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Synthesis of the PMB Ether of 5,6-Epoxyisoprostane E2 through Aldol Reaction of the α-Bromocyclopentanone

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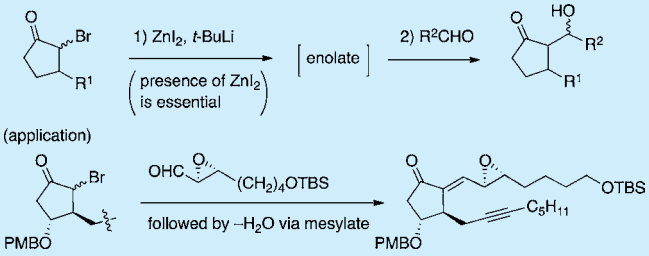
Supporting Information

ABSTRACT: 5,6-Epoxyisoprostane E2 was synthesized via bromohydrination of the cyclopentene and aldol reaction of the α-bromocyclopentanone with the epoxyaldehyde. High regioselectivity in the bromohydrination was attained with recrystallized NBS and pyridine in aqueous DMSO. The enolate for the aldol reaction was generated by adding *t*-BuLi to the mixture of the α-bromocyclopentanone and ZnI_2. This aldol protocol was applied successfully to several cyclopentanones and aldehydes.



Oxidation products of 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine (PAPC) have been isolated from rabbit atherosclerotic lesions, mildly oxidized low-density lipoproteins (ox-LDL), and autoxidized PAPC.[1,2] The oxidation products were separated by LC/MS, and the two of them were identified as those that possess 5,6-epoxyisoprostanes E2 and A2 at the *sn*-2 position of the phospholipid. Based on UV analysis, the other compounds were suggested to be the stereo- and regioisomers of 5,6-epoxyisoprostanes E2 and A2. The relative stereochemistry of 5,6-epoxyisoprostane A2 was assigned as **5** by total synthesis[3] (Figure 1),

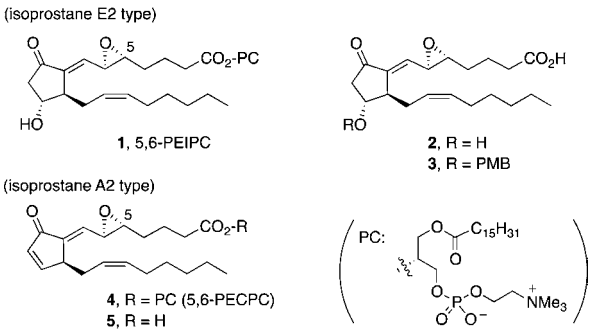


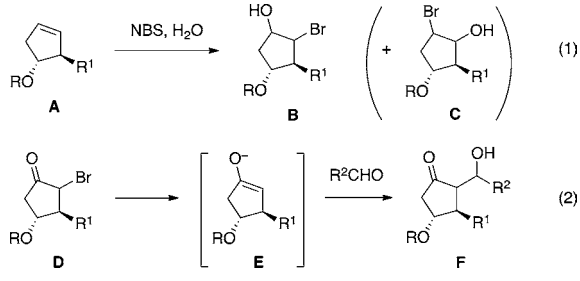
Figure 1. 5,6-PEIPC, -PECPC, and related compounds.

and the Yamaguchi esterification with lyso-PC afforded 5,6-PECPC (**4**).[3,4] Subsequently, 5,6-PEIPC (**1**), with the absolute structure (as depicted in Figure 1), was synthesized and the occurrence of **1** in the oxidation products was identified by HPLC and MS analysis,[5] thus establishing the *trans* stereochemistry between the epoxide part and the 2-octenyl chain as is seen in **5**. Compounds **1** and **4** have been reported to increase the production of pro-inflammatory mediators—interleukin-8 (IL-8) and monocyte chemotactic protein-1 (MCP-1).[2] In contrast, recent biological studies with synthesized **1**, **2**, **4**, and **5** showed that these compounds exhibit anti-inflammatory activity by suppressing IL-6 and IL-12 production.[6] Taken together, these results suggest that further studies of these products as well as their stereo- and regioisomers are needed to better understand their biological roles.[7]

To support such biological investigations, the development of an efficient synthesis of these compounds is the subject of organic synthesis. After synthesizing 5,6-PECPC (**4**) and its regioisomer,[3,4] we have shifted our focus toward synthesis of the PMB derivative of **2**, i.e., **3**, which is esterified to 5,6-PEIPC (**1**) by Jung.[5b] Herein, a new protocol for aldol reaction of α-bromocyclopentanones with aldehydes was developed and successfully utilized for the synthesis of **3**.

Previously, Stork[8] developed a scheme for the conversion of olefin **A** to aldol **F** (Scheme 1), in which the key reactions were the bromohydrination of olefin **A** (eq 1) and aldol reaction of α-bromocyclopentanone **D** (eq 2). This strategy was used in the recent synthesis of ophiobolin A, in which the two substituents are *cis* oriented (diastereomer of **A**).[9] Regarding the regioselectivity of the bromohydrination, pure **B** was obtained by Stork,[8] while a ca. 5:1 ratio of **B** and **C**

Scheme 1. Highlights of the Present Study



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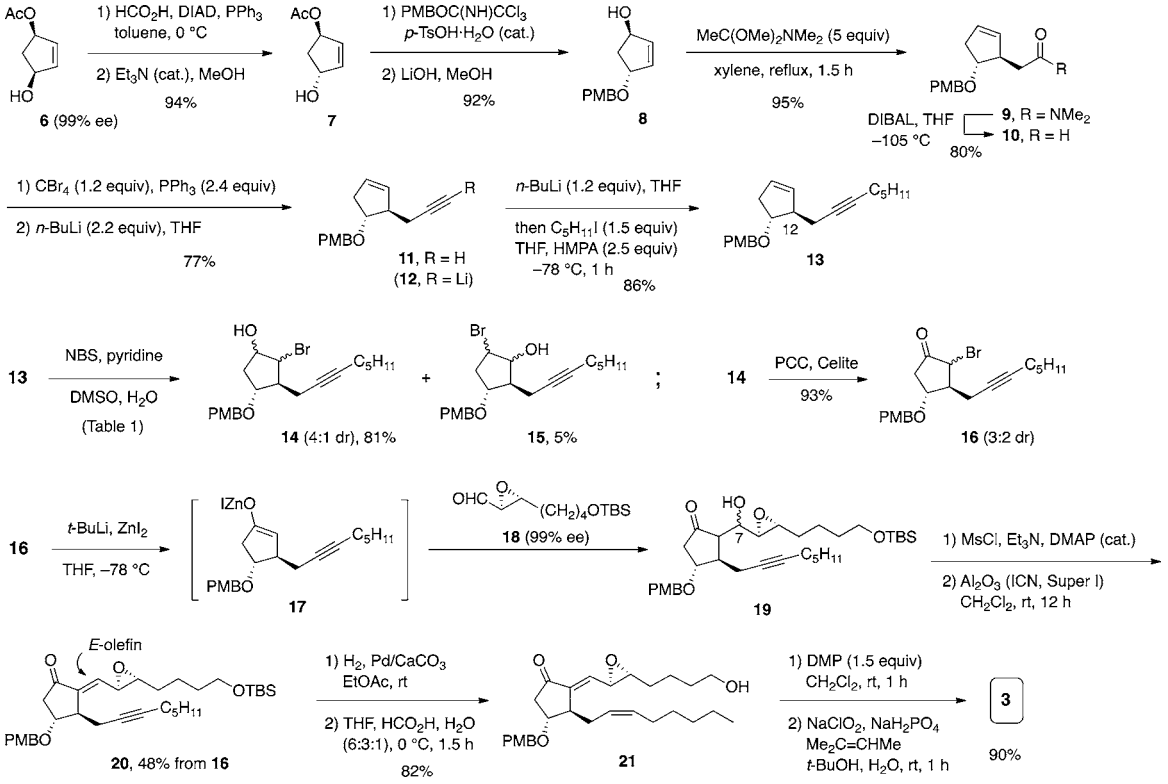
Scheme 2. Synthesis of the 5,6-Epoxyisoprostanes E2 Derivative

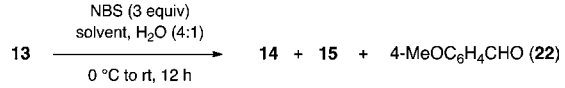


was described by Walker,[10] who converted **B** to the prostaglandin-like heterocycles via **D**. In the present study, the motif **A** occurs in the form of the PMB ether **13** (Scheme 2).

We envisaged a Claisen rearrangement on **8** as a means of installing the requisite side chain shown in olefin **13** (Scheme 2). Toward this, Mitsunobu inversion of the cyclopentene monoacetate **6** (99% ee) gave alcohol **7**, which was converted to alcohol **8**. Eschenmoser−Claisen rearrangement[11] on **8** with $MeC(OMe)_2NMe_2$ afforded amide **9** in 95% yield. Reduction of **9** with DIBAL at −105 °C (liquid nitrogen and MeOH) produced aldehyde **10** in 80% yield, whereas the yield was only 40% at −78 °C. The Corey−Fuchs reaction of **10** followed by debromination with *n*-BuLi afforded the Li anion **12**, which was quenched to produce **11**. We avoided the direct use of the anion **12** for alkylation with $C_5H_{11}I$ because of the possible competition with *n*-BuBr generated *in situ* (from *n*-BuLi). Thus, alkylation of **11** with $C_5H_{11}I$ under the given conditions afforded **13** in 86% yield. Previously, similar intermediates possessing the alkoxy group and the side chain at C11 and C12, respectively, have been synthesized with the 2−4:1[5b,7] and 9:1[6] diastereomeric ratios, whereas our synthesis of **13** is completely stereoselective.

Various aqueous conditions were evaluated for the bromohydrination of **13** with NBS (Table 1). The product distributions of the desired bromohydrin **14**, the regioisomer **15**, 4-$MeOC_6H_4CHO$ (**22**), and the substrate **13** were determined by ^1H NMR integration and used to assess regioselectivity (**14** over **15**), the extent of decomposition of the products and/or **13**, and conversion. Initial attempts (entries 1−3) indicated the unstable nature of **13** under these conditions since bromohydrination of a simple olefin **23**[12] proceeded smoothly (with ca. 2:1 rations of **24** and **25** in the all entries) (eq 3). Gratifyingly, further investigation in

Table 1. Bromohydrination of Olefin 13



entry	purity grade of NBS	additive[a]	solvent[b]	14:15:13:22
1	purchased	–	acetone	–[c]
2	purchased	–	DMSO	52:<10:14:24[d]
3	purchased	$NaHCO_3$	DMSO	15:<10:7:68[d]
4	purchased	pyridine	DMSO	74:15:9:2
5	recrystallized	pyridine	DMSO	91(81)[e]:5:2:2
6	recrystallized	–	DMSO	67:26:7:0
7	recrystallized	$NaHCO_3$	DMSO	21:<10:20:49[d]
8	recrystallized	Et_3N[f]	DMSO	0:0:11:89

[a]6 equiv. [b]Solvent/H_2O (4:1). [c]Unidentified compounds. [d]Unidentified compounds were also produced. [e]Isolated yield. [f]A similar result with *i*-Pr_2NEt.

aqueous DMSO disclosed acceleration of the reaction by pyridine (entry 4). Furthermore, the use of recrystallized NBS with pyridine produced **14** with high regioselectivity and product selectivity in 81% isolated yield (entry 5, **14**/**15** = 18:1). In contrast, the use of recrystallized NBS alone (without pyridine) reduced the regioselectivity (entry 6), while its use in the presence of other bases, such as $NaHCO_3$, Et_3N, and *i*-Pr_2NEt, retarded or prevented the reaction (entries 7 and 8, footnote f). These results suggest the slightly acidic conditions realized by HBr (generated *in situ*) and pyridine probably assist the nucleophilic attack by DMSO and/or decomposition of the sulfoxonium ion to bromohydrin **14**. The ^1H NMR analysis of **14** showed it to be a 4:1 diastereomeric ratio (dr) though this ratio had no meaning for further transformation. Indeed, this diastereomeric mixture was subjected to oxidation with PCC to afford ketone **16**

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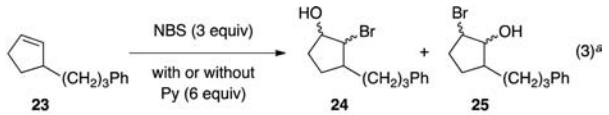
(93%), which was a 3:2 diastereomeric mixture by ^{1}H NMR analysis (δ 4.31 (d) and 4.61 (d) ppm for the major and minor isomers).



reagent	24:25	combined yield (%)
NBS (purchased)	2:1	84
NBS (purchased) with Py	2:1	85
NBS (recrystallized)	2:1	84
NBS (recrystallized) with Py	2:1	86

[a]DMSO, H_2O (4:1), 0 °C to rt, 12 h.

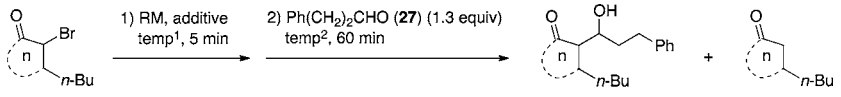
Among the possible methods for conversion of α-bromoketones to enolates, organometal−bromine exchange[14] was examined for the present investigation, whereas the radical−bromine exchange[15] was not considered because of the presence of a triple bond which is generally radical-sensitive. The other possible two-step procedures[8] (formation of an enol derivative followed by regeneration of enolate) were also excluded from our examination. First, EtMgBr−Br exchange of a model α-bromocyclopentanone **26a** (n = 5) was attempted according to the previous generation of enolate from α-iodocyclohexanones with EtMgBr.[14,16] However, an attempted aldol reaction with aldehyde **27** gave a mixture of unidentified products (Table 2, entry 1). In comparison, cyclohexanone **26b** (n = 6) afforded **28b** in good yield (entry 2). The use of n- and t-BuLi in place of EtMgBr was also unsuccessful (entries 4 and 6). In contrast, the presence of ZnI_2 in the exchange with n- and t-BuLi followed by the aldol reaction with **27** produced aldol **28a** (entries 5 and 7). As the t-BuLi/ZnI_2 system gave slightly higher product selectivity (**28a** over **29a**) than n-BuLi/ZnI_2, combinations of t-BuLi and other zinc salts were also investigated. The t-BuLi−Br exchange in the presence of ZnI_2·TMEDA and ZnX_2 (X = Br, OAc) proceeded with an efficiency similar to that of entry 7 (entries 8, 10, and 11), whereas $ZnCl_2$ lowered the selectivity (**28a**/**29a**) (entry 9) and $Zn(OTs)_2$ gave unidentified products (data not shown). Comparable outcomes were also obtained in Et_2O with t-BuLi alone and t-BuLi/ZnX_2 (X = I, Br) (entries not shown). In contrast, the t-BuLi−Br exchange of cyclohexanone **26b** (n = 6) proceeded cleanly without ZnI_2, and the subsequent aldol reaction afforded **28b** efficiently (entry 12; cf. entry 13).

Among the several successful combinations of t-BuLi and the zinc salts, t-BuLi/ZnI_2 was applied to the real α-bromoketone **16** because of the comparatively nonhygroscopic nature and the ready-to-use convenience of commercial ZnI_2. The exchange proceeded well, and the subsequent aldol reaction with epoxyaldehyde **18** (99% ee) (see Supporting Information for the preparation) afforded **19** as a diastereomeric mixture at C7 (and C8). Dehydration of **19** via mesylate according to the procedure developed by us[3] for the synthesis of PECPC afforded exoenone **20** as the sole product in 48% yield over three steps. The acetylene in **20** was reduced to the *cis* olefin, and the TBS group was removed to produce alcohol **21** in 82% yield.[17] Finally, a two-step oxidation of **21** furnished acid **3**. The ^{1}H NMR spectrum of **3** was consistent with that reported.[5b]

The ZnI_2-assisted protocol for t-BuLi−Br exchange (Table 2, entry 7) was applied to various α-bromoketones. Cyclopenta-nones **26c−e** possessing i-Pr, t-Bu, and Ph substituents underwent the exchange, and the subsequent aldol reaction with $Ph(CH_2)_2CHO$ (**27**) afforded aldols **28c−e** in good yields (Scheme 3, eq 4). Similarly, the enolate was derived from **26a** and the aldol reaction with c-C_6H_{11} and PhCHO furnished aldols **28f** and **28g**, respectively. In contrast, the t-BuLi−Br exchange of acyclic ketone **26h** was accomplished without ZnI_2 and the aldol reaction with **27** afforded aldol **28h** in good yield (eq 5).

In summary, the PMB ether of 5,6-epoxyisoprostane E2 **3** was synthesized in 11.6% overall yield through bromohydrination of **13** and the subsequent aldol reaction of α-bromocyclopentanone **16**. Furthermore, the t-BuLi−Br

Table 2. Aldol Reaction of Model Bromoketones



entry	ketone[a]	n	RM (equiv)	additive (equiv)	solvent	temp^1 (°C)	temp^2 (°C)	28:29	yield of 28 (%)
1	**26a**	5	EtMgBr (1.1)	–	THF	0	0	–[b,c]	–
2	**26b**	6	EtMgBr (1.1)	–	THF	0	0	98:2	71
3	**26a**	5	EtMgBr (1.1)	ZnX_2[d] (2)	THF	−78	−78	–[b]	–
4	**26a**	5	n-BuLi (2.2)	–	THF	−78	−78	–[b]	–
5	**26a**	5	n-BuLi (2.2)	ZnI_2[e] (2)	THF	−78	−78	95:5	nd[f]
6	**26a**	5	t-BuLi (2.2)	–	THF	−78	−78	–[b]	–
7	**26a**	5	t-BuLi (2.2)	ZnI_2 (2)	THF	−78	−78[g]	99:1	70
8	**26a**	5	t-BuLi (2.2)	$ZnBr_2$ (2)	THF	−78	−78	98:2	67
9	**26a**	5	t-BuLi (2.2)	$ZnCl_2$ (2)	THF	−78	−78	87:13	nd[f]
10	**26a**	5	t-BuLi (2.2)	ZnI_2·TMEDA (2)	THF	−78	−78	99:1	69
11	**26a**	5	t-BuLi (2.2)	$Zn(OAc)_2$ (2)	THF	−78	−78	97:3	61
12	**26b**	6	t-BuLi (2.2)	–	THF	−78	−78	99:1	65
13	**26b**	6	t-BuLi (2.2)	ZnI_2[h] (2)	THF	−78	−78	95:5	62

[a]Mixture of ca. 1:1 diastereomers. [b]Complex mixture was obtained. [c]Reaction at −78 °C also gave a complex mixture. [d]X = Cl, Br, I. [e]$ZnBr_2$ and $ZnCl_2$ produced a 91:9 ratio of **28a**:**29a** and a complex mixture, respectively. [f]Not determined. [g]Aldol reaction at 0 °C gave a complex mixture. [h]$ZnBr_2$ produced a 94:6 ratio of **28b**:**29b** in 60% yield, whereas $ZnCl_2$ gave a complex mixture.

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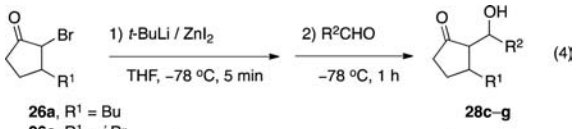
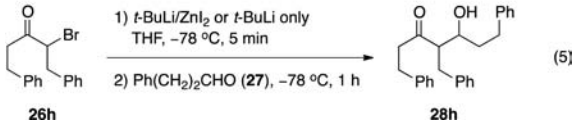
Scheme 3. *t*-BuLi-Br Exchange and Aldol Reaction[a,b]



product	R^1	R^2	yield
28c	*i*-Pr	$(CH_2)_2Ph$	82%
28d	*t*-Bu	$(CH_2)_2Ph$	77%
28e	Ph	$(CH_2)_2Ph$	80%
28f	Bu	*c*-C_6H_{11}	84%
28g	Bu	Ph	83%



[a] *t*-BuLi (2.2 equiv), ZnI_2 (2 equiv), and RCHO (1.3 equiv) were used. [b] Diastereomeric ratios of **26a,c–e** were 1:1, 4:1, 6:1, and 1:1.

exchange in the presence of ZnI_2 was successfully applied to several α-bromocyclopentanones.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data of compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(12) Olefin **23** was prepared from 2-cyclopenten-1-one in 67% yield: (i) $NaBH_4$, $CeCl_3{\cdot}7H_2O$; (ii) $PyCO_2H$, DCC, DMAP; (iii) $Ph(CH_2)_3MgBr$/CuI (2:1).

(13) Determination of the stereochemistry of **14** by the ^1H NMR decoupling study was unsuccessful because of the overlap in signals.

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(17) The ^1H and ^{13}C NMR spectra of **21** were consistent with those scanned,[5b] and the ^{13}C NMR data were revised.