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Synthesis of phosphorylcholines possessing 5,6- or 14,15-epoxyisoprostane A_2 at *sn*-2 position

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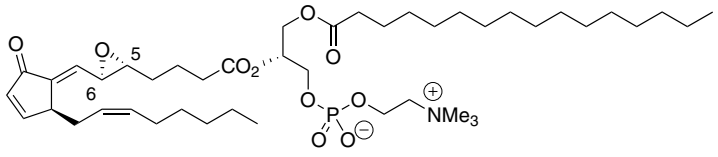
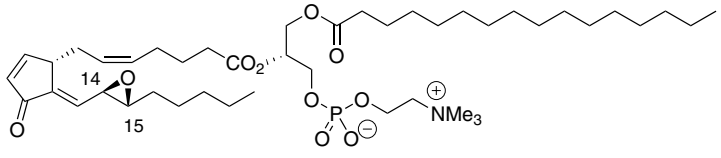
Abstract—Use of the $PMBOCH_2$ group (PMB: *p*-$MeOC_6H_4CH_2$) as a substitute of CO_2H provided high level of reproducibility and efficiency in construction of the full structure of 5,6-epoxyisoprostane A_2. After the construction, the $PMBOCH_2$ group was converted to CO_2H by using (1) DDQ, (2) SO_3·pyridine and (3) $NaClO_2$ at pH 7. The acid, thus synthesized, was condensed with lyso-PC to furnish one of the title compounds. Similarly, 14,15-regioisomer was synthesized.

A series of planar structures of phosphorylcholines possessing epoxyisoprostane A_2 (Fig. 1) or E_2 has been isolated by the Berliner's group in their study of elucidating compounds responsible for atherosclerosis.[1,2] These phosphorylcholines induce endothelial cell to synthesize IL-8 and MCP-1 in a dose-dependent fashion between 0.1 and 5 μM concentrations. It is also reported that these compounds are potent activators of PPARα.

Recently, we reported a synthesis of 5,6-epoxyisoprostane A_2 phosphorylcholine (**1**), for the first time (Scheme 1), and determined the relative stereostructure as depicted in Figure 1,[3] while a simpler model diastereomer[4a] and, quite recently, a mixture of 5,6-epoxyisoprostanes A_2 and E_2[4b] have been synthesized by another group, who used the CH_2OPMB group as the carboxylic acid equivalent in the latter synthesis.



2-(5,6-epoxyisoprostane A_2)phosphorylcholine (**1**)



2-(14,15-epoxyisoprostane A_2)phosphorylcholine (**2**)

Figure 1. Two regioisomeric phosphorylcholines possessing the epoxyisoprostane A_2 moiety.

We have also chosen the same group in the present synthesis. 5,6-Epoxyisoprostane A_2 intermediate **8** in our synthesis was constructed through aldol reaction[5] between the γ-substituted cyclopentenone **5** and the

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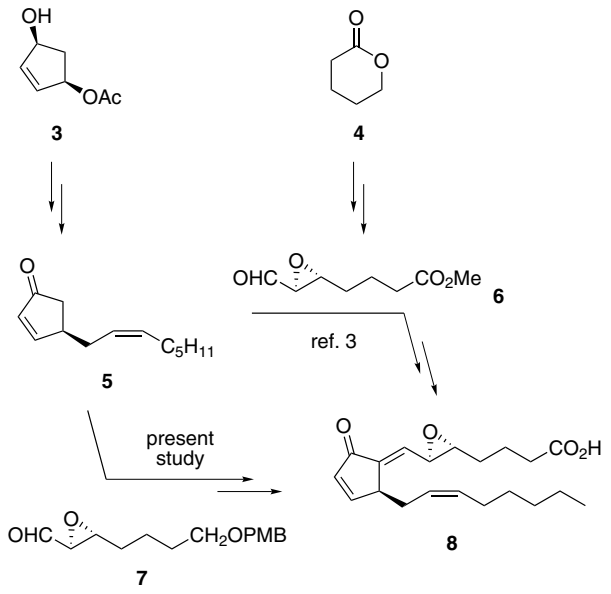


Scheme 1. Two routes leading to 5,6-epoxyisoprostane A_2 (**8**).

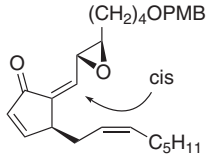
α-chain aldehyde **6** possessing the necessary epoxy function. Of the two partners, cyclopentenone **5** was synthesized from **3**[6] by a method developed by us, while epoxy aldehyde **6** was prepared starting from δ-valerolactone (**4**) according to the method of Kukhar.[7] However, the synthesis of **6** in our experimentation suffered from low reproducibility due to the titanium-assisted side reaction of the CO_2Me moiety with the epoxy function in the asymmetric epoxidation of the corresponding allylic alcohol and in the accompanying isolation step.[8] Attempted modification of work-up by us was fruitless. Moreover, extremely unstable nature of the epoxy aldehyde **6** obtained by oxidation of the epoxy alcohol imposed high level of discipline for purification before subjecting to the aldol reaction.

On the other hand, application of the strategy to synthesis of 11,12-epoxy- and 14,15-epoxyisoprostanes A_2 phosphorylcholines obviously requires an aldol-compatible equivalent to the CO_2R that, after the aldol reaction, is convertible to the key acid (i.e., epoxyisoprostane A_2) under mild conditions so that the highly reactive olefin-conjugated epoxide moiety can tolerate.

We selected a PMB ether **7**[9] as an alternative of **6** (Scheme 1), though the compatibility of the epoxide with slightly acidic conditions for PMB deprotection with DDQ and for oxidation of aldehyde to acid with $NaClO_2$ in a transformation of the CH_2OPMB into CO_2H had not been secured when we started the investigation. In this letter, we describe results of our study along this line and application of the PMB manipulation to synthesis of 14,15-regioisomer (**2**).

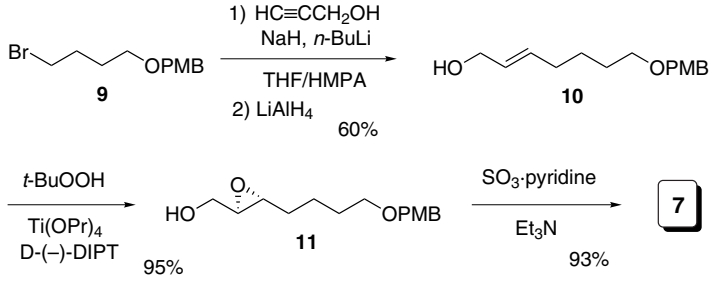
Synthesis of the epoxy aldehyde **7** delineated in Scheme 2 was executed uneventfully. Thus, reaction of bromide **9** with the dianion derived from propargyl alcohol (NaH then *n*-BuLi) followed by reduction afforded allylic alcohol **10** in 60% yield. Sharpless[10] epoxidation of **10** using D-(−)-DIPT as a chiral ligand proceeded cleanly, and the epoxy alcohol **11** was isolated easily after alkaline hydrolysis of DIPT followed by chromatography. Finally, oxidation of **11** with SO_3·pyridine produced **7**[11] in good yield.

With the new epoxy aldehyde **7** in hand, synthesis of **1** was investigated and results are presented in Scheme 3. Cyclopentenone **5** was synthesized from **3** (>95% ee) by using the previous procedure.[3] Aldol reaction of the enolate anion derived from **5** and LDA with aldehyde **7** at −78 °C afforded aldol adduct **12** in 78% yield, which was a mixture of anti and syn stereoisomers in ca. 2:1 by TLC. Without separation, the aldol mixture was transformed into the mesylate, which underwent elimination in the presence of alumina[12] to furnish dienone **13**[11] in 84% yield in two steps. The C(7)-H of the undesired stereoisomer **17** possessing the cis olefin was not detected at the expected[13] 0.5 ppm up field region in the ^1H NMR spectrum of the crude dienone **13**.

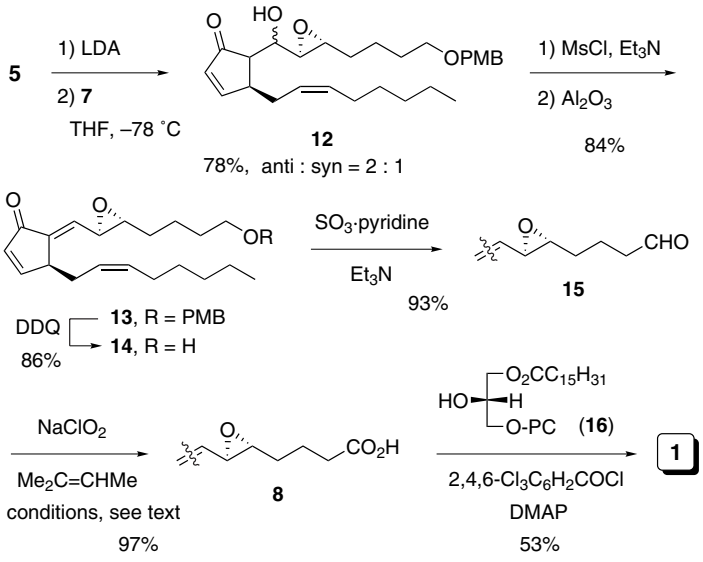


17: cis isomer of **13**

The PMB group in dienone **13** was cleaved with DDQ in wet CH_2Cl_2 at 0 °C for 45 min to afford alcohol **14**[11] in 86% yield. Although the conditions were slightly acidic (pH ca. 4–5), the epoxide moiety was, to our delight, not at all destroyed. Oxidation of alco-



Scheme 2. Preparation of epoxyaldehyde **7**.

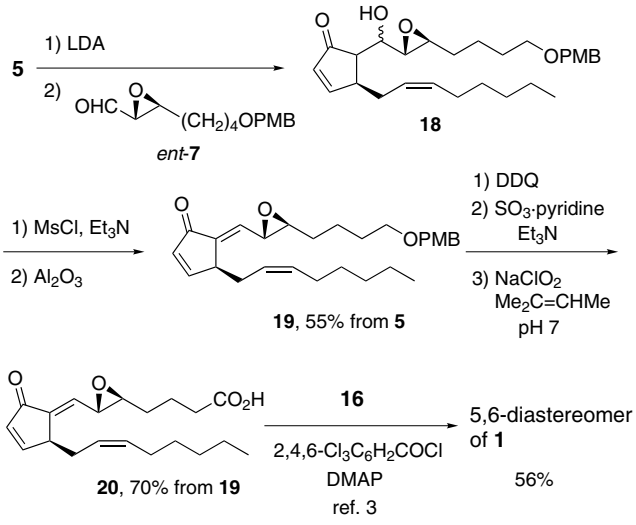


Scheme 3. Synthesis of **1**.

hol **14** to aldehyde **15**[11] was investigated with SO_3·pyridine due to mildness and simplicity of the operation. This reagent with Et_3N in CH_2Cl_2/DMSO at 0 °C for 2 h proceeded cleanly by TLC. Aldehyde **15** isolated in 93% yield was then subjected to further oxidation with $NaClO_2$. However, the oxidation carried out under the standard conditions[14] (pH 3.6) at 0 °C for 1 h afforded a mixture of products containing the desired acid **8** as a minor product. The oxidation with $NaClO_2$ requires acidic conditions in theory. Nevertheless, the reaction was studied under the neutral conditions at pH 7. Fortunately, the reaction took place quite cleanly without delay in reaction to furnish acid **8**[11] in 97% yield after chromatography. Finally, the acid was condensed with optically active lyso-PC (**16**) by using the highly efficient reagent system[3] (2,4,6-$Cl_3C_6H_2COCl$ and DMAP) in CH_2Cl_2 at room temperature for 36 h to afford a mixture of **1** and DMAP after normal phase chromatography. The mixture was subsequently subjected to reverse phase chromatography to furnish the title compound **1** in 53% yield. The ^1H NMR spectrum of **1** was identical with that synthesized previously.[3]

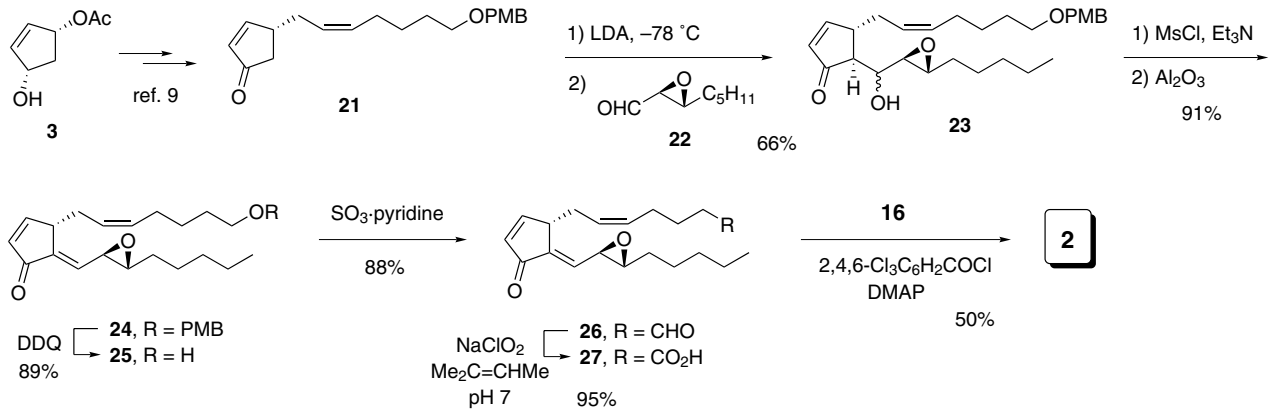
Similarly, enantiomer of **7** (i.e., *ent*-**7**) was subjected to aldol reaction with **5** (Scheme 4). Aldol **18**, thus obtained, was converted into dienone **19** in 55% yield from **5**. Conversion of the C(1) carbon to CO_2H by using the procedure developed above was executed quite efficiently to furnish **20** in 70% yield. This isoprostane was transformed into 5,6-diastereomer of **1** in 56% yield.[3,11]

The PMB strategy is highlighted by the synthesis of 14,15-epoxyisoprostane A_2 phosphorylcholine (**2**),[2] which is summarized in Scheme 5. The key cyclopentenone **21** was synthesized again from **3** (>95% ee) by the method previously reported for synthesis of Δ^{12}-PGJ_2.[9] Aldol reaction with epoxy aldehyde **22**, obtained by asymmetric epoxidation of the corresponding allylic alcohol followed by oxidation with SO_3·pyridine, afforded aldol **23** in 66% yield, which was transformed into the cross-conjugated dienone **24**[11] stereoselectively in 91% yield. Transformation of **24** to 14,15-epoxyisoprostane A_2 (**27**)[11] by the method mentioned above proceeded successfully in good overall yield. Finally, the acid was subjected to condensation with lyso-PC (**16**) using 2,4,6-$Cl_3C_6H_2COCl$/DMAP to produce **2** in 50% yield after chromatography.



Scheme 4. Synthesis of 5,6-diastereomer of **1**.

In summary, we have utilized the $PMBOCH_2$ group as the successful substituent of CO_2H in the synthesis of **1** and the diastereomer of **1**. Moreover, the PMB method was applied to the first synthesis of 14,15-regioisomer **2**. In addition, we found oxidation of the aldehyde to acid with $NaClO_2$ proceeds unexpectedly under the neutral conditions, which would be useful in organic synthesis of acid labile compounds.



Scheme 5. Synthesis of **2**.

Acknowledgements

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11. ^{1}H NMR ($CDCl_3$) spectra: compound **7** (300 MHz) δ 1.50–1.78 (m, 6H), 3.13 (dd, $J = 6$, 2 Hz, 1H), 3.22 (dt, $J = 2$, 6 Hz, 1H), 3.45 (t, $J = 6$ Hz, 2H), 3.80 (s, 3H), 4.43 (s, 2H), 6.88 (d, $J = 9$ Hz, 2H), 7.25 (d, $J = 9$ Hz, 2H), 9.00 (d, $J = 6$ Hz, 1H); compound **13** (300 MHz) δ 0.88 (t, $J = 7$ Hz, 3H), 1.14–1.40 (m, 6H), 1.46–1.78 (m, 6H), 1.97 (q, $J = 6$ Hz, 2H), 2.20–2.37 (m, 1H), 2.48–2.60 (m, 1H), 2.94–3.02 (m, 1H), 3.37 (dd, $J = 8$, 2 Hz, 1H), 3.45 (t, $J = 6$ Hz, 2H), 3.60–3.69 (m, 1H), 3.79 (s, 3H), 4.42 (s, 2H), 5.28–5.40 (m, 1H), 5.44–5.62 (m, 1H), 6.19 (d, $J = 8$ Hz, 1H), 6.35 (d, $J = 6$ Hz, 1H), 6.87 (d, $J = 9$ Hz, 2H), 7.25 (d, $J = 9$ Hz, 2H), 7.54 (dd, $J = 6$, 2 Hz, 1H); compound **14** (300 MHz) δ 0.88 (t, $J = 7$ Hz, 3H), 1.14–1.44 (m, 6H), 1.48–1.84 (m, 7H), 1.97 (q, $J = 6$ Hz, 2H), 2.31 (dt, $J = 15$, 7 Hz, 1H), 2.55 (dt, $J = 15$, 7 Hz, 1H), 2.96–3.02 (m, 1H), 3.39 (dd, $J = 8$, 2 Hz, 1H), 3.60–3.72 (m, 3H), 5.28–5.40 (m, 1H), 5.45–5.58 (m, 1H), 6.19 (d, $J = 8$ Hz, 1H), 6.35 (dd, $J = 6$, 2 Hz, 1H), 7.54 (dd, $J = 6$, 2 Hz, 1H); compound **15** (300 MHz) δ 0.88 (t, $J = 7$ Hz, 3H), 1.15–1.40 (m, 6H), 1.54–2.02 (m, 6H), 2.32 (dt, $J = 15$, 8 Hz, 1H), 2.48–2.62 (m, 3H), 2.95–3.02 (m, 1H), 3.39 (dd, $J = 8$, 2 Hz, 1H), 3.62–3.70 (m, 1H), 5.27–5.38 (m, 1H), 5.45–5.58 (m, 1H), 6.18 (d, $J = 8$ Hz, 1H), 6.35 (dd, $J = 6$, 2 Hz, 1H), 7.54 (dd, $J = 6$, 2 Hz, 1H), 9.79 (t, $J = 1$ Hz, 1H); compound **24** (300 MHz) δ 0.89 (t, $J = 7$ Hz, 3H), 1.20–1.75 (m, 12H), 1.97 (q, $J = 6$ Hz, 2H), 2.22–2.40 (m, 1H), 2.48–2.64 (m, 1H), 2.99 (dt, $J = 1.5$, 5 Hz, 1H), 3.37 (dd, $J = 8$, 1.5 Hz, 1H), 3.42 (t, $J = 6$ Hz, 2H), 3.62–3.70 (m, 1H), 3.80 (s, 3H), 4.42 (s, 2H), 5.28–5.40 (m, 1H), 5.44–5.56 (m, 1H), 6.19 (d, $J = 8$ Hz, 1H), 6.34 (dd, $J = 6$, 2 Hz, 1H), 6.87 (d, $J = 9$ Hz, 2H), 7.25 (d, $J = 9$ Hz, 2H), 7.52 (dm, $J = 6$ Hz, 1H); compound **27** (300 MHz) δ 0.89 (t, $J = 7$ Hz, 3H), 1.2–1.8 (m, 10H), 1.98–2.14 (m, 2H), 2.24–2.38 (m, 3H), 2.48–2.64 (m, 1H), 2.97 (dt, $J = 1.5$, 5 Hz, 1H), 3.36 (dd, $J = 8$, 1.5 Hz, 1H), 3.63–3.73 (m, 1H), 5.32–5.58 (m, 2H), 6.22 (d, $J = 8$ Hz, 1H), 6.36 (dd, $J = 6$, 2 Hz, 1H), 7.53 (dm, $J = 6$ Hz, 1H); 5,6-diastereomer of **1** (500 MHz, $CHCl_3$ in $CDCl_3$ at 7.24 ppm) δ 0.86 (t, $J = 7$ Hz, 6H), 1.1–2.7 (m, 44 H), 2.93–3.05 (m, 1H), 3.19–3.43 (m, 10H), 3.58–4.43 (m, 9H), 5.14–5.24 (m, 1H), 5.26–5.38 (m, 1H), 5.45–5.54 (m, 1H), 6.07 (d, $J = 9$ Hz, 1H), 6.33 (dd, $J = 6$, 2 Hz, 1H), 7.54 (dd, $J = 6$, 2 Hz, 1H).
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