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Total Synthesis of the Epoxy Isoprostane Phospholipids PEIPC and PECPC

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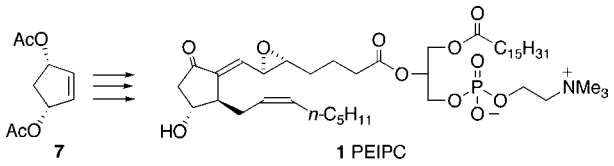
ABSTRACT



A total synthesis of the naturally occurring hydroxy ketone PEIPC 1, a compound that plays a role in endothelial activation in atherosclerosis, has been completed via a triply convergent preparation of a protected EI derivative 13 from 3,5-diacetoxycyclopentene 7, pentane-1,5-diol, and vinyllithium, using Sharpless epoxidation and enzymatic resolution as key steps. Final coupling with lyso-PC 16 and silyl group deprotection gave PECPC 2 and PEIPC 1, which showed the same activity as natural PECPC and PEIPC.

We have previously[1] isolated, identified, and described the biological activity of an in vitro oxidation product of arachidonoyl phosphatidylcholine, 1-palmitoyl-2-(5,6)-epoxyisoprostane E_2-*sn*-glycero-3-phosphocholine (PEIPC). This lipid accumulates in oxidized lipoproteins, the membranes of cells exposed to oxidative stress, and in apoptotic and necrotic cells.[2] PEIPC has also been demonstrated to be present at high levels in atherosclerotic lesions. We have demonstrated that five HPLC-separable isomers of PEIPC were formed from the oxidation of 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine (PAPC). The most active isomer **1** was demonstrated to activate several important inflammatory responses that contribute to atherosclerosis, including endothelial−monocyte interaction, cAMP responsive element binding protein (CREB) activation, and synthesis of monocyte activators.[3,4] On the basis of mass spectrometry of the natural compound and the proton NMR spectra of the dehydration product, the compound was tentatively assigned the structure **1**.[5] The small amount of material precluded a complete structural analysis, and the assignment of the relative stereochemistry, e.g., the *trans*-epoxide and the (*E*)-trisubstituted alkene, was tentative. We reported recently the development of a three-component coupling that permitted the total synthesis of two close structural analogues of the isoprostane portion of this interesting phospholipid, namely, the epoxide **3** and its dehydration product **4** and their (*Z*)-stereoisomers, which lends evidence for the correctness of the structure of **1** (Scheme 1).[6] We report herein the total synthesis of PEIPC **1**, which involves the development of a new route for the synthesis of this class of epoxyisoprostanes utilizing a triply

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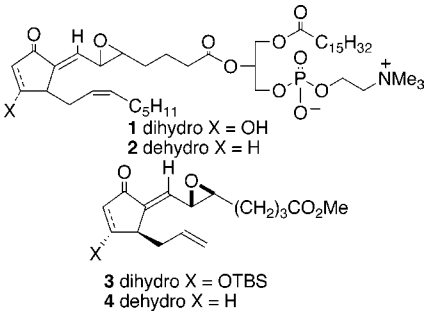
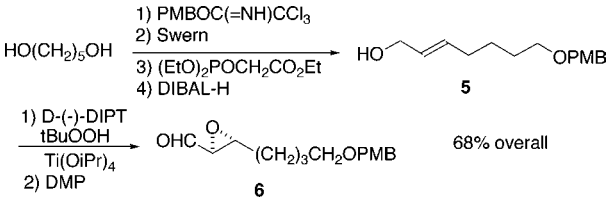
Scheme 1



convergent[7] preparation of the key protected EI derivative **13** and its coupling to lyso-PC **16**. This route also allows the preparation of the corresponding enone PECPC **2**.

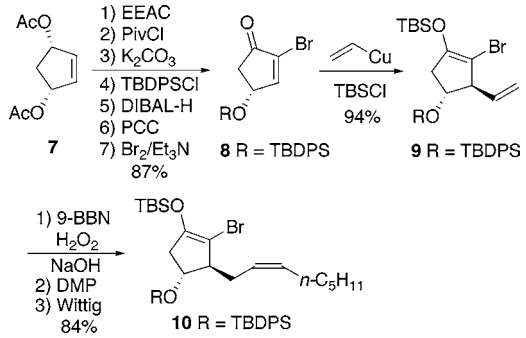
The two components for the key coupling were prepared as follows: monoprotection of pentane-1,5-diol followed by Swern oxidation, Horner−Emmons reaction, and reduction gave the (*E*)-allylic alcohol **5**, which was subjected to Sharpless asymmetric epoxidation and finally oxidized (Dess−Martin periodinane) to give the epoxide **6** (Scheme 2). The second key component was prepared in the same

Scheme 2



manner as described earlier,[6] namely, conversion of the diacetate **7** via seven steps into the 2-bromo-4-silyloxy cyclopentenone **8** in an overall yield of 87% (Scheme 3).

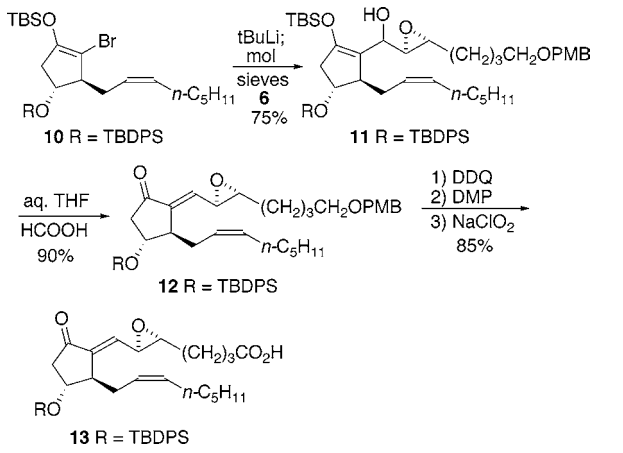
Scheme 3



We chose to use the very stable *tert*-butyldiphenylsilyl (TBDPS) ether as the cyclopentanol protecting group. 1,4-Addition of vinylcopper to the enone **8** in the presence of *tert*-butyldimethylsilyl (TBS) chloride[8] gave the trans-disubstituted bromoenol ether **9** in 94% yield. The elaboration of the bottom side chain was easily accomplished by selective hydroboration−oxidation of the vinyl group at −78 °C to give the primary alcohol followed by oxidation to the aldehyde. Wittig reaction with the ylide from hexyl bromide afforded the desired (*Z*)-alkene **10** in 84% overall yield.

The crucial coupling was carried out by first forming the vinyllithium species by treatment of **10** (dried with molecular sieves) with *tert*-butyllithium followed by addition of the epoxyaldehyde **6** to give the allylic alcohol **11** in 75% yield (Scheme 4). Hydrolysis of the silyl enol ether and dehydra-

Scheme 4



tion to the enone **12** was effected in 90% yield with formic acid in aqueous THF. The final three steps involve conversion of the primary PMB ether into the desired acid. Deprotection of the ether with DDQ, followed by two-stage oxidation, initial Dess−Martin periodinane and final sodium chlorite oxidation gave the desired acid, namely, the silyl ether of EI, **13**, in 85% yield over the three steps.

Deprotection of the TBDPS ether proved to be somewhat difficult due to the sensitivity of the system to both acid and base. The use of tetrabutylammonium fluoride (TBAF) at low temperatures gave mostly the trienone **14** (EC), the product of β-elimination, although by using an acetic acid buffered solution of TBAF at 23 °C, one could isolate the desired β-hydroxy enone (EI) **15** in 40% yield along with the trienone **14** in 53% yield (Scheme 5). Biological testing of **15** demonstrated its ability to activate CREB using a promoter−reporter construct.

The final steps in the synthesis of PEIPC involved coupling to commercially available lyso-PC **16** and final deprotection (Scheme 6). Although older methods of coupling could be made to work, e.g., DCC, DMAP,[9] a variation of the recent

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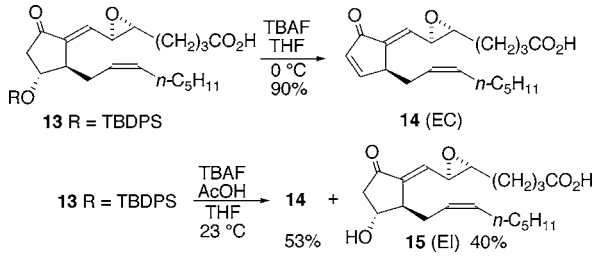
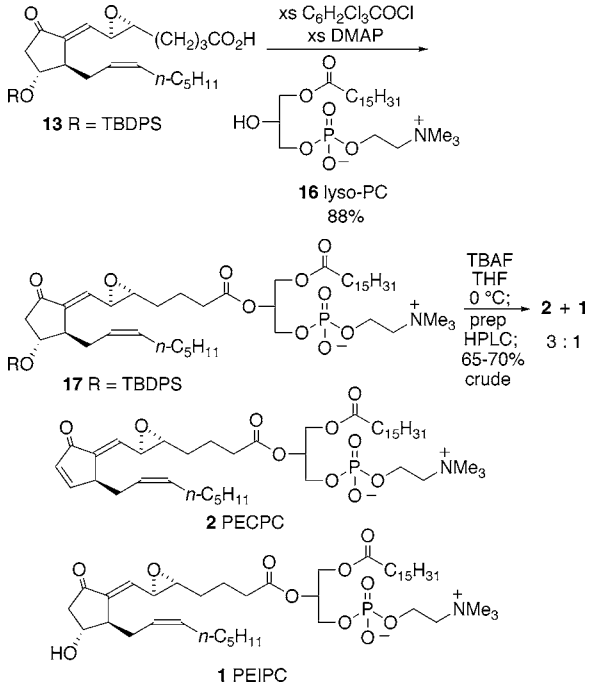
Scheme 5



Scheme 6



method of Acharya and Kobayashi provided the best yields.[10] Thus, treatment of the acid **13** with 10 equiv of the Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride) and DMAP at 23 °C for 1 h in the presence of lyso-PC **16** afforded an 88% yield of the coupled product **17**. Removal of the TBDPS protecting group was effected using TBAF in THF at 0 °C, which seemed quite clean by TLC analysis and produced a mixture of the desired compound PEIPC **1** and the elimination product PECPC **2** in 65−70% crude yield. However, isolation of the water-soluble products proved to be somewhat difficult. The best procedure was evaporation to dryness (during which significant β-elimination to the enone occurred) and then purification by reverse-phase HPLC, which showed a 3:1 mixture of **2** and **1**. Synthetic PEIPC **1** eluted as an essentially pure single peak and had an identical HPLC retention time and mass spectrometric profile as the naturally occurring compound.[1,3] Furthermore, negative ion ESI-MS/MS of synthetic EC **14** and naturally occurring EC had identical daughter ion fragmentation patterns (data not shown).

Thus, we have synthesized the important naturally occurring material PEIPC **1** and its dehydration product PECPC **2** by a route that should allow for the preparation of many structural analogues that may block the activity of these oxidized phospholipids and inhibit atherogenesis. Further work in this area is underway.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, except **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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