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Palladium-catalyzed Coupling Reactions of Bromobenzaldehydes with 3,4-Di(*tert*-butyldimethylsilyloxy)-1-alkene to (3,4-Dihydroxyalkenyl)benzaldehydes in the Synthesis of Lipoxin Analogues

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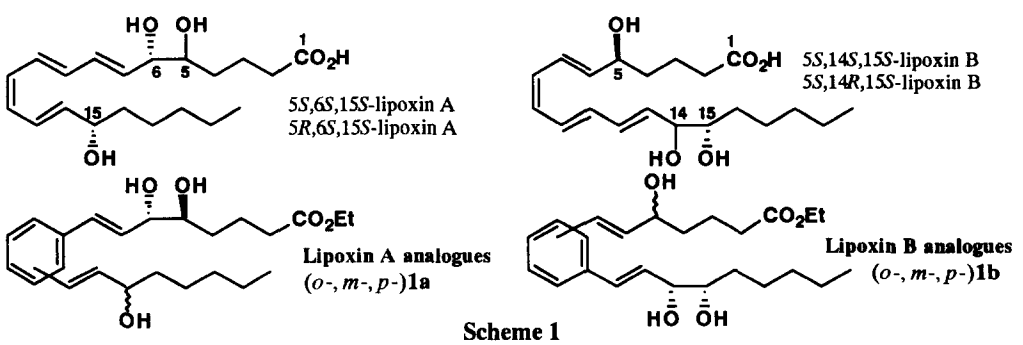
Abstract: *o-, m-, and p-(3,4-Dihydroxyalkenyl)benzaldehydes were selectively prepared via palladium-catalyzed Heck-type coupling reactions of o-, m-, and p-bromobenzaldehydes with 3,4-di(tert-butyldimethylsilyloxy)-1-alkene. The products were employed for the synthesis of lipoxin analogues, o-, m-, and p-3-hydroxyalkenyl-3,4-dihydroxyalkenylbenzenes.*

Lipoxins (LXs) are a known series of unstable eicosanoids discovered by the Samuelsson group.[1] Synthetic studies have been used to determine their complete structure and to investigate their biological activities.[2] As yet, however, the active conformational structure of LXs is still undetermined, and the role of the conjugate tetraene functionality in their biological activities is unclear. There is also some debate about the difference in biological activities between LXA and LXB.

In order to clarify these points, we focused our attention to the synthesis of stable lipoxin analogues, in which the C_9-C_{12}-diene moiety of the conjugate tetraene functionality is mimiced by a benzene ring, as shown in Scheme 1. Our synthetic approach to the LX analogues **1** consists of two types of alkenylation of commercially available *o-*, *m-*, and *p*-bromobenzaldehydes (Scheme 2); (i) a palladium-catalyzed Heck-type coupling reaction with 3,4-dihydroxy-1-alkene to yield (3,4-dihydroxyalkenyl)benzaldehyde and (ii) the Horner-Wadsworth-Emmons reaction with diethyl 2-oxoalkylphosphonate to give the corresponding dialkenylbenzene.



Scheme 1

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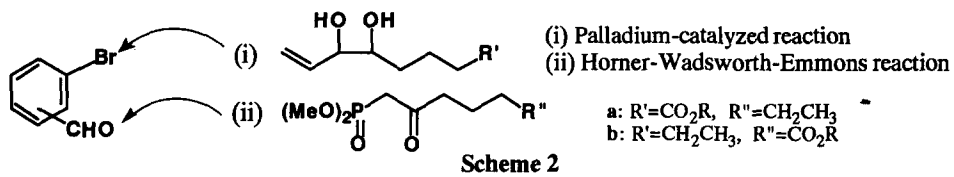
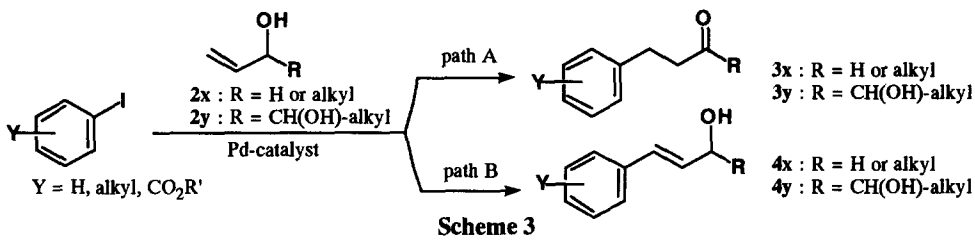


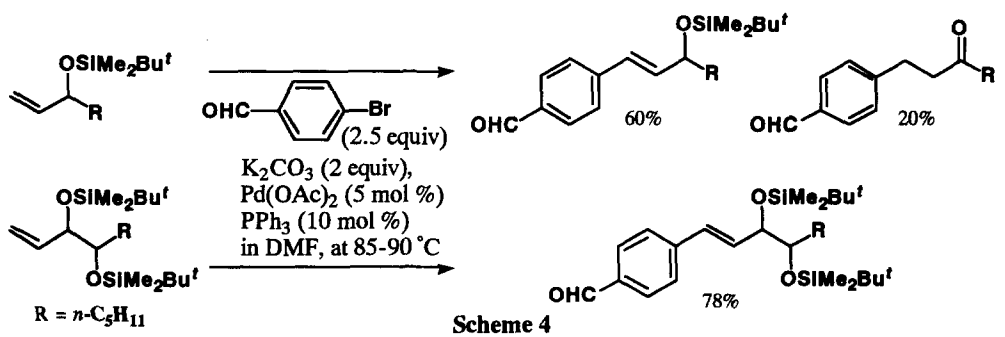
Scheme 2

It is well known that the palladium-catalyzed coupling reaction of iodobenzene with 3-hydroxy-1-alkene leads to 3-oxoalkylbenzene **3** (path A in Scheme 3) under standard Heck reaction conditions.[3] However, much effort has recently been devoted to the formation of (3-hydroxyalkenyl)benzene **4x** and (3,4-dihydoxyalkenyl)benzene **4y** by a coupling reaction of iodobenzene with 3-hydroxy-1-alkene **2x** and 3,4-dihydroxy-1-alkene **2y** (path B in Scheme 3). Jeffery reported a selective formation of **4x** by a palladium-catalyzed reaction of iodobenzenes with **2x** using AgOAc or Ag_2CO_3.[4] Kang showed that a similar reaction of iodobenzene with **2y** gave **4y** using $Pd(OAc)_2$, *n*-Bu_3P, and K_2CO_3,[5a] and that a palladium-catalyzed reaction of hypervalent iodonium salts (diphenyliodonium tetrafluoroborate) with **2** gave **4** effectively.[5b] Tamaru discovered a successful synthesis of cinnamylic alcohols **4x** *via* a Heck-type reaction of iodobenzene with 3-(*N*-alkylcarbamoyloxy)-1-alkenes.[6] These reactions seem to be advantageous for the synthesis of (3-hydroxyalkenyl)benzene and (3,4-dihydroxyalkenyl)benzene which are obtained by a coupling reaction of *iodobenzene* with 3-hydroxy- or 3,4-dihydroxy-1-alkene or their synthetic equivalents.



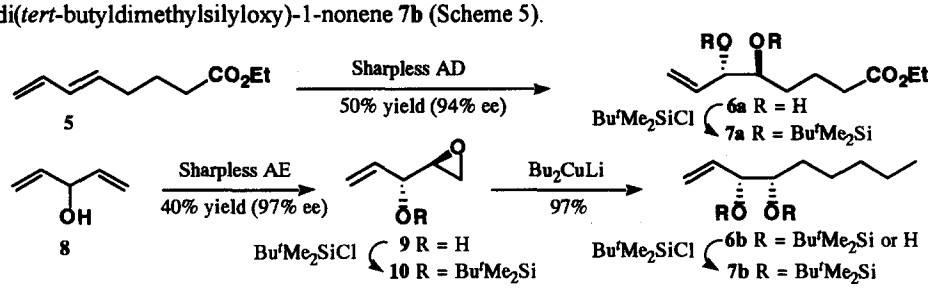
Scheme 3

Here, we used *bromobenzaldehyde* as an arylic halide in the palladium-catalyzed coupling reaction with 3,4-dihydroxy-1-alkene because *o*-, *m*-, and *p*-bromobenzaldehydes are commercially available. However, we could not obtain the desired product under the standard Heck reaction conditions or under the conditions reported by Jeffery[4] and Kang[5a] using iodobenzene, in which bromobenzaldehyde was unreactive. Therefore, we studied the coupling of bromobenzaldehyde with *O*-protected 3,4-dihydroxy-1-alkene. Although 3-*tert*-butyldimethylsilyloxy-1-alkene gave (3-*tert*-butyldimethylsilyloxyalkenyl)benzaldehyde in 60% yield together with 3-oxoalkylbenzaldehyde (20%), 3,4-di(*tert*-butyldimethylsilyloxy)-1-alkenes gave the desired products selectively in good yield (Scheme 4).



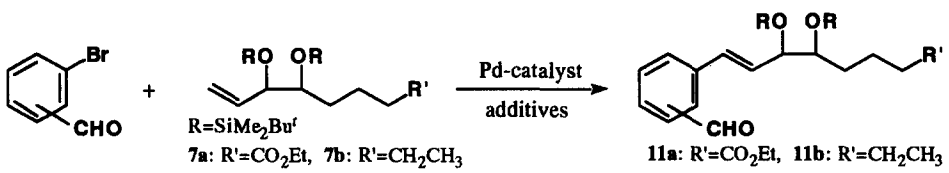
Scheme 4

3,4-Dihydroxy-1-alkene **6a**, which was designed to provide the LXA analogues, was obtained by Sharpless asymmetric dihydroxylation of ethyl 5,7-octadienoate **5** (5 mmol) using AD-mix-α (1.4 g/mmol) and methylsulfonamide (1 equiv) in aq. *t*-butanol (50%) at 0 °C in 50% yield (94% ee) together with 1,2-dihydroxy-3-alkene (25%).[7] The diol **6a** was converted to ethyl 5,6-di(*tert*-butyldimethylsilyloxy)-7-octenoate **7a** by treatment with *tert*-butyldimethylsilylchloride and imidazole in DMF. To provide the LXB analogues, **6b** was prepared by a three-step conversion of 1,4-pentadien-3-ol **8** through Sharpless asymmetric epoxidation of **8** (30 mmol) to **9** using L-(+)-DIPT in 40% yield (97% ee),[8] protection of the epoxy alcohol **9** to 3-(*tert*-butyldimethylsilyloxy)-4-penten-1,2-epoxide **10**, and C4 homologation of **10** using lithium di-*n*-butylcuprate (1.5 equiv) to 3-*tert*-butyldimethylsilyloxy-4-hydroxy-1-nonene **6b**. This was then converted to 3,4-di(*tert*-butyldimethylsilyloxy)-1-nonene **7b** (Scheme 5).



Scheme 5

Both 3,4-di(*tert*-butyldimethylsilyloxy)-1-alkenes **7a** and **7b** (1-3 mmol) were treated with 1.5-2.5 equivalents of bromobenzaldehydes in the presence of a palladium-catalyst and additives (Scheme 6). The results are summarized in Table 1.



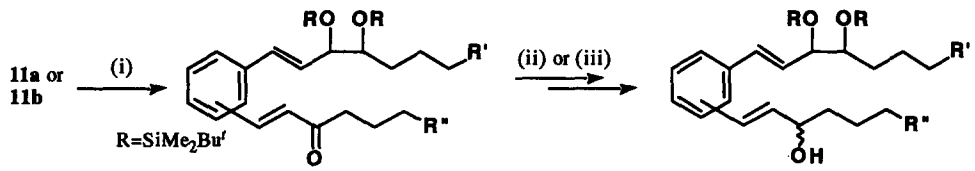
Scheme 6

Table 1 Palladium-catalyzed Coupling Reactions of *o*-, *m*-, *p*-Bromobenzaldehydes with **7** [a]

7	Bromobenzaldehyde (mol equiv)	Catalyst and Additives [b]	Reaction Time (h)	Yield of **11** (%)
7a	*o*- (1.5)	[A]	12	78
7a	*m*- (1.5)	[A]	43	87
7a	*p*- (1.5)	[A]	12	88
7a	*p*- (1.5)	[B]	100	47
7b	*o*- (2.0)	[B]	140	50
7b	*m*- (1.5)	[B]	48	71
7b	*p*- (2.5)	[B]	72	78

a. Reaction was carried out in *N,N*-dimethylformamide (DMF) at 85-90 °C under Argon atmosphere.
b. Catalyst system [A]: $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (1.3 equiv), Bu_4NBr (1 equiv); [B]: $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), K_2CO_3 (2 equiv).

The products **11a** and **11b** were allowed to react with Horner-Wadsworth-Emmons reagent (dimethyl 2-oxoalkylphosphonate/NaH) to give **12**.[9] Conversion of **12a** to **1a** was carried out by treatment of **12a** with $NaBH_4$[10] and then with HF•pyridine. The conversion of **12b** to **1b**, on the other hand, was achieved by treatment of **12b** with aq. HF and then with $NaBH_4$ to avoid formation of the corresponding lactone which was formed when the δ-hydroxy ester was treated with a desilylation reagent such as aq. HF or Bu_4NF.



(i) $(MeO)_2POCH_2CO(CH_2)_4CH_3$/NaH or $(MeO)_2POCH_2CO(CH_2)_3CO_2Et$/NaH;
(ii) $NaBH_4$ and then HF•pyridine; (iii) aq. HF and then $NaBH_4$

Scheme 7

Preliminary biological activities of these artificial compounds were evaluated using *in vitro* systems on chemotaxis and IgE production. Both *m*-**1a** and *m*-**1b** showed chemotaxis inhibition activity (IC_{50} = 10 μM), and *o*-**1a** showed remarkable inhibition activity on IgE production. It has been reported that LXA shows a chemotactic inhibitory effect on human neutrophiles, whereas it has separately been reported that both LXA and LXB show chemotactic activity (A>B).[2a] These results suggest that lipoxins may participate in the regulation of cellular responses of interest in inflamation.[2a] Further detailed studies of these analogues and their pharmacological activities are in due course.

Acknowledgement

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10. We examined enantioselective reduction of the enones *o*-**12a**, *p*-**12a**, and *o*-**12b** to give the corresponding (*S*)-alcohols by (*S*)-BINAL-H (3 equiv) in THF at -78°C, and obtained 48% ee (89% yield), 62% ee (84% yield), and 72% ee (93% yield), respectively. Similar treatment of *o*-**12a** and *p*-**12a** with (*R*)-BINAL-H gave (*R*)-alcohols 63% ee and 71% ee, respectively.