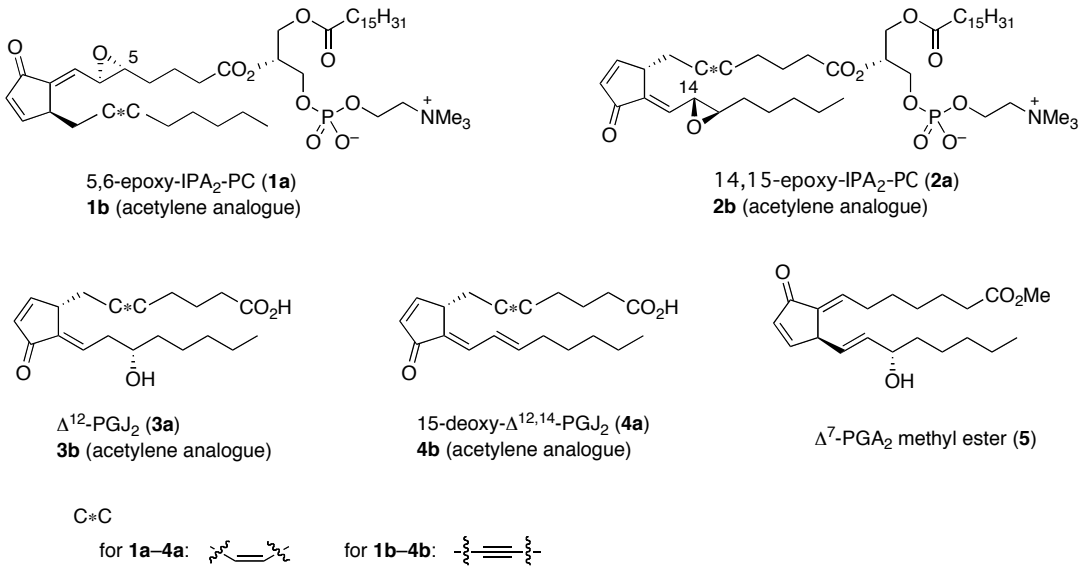
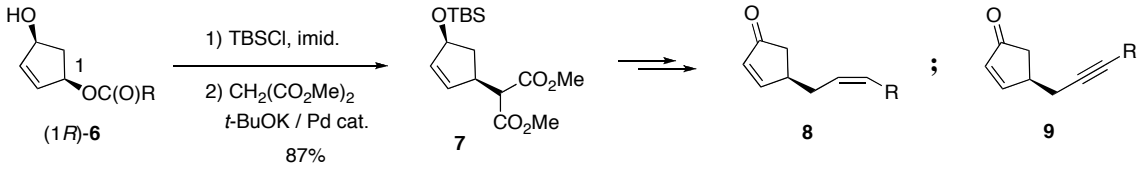
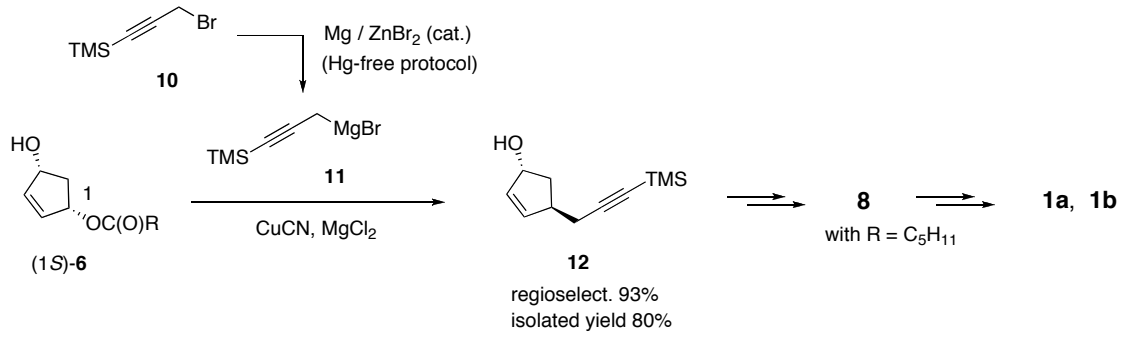


Figure 1. Isoprostanes and prostaglandins with the cross-conjugated dienone structure.[a]
[a] IPA_2-PC, isoprostane A_2 phosphorylcholine.



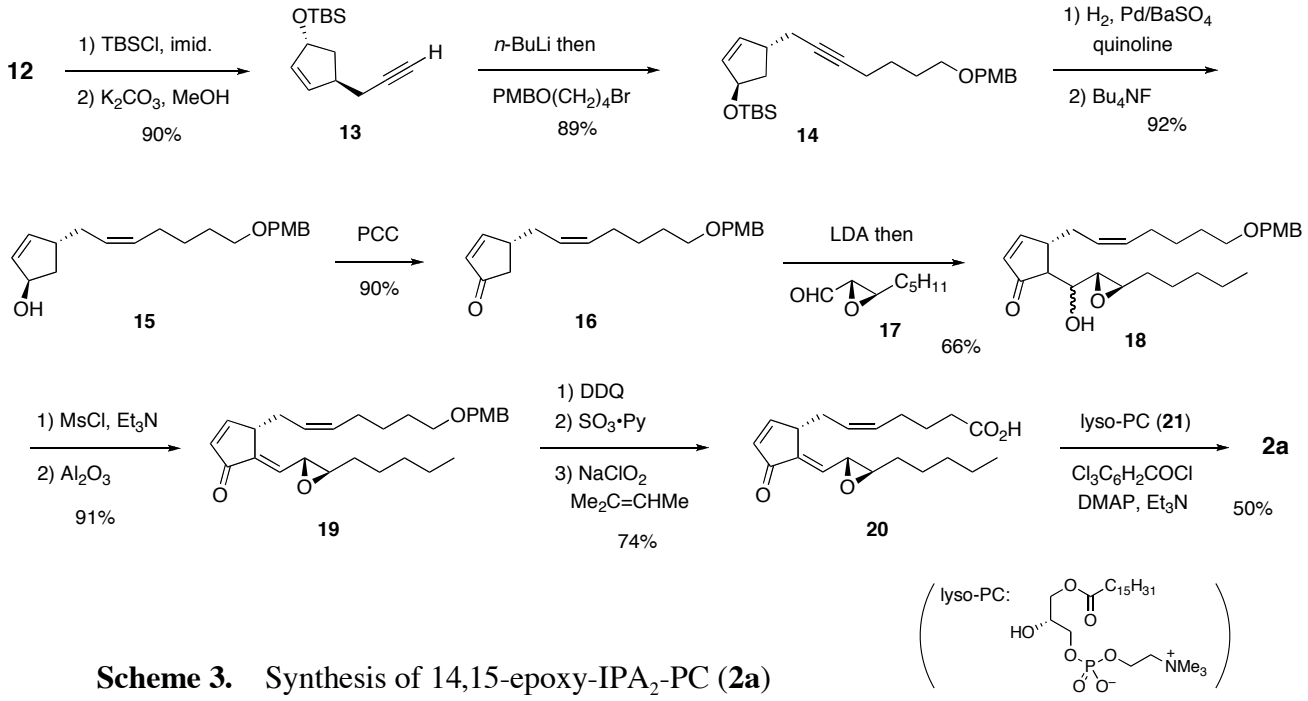
Scheme 1. Preparation of enones **8** and **9** through Pd-catalyzed allylic substitution of monoester **6** with malonate anion



Scheme 2. Preparation of acetylene **12** through Cu-promoted allylic substitution of monoester **6** with the propargyl-MgBr (**11**)

anion **11** and CuCN in the presence of excess $MgCl_2$ (Scheme 2). The product **12** was utilized for synthesis of **1a** and **1b** through enone **8** (R = C_5H_{11}). Herein, we describe another utilization of **12** for synthesis of 14,15-epoxy-IPA$_2$-PC (**2a**)[2] through the key enone **16**. In addition, **16** is also the intermediate leading to Δ^{12}-PGJ$_2$ (**3a**) and the deoxy derivative **4a**.

First, alcohol **12** was protected as the TBS ether and the TMS group at the acetylene carbon was removed to produce **13** in 90% yield (Scheme 3). The PMBO$(CH_2)_4$ group was attached to the acetylene terminus by alkylation with PMBO$(CH_2)_4$Br to afford **14** in good yield. Lindlar hydrogenation of **14** and subsequent deprotection of the TBS group produced alcohol **15**, which upon oxidation with PCC furnished the key enone **16** (= **8** with PMBO$(CH_2)_4$ as R).

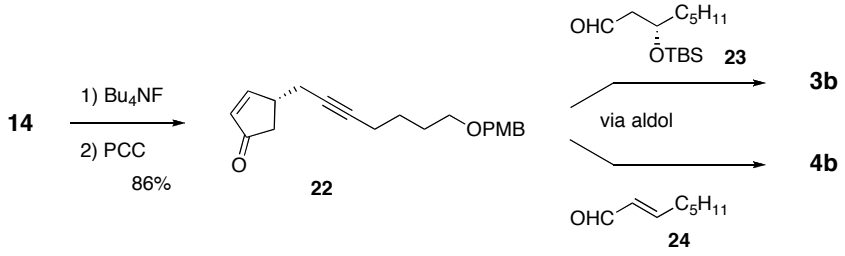


Scheme 3. Synthesis of 14,15-epoxy-IPA$_2$-PC (**2a**)

Optically active epoxy aldehyde **17**, the aldol partner, was prepared from (*E*)-oct-2-en-1-ol by the Sharpless epoxidation[8] followed by oxidation with SO_3•pyridine. Aldol reaction of **16** with the aldehyde was carried out at –78 °C to afford a mixture of anti and syn aldols **18** in a 2 : 1 ratio by TLC analysis. Without separation, the mixture was converted to the mesylates, which upon exposure to Al_2O_3 produced the cross-conjugated dienone **19**. The stereoisomer at the newly formed olefin was not detected by ^{1}H NMR spectroscopy. The PMB group was removed with DDQ and the resulting alcohol was converted to 14,15-epoxy-IPA$_2$ (**20**) by the two-step oxidation. Finally, condensation of acid **20** with lyso-PC (**21**) according to the protocol[9] using the Yamaguchi reagent furnished **2a** in 50% yield.

Similarly, the synthetic intermediate **14** was converted into enone **22** with the propargylic side chain on the cyclopentane ring (corresponding to acetylene **9**) as delineated in Scheme 4. The enone was

previously converted to acetylene analogues **3b** and **4b**.[6]



Scheme 4. Synthesis of the key intermediate **22** leading to **3b** and **4b**

In summary, enone **16** was synthesized by a new route through **12** and converted to 14,15-epoxy-IPA_2-PC (**2a**), in which aldol reaction with epoxy aldehyde **17** played a key role for construction of the cross-conjugated dienone structure of **2a**.

EXPERIMENTAL

General. Infrared (IR) spectra are reported in wave numbers (cm^{-1}). The ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ (δ = 0 ppm) and the center line of $CDCl_3$ triplet (δ = 77.1 ppm) as internal standards, respectively. Signal patterns are indicated as br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (*J*) are given in hertz (Hz). In some cases chemical shifts of carbons accompany plus (for C and CH_2) and minus (for CH and CH_3) signs of APT experiments. After the reactions, organic extracts were concentrated by using a rotary evaporator and residues were purified by chromatography on silica gel (Merck, silica gel 60).

Acetylene 13. A solution of alcohol **12** (> 95% ee, 110 mg, 0.57 mmol), TBSCl (130 mg, 0.86 mmol), and imidazole (80 mg, 1.14 mmol) in DMF (6 mL) was stirred at rt for 1 h and diluted with saturated aqueous $NaHCO_3$ and hexane with vigorous stirring. The layers were separated, and the aqueous layer was extracted with hexane three times. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography to give the TBS ether of **12** (164 mg, 93%). A mixture of the TBS ether and K_2CO_3 (215 mg, 1.56 mmol) in MeOH (5 mL) was stirred at rt for 3 h and diluted with saturated aqueous NH_4Cl and Et_2O with vigorous stirring. The phases were separated, and the aqueous phase was extracted with Et_2O three times. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography to produce acetylene **13** (121 mg, 90% from **12**): $[\alpha]_D^{27}$ +142 (*c* 0.166, $CHCl_3$); IR (neat) 3313, 1252, 1070, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6 H), 0.89 (s, 9 H), 1.89–1.95 (m, 3 H), 2.22 (dd, *J* = 7, 3 Hz, 2 H), 3.04–3.16 (m, 1 H), 4.86–5.00 (m, 1 H), 5.79 (dt, *J* = 5, 1 Hz, 1 H), 5.84–5.92 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.5 (–), 18.4 (+), 24.7 (+), 26.0 (–), 40.0 (+), 43.5 (–), 68.9 (+), 77.5 (–), 83.0 (+), 134.7

(–), 136.7 (–).

Acetylene 14. To a solution of acetylene **13** (150 mg, 0.634 mmol) in THF (4 mL) at –78 ºC was added *n*-BuLi (0.35 mL, 2.50 M in hexane, 0.88 mmol) dropwise. After 30 min of stirring at –78 ºC, HMPA (1.5 mL) and a solution of $PMBO(CH_2)_4Br$ (210 mg, 0.77 mmol) in THF (1 mL) were added. The solution was stirred at –78 ºC for 2 h, gradually warmed to rt over 9 h, and diluted with saturated aqueous NH_4Cl and hexane. The organic layer was separated and the aqueous layer was extracted with hexane twice. The combined organic layers were dried over $MgSO_4$ and concentrated to leave an oil, which was purified by chromatography to afford **14** (242 mg, 89%): $[\alpha]_D^{24}$ +105 (*c* 0.762, $CHCl_3$); IR (neat) 1513, 1249, 1069, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.89 (s, 9 H), 1.48–1.75 (m, 4 H), 1.85–1.92 (m, 2 H), 2.11–2.19 (m, 4 H), 2.96–3.08 (m, 1 H), 3.45 (t, *J* = 7 Hz, 2 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 4.85–4.99 (m, 1 H), 5.72–5.77 (m, 1 H), 5.84–5.90 (m, 1 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.25 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.5, 18.6, 25.1, 25.7, 25.9, 26.1, 28.9, 40.1, 44.1, 55.3, 69.7, 72.6, 77.7, 78.8, 80.7, 113.8, 129.3, 130.7, 134.3, 137.3, 159.2.

Alcohol 15. A mixture of acetylene **14** (270 mg, 0.63 mmol), quinoline (0.04 mL), and $Pd/BaSO_4$ (10 mg) in MeOH (8 mL) was stirred under argon for 20 min, and hydrogen was flushed into the flask. After 20 min of vigorous stirring, hydrogen uptake was stopped. The mixture was diluted with hexane and filtered through a pad of Celite. The filtrate was concentrated and the residue was passed through a short pad of silica gel to afford the TBS ether of **15** (266 mg, 98%): $[\alpha]_D^{25}$ +91.4 (*c* 0.672, $CHCl_3$); IR (neat) 1513, 1249, 1041, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.89 (s, 9 H), 1.34–1.47 (m, 2 H), 1.54–1.66 (m, 2 H), 1.72–1.90 (m, 2 H), 1.94–2.14 (m, 4 H), 2.84–2.96 (m, 1 H), 3.43 (t, *J* = 6 Hz, 2 H), 3.78 (s, 3 H), 4.42 (s, 2 H), 4.86–4.94 (m, 1 H), 5.34–5.46 (m, 2 H), 5.66–5.73 (dm, *J* = 5 Hz, 2 H), 5.81–5.88 (dm, *J* = 5 Hz, 1 H), 6.87 (d, *J* = 8 Hz, 2 H), 7.25 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.5 (–), 18.4, 26.0 (+), 26.1 (–), 26.3 (+), 27.2 (+), 29.5 (+), 33.3 (+), 40.2 (+), 44.4 (–), 55.3 (–), 70.1 (+), 72.6 (+), 77.7 (–), 113.8 (–), 128.0 (–), 129.3 (–), 130.8 (–), 133.4 (–), 138.3 (–), 159.2 (+). To an ice-cold solution of the above TBS ether (115 mg, 0.27 mmol) in THF (3 mL) was added *n*-Bu_4NF (0.42 mL, 0.95 M in THF, 0.40 mmol). The solution was stirred at rt for 1.5 h and diluted with saturated aqueous NH_4Cl and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc three times. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to leave an oil, which was purified by chromatography to afford alcohol **15** (80 mg, 94%): $[\alpha]_D^{25}$ +116 (*c* 0.42, $CHCl_3$); IR (neat) 3384, 1513, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35–1.48 (m, 2 H), 1.54–1.67 (m, 2 H), 1.74–1.92 (m, 2 H), 1.96–2.16 (m, 4 H), 2.84–2.98 (m, 1 H), 3.43 (t, *J* = 7 Hz, 2 H), 3.80 (s, 3 H), 4.42 (s, 2 H), 4.80–4.88 (m, 1 H), 5.28–5.47 (m, 2 H), 5.82 (dt, *J* = 5, 2 Hz, 1 H), 5.92 (dd, *J* = 5, 2 Hz, 1 H), 6.87 (d, *J* = 8 Hz, 2 H), 7.25 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 27.2, 29,4, 33.1, 40.1, 44.3, 55.3, 70.0, 72.6, 77.2, 113.8, 127.6, 129.3, 130.8, 131.0,

133.0, 139.7, 159.2.

Enone 16. A mixture of alcohol **15** (80 mg, 0.25 mmol) and PCC (82 mg, 0.38 mmol) in CH_2Cl_2 (3 mL) was stirred vigorously for 1 h and diluted with Et_2O. The resulting mixture was filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by chromatography to furnish enone **16** (69 mg, 90%). The ^1H and ^{13}C NMR spectra of **16** were consistent with those reported previously.[6]

Dienone 19. To a solution of *i*-Pr_2NH (0.26 mL, 1.86 mmol) in THF (12 mL) at 0 ºC was added *n*-BuLi (0.80 mL, 2.0 M in hexane, 1.60 mmol). The solution was stirred at 0 ºC for 20 min, and then cooled to –78 ºC. A solution of enone **16** (250 mg, 0.80 mmol) in THF (2 mL) was added to the LDA solution dropwise, and the solution was stirred for 20 min. Then, a solution of epoxy aldehyde **17** (226 mg, 1.59 mmol) in THF (2 mL) was added to the solution. After 20 min at –78 ºC, the solution was poured into a flask containing saturated aqueous NH_4Cl and Et_2O with vigorous stirring. The phases were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated to afford a mixture of anti and syn aldols **18** (2 : 1 ratio by TLC), which was subjected to chromatography to afford a mixture of aldol products **18** (240 mg, 66%) as an oil: ^1H NMR (300 MHz, $CDCl_3$) (characteristic peaks only) δ 3.45 (t, *J* = 6 Hz, 2 H), 3.50–3.60 (m, 1 H for *anti*-), 3.65 (br s, 1 H for *anti*-), 3.80 (s, 3 H), 4.42 (s, 2 H), 5.32–5.44 (m, 1 H), 5.48–5.60 (m, 1 H), 6.16 (dd, *J* = 6, 2 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.25 (d, *J* = 9 Hz, 2 H), 7.66 (dd, *J* = 6, 2 Hz, 1 H). To an ice-cold solution of **18** (240 mg, 0.526 mmol) and Et_3N (0.90 mL, 6.5 mmol) in CH_2Cl_2 (5 mL) was added MsCl (0.20 mL, 2.6 mmol). After 45 min of stirring at 0 ºC, the solution was diluted with saturated aqueous $NaHCO_3$ and EtOAc. The phases were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated to furnish the corresponding mesylates, which was subjected to the next reaction without further purification: ^1H NMR (300 MHz, $CDCl_3$) (characteristic peaks only) δ 3.45 (t, *J* = 6 Hz, 2 H), 3.80 (s, 3 H), 4.42 (s, 2 H), 5.30–5.43 (m, 1 H), 5.48–5.60 (m, 1 H), 6.16 (dd, *J* = 6, 2 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.25 (d, *J* = 9 Hz, 2 H), 7.64 (dd, *J* = 6, 2 Hz, 1 H). To a slurry of alumina (ICN, N–Super I, 540 mg, 5.30 mmol) in CH_2Cl_2 (3 mL) was added a solution of the mesylates in CH_2Cl_2 (2 mL). The mixture was stirred vigorously at rt for 6 h, and filtered through a pad of Celite. The filtrate was concentrated and the residue was subjected to chromatography to afford dienone **19** (210 mg, 91% from **16**): ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7 Hz, 3 H), 1.20–1.75 (m, 12 H), 1.97 (q, *J* = 6 Hz, 2 H), 2.22–2.40 (m, 1 H), 2.48–2.64 (m, 1 H), 2.99 (dt, *J* = 1.5, 5 Hz, 1 H)), 3.37 (dd, *J* = 8, 1.5 Hz, 1 H), 3.42 (t, *J* = 6 Hz, 2 H), 3.62–3.70 (m, 1 H), 3.80 (s, 3 H), 4.42 (s, 2 H), 5.28–5.40 (m, 1 H), 5.44–5.56 (m, 1 H), 6.19 (d, *J* = 8 Hz, 1 H), 6.34 (dd, *J* = 6, 2 Hz, 1 H), 6.87 (d, *J* = 9 Hz, 2 H), 7.25 (d, *J* = 9 Hz, 2 H), 7.52 (dd, *J* = 6, 2 Hz, 1 H).

14,15-Epoxy-IPA$_2$ (20). To an ice-cold solution of dienone **19** (110 mg, 0.251 mmol) in CH_2Cl_2 (4.7 mL) and H_2O (0.3 mL) was added DDQ (85 mg, 0.374 mmol). The mixture was stirred vigorously for 45 min

and diluted with saturated aqueous $NaHCO_3$ and Et_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O twice. The combined organic fractions were dried over $MgSO_4$ and concentrated to obtain an yellow residue, which was purified by chromatography to furnish the corresponding alcohol (71 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7 Hz, 3 H), 1.2–1.7 (m, 13 H), 2.02 (q, *J* = 7 Hz, 2 H), 2.31 (dt, *J* = 15, 8 Hz, 1 H), 2.55 (dt, *J* = 15, 6 Hz, 1 H), 2.98 (dt, *J* = 1.5, 5 Hz, 1 H), 3.37 (dd, *J* = 8, 1.5 Hz, 1 H), 3.63 (t, *J* = 6 Hz, 2 H), 3.57–3.72 (m, 1 H), 5.28–5.41 (m, 1 H), 5.46–5.57 (m, 1 H), 6.21 (d, *J* = 8 Hz, 1 H), 6.35 (dd, *J* = 6, 2 Hz, 1 H), 7.54 (dd, *J* = 6, 2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 25.68, 25.75, 27.1, 31.7, 31.9, 32.0, 32.4, 43.3, 55.3, 60.6, 62.7, 124.9, 131.5, 132.9, 134.6, 140.8, 161.9, 195.9. To an ice-cold solution of the above alcohol (15 mg, 0.047 mmol) and Et_3N (0.065 mL, 0.47 mmol) in CH_2Cl_2 (3 mL) and DMSO (1 mL) was added SO_3•pyridine (23 mg, 0.144 mmol). The solution was stirred vigorously at the same temperature for 2 h and poured into cold water and Et_2O. The resulting mixture was stirred vigorously at rt for 20 min. The phases were separated and the aqueous layer was extracted with Et_2O twice. The combined organic layers were dried over $MgSO_4$ and concentrated to obtain a residue, which was purified by chromatography to afford the corresponding aldehyde as (13 mg, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7 Hz, 3 H), 1.2–1.8 (m, 10 H), 2.04 (q, *J* = 6 Hz, 2 H), 2.24–2.38 (m, 1 H), 2.43 (dt, *J* = 1.5, 7 Hz, 2 H), 2.51–2.62 (m, 1 H), 2.97 (dt, *J* = 2, 5 Hz, 1 H), 3.36 (dd, *J* = 8, 2 Hz, 1 H), 3.64–3.72 (m, 1 H), 5.32–5.54 (m, 2 H), 6.22 (d, *J* = 8 Hz, 1 H), 6.35 (dd, *J* = 6, 2 Hz, 1 H), 7.52 (dd, *J* = 6, 2 Hz, 1 H), 9.76 (t, *J* = 1.5 Hz, 1 H): ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.3, 23.0, 26.1, 27.0, 32.1, 32.2, 32.4, 43.6, 43.7, 55.6, 61.0, 126.3, 131.9, 132.2, 135.1, 141.0, 162.1, 196.2, 202.6. To an ice-cold slurry of the above aldehyde (13 mg, 0.041 mmol) and 2-methyl-2-butene (0.044 mL, 0.414 mmol) in *t*-BuOH (0.53 mL) and phosphate buffer of pH 7 (0.25 mL) was added a aqueous solution of $NaClO_2$ (7 mg, 0.062 mmol, purity 80%) in H_2O (0.2 mL). After 45 min of stirring, brine and EtOAc were added to the mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated to afford an oily residue, which was purified by chromatography to give acid **20** (13 mg, 95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7 Hz, 3 H), 1.2–1.8 (m, 10 H), 1.98–2.14 (m, 2 H), 2.24–2.38 (m, 3 H), 2.48–2.64 (m, 1 H), 2.97 (dt, *J* = 1.5, 5 Hz, 1 H), 3.36 (dd, *J* = 8, 1.5 Hz, 1 H), 3.63–3.73 (m, 1 H), 5.32–5.58 (m, 2 H), 6.22 (d, *J* = 8 Hz, 1 H), 6.36 (dd, *J* = 6, 2 Hz, 1 H), 7.53 (dd, *J* = 6, 2.5 Hz, 1 H).

Methyl Ester of 14,15-IPA$_2$. The above acid **20** was converted to the methyl ester with excess CH_2N_2 in Et_2O at 0 °C for 30 min in 96% to confirm the structure by ^{1}H NMR spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7 Hz, 3 H), 1.2–1.8 (m, 10 H), 1.98–2.12 (m, 2 H), 2.24–2.48 (m, 3 H), 2.50–2.64 (m, 1 H), 2.97 (dt, *J* = 2, 6 Hz, 1 H), 3.36 (dd, *J* = 8, 2 Hz, 1 H), 3.62–3.72 (m, 1 H), 3.67 (s, 3 H) 5.33–5.56 (m, 2 H), 6.22 (d, *J* = 9 Hz, 1 H), 6.35 (dd, *J* = 6, 2 Hz, 1 H), 7.53 (dd, *J* = 6, 2 Hz, 1 H).

14,15-Epoxy-IPA$_2$-PC (2a). To a solution of lyso-PC (**21**) (10 mg, 0.020 mmol), 14,15-epoxyisoprostane A$_2$ **(20)** (20 mg, 0.060 mmol), DMAP (44 mg, 0.36 mmol), and Et_3N (0.084 mL, 0.60 mmol) in CH_2Cl_2 (2 mL) was added 2,4,6-$Cl_3C_6H_2COCl$ (0.019 mL, 0.12 mmol). After being conducted at rt for 26 h, the reaction was quenched by addition of a few drops of H_2O. The mixture was concentrated, and the residue was subjected to chromatography (SiO_2, CH_2Cl_2/MeOH) to give a mixture of **2a** and DMAP. The mixture was then subjected to a reversed phase chromatography by using Et_2O/CH_2Cl_2 as an eluent to separate **2a** (8 mg, 50%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7 Hz, 6 H), 1.1–1.7 (m, 38 H), 1.9–2.8 (m, 6 H), 2.94–3.02 (m, 1 H), 3.20–3.50 (m, 10 H), 3.60–4.45 (m, 9 H), 5.18–5.28 (m, 1 H), 5.30–5.60 (m, 2 H), 6.21 (d, *J* = 8 Hz, 1 H), 6.35 (dd, *J* = 6, 2 Hz, 1 H), 7.54 (dd, *J* = 6, 2 Hz, 1 H).

Alcohol Derivative of 14. To an ice-cold solution of the TBS ether **14** (236 mg, 0.551 mmol) in THF (6 mL) was added *n*-Bu_4NF (1.0 mL, 0.95 M in THF, 0.95 mmol). The solution was stirred at rt for 2 h and diluted with saturated aqueous NH_4Cl and EtOAc. The organic layer was separated, and the aqueous layer was extracted with EtOAc three times. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to leave an oil, which was purified by chromatography to afford the corresponding alcohol (156 mg, 90%): $[\alpha]_D^{23}$ +89 (*c* 0.438, $CHCl_3$); IR (neat) 3398, 1513, 1248, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48-1.75 (m, 4 H), 1.88–1.94 (m, 2 H), 2.10–2.21 (m, 4 H), 2.98–3.10 (m, 1 H), 3.45 (t, *J* = 7 Hz, 2 H), 3.79 (s, 3 H), 4.42 (s, 2 H), 4.84–4.92 (m, 1 H), 5.83–5.88 (m, 1 H), 5.92–5.97 (m, 1 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 7.25 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 24.9, 25.8, 28.9, 39.9, 43.9, 55.3, 69.6, 72.6, 77.3, 78.5, 80.9, 113.8, 129.3, 130.7, 133.8, 138.8, 159.2.

Enone 22. A mixture of the above alcohol (50 mg, 0.16 mmol) and PCC (52 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was stirred vigorously for 1 h and diluted with Et_2O. The resulting mixture was filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by chromatography to furnish enone **22** (47 mg, 95%). The ^{1}H and ^{13}C NMR spectra of **22** were consistent with those reported previously.[6]

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