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Stereoselective Synthesis of 10,11-Dihydro-leukotriene B_4 and Related Metabolites

Yuichi Kobayashi,* Yuji Nakayama, and G. Biju Kumar

Department of Biomolecular Engineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan

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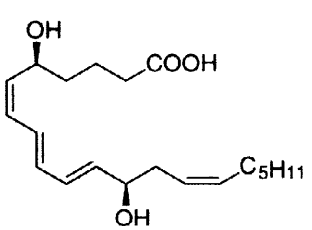
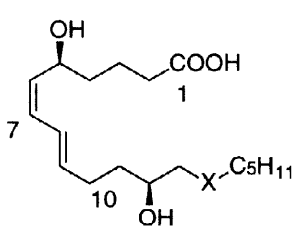
Abstract: Nickel-catalyzed coupling reaction of *cis* bromide **6** and the borates **5a** and **5b**, prepared from the boronate esters **4a** and **4b**, proceeded stereospecifically to furnish **7a** and **7b**, which upon treatment with Bu_4NF in THF afforded 10,11-dihydro-leukotriene B_4 (**1**) and the B_3 (**2**), respectively. In a similar way, EE ether **19** and *rac*-**4a** gave **20** and the subsequent functional group transformation afforded 10,11-dihydro-12-oxo-LTB_4 (**3**). © 1998 Elsevier Science Ltd. All rights reserved.

Key words: boron and compounds; coupling reactions; dienes; nickel and compounds

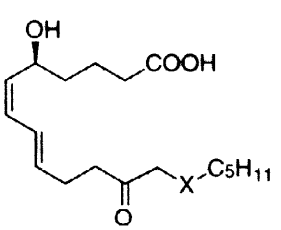
Since lipoxygenase metabolites of unsaturated fatty acids stimulate leukocytes, they are believed to be mediators of inflammation and allergic responses.[1] Among them, leukotriene B_4 (LTB_4) has been shown to be a most potent activator. The activation is triggered by binding to the specific receptor and the sequence of the amino acids has recently been determined by Shimizu.[2] To clarify further the biological aspects of LTB_4 and related metabolites, supply of LTB_4 is still required. One approach for this study is probably that which involves chemical derivation for installation of LTB_4 onto peptides and polymer supports, labeling of LTB_4 to the receptor, *etc.* However, the extremely unstable nature of LTB_4 would certainly incur difficulties during the derivation.[3] Consequently, we are interested in 10,11-dihydro-LTB_4 (**1**) which is the first catabolite of LTB_4,[4] because it still retains the biological property of LTB_4[5] and because the diene system is chemically more stable than the triene system on LTB_4. It is apparent that these properties expand the entry of chemical reactions for the derivation to those requiring rather drastic conditions. In spite of its importance as a substitute for LTB_4, only one synthesis is published.[6] However, the synthesis suffers from the drawback of low stereoselectivity in the formation of a *cis* double bond at C(6) (LTB_4 numbering). Recently, we have developed the method for synthesis of the conjugated *cis,trans* diene structure.[7] By using this reaction, we succeeded in achieving a stereoselective synthesis of **1**. Moreover, 10,11-dihydro-LTB_3 (**2**)[8] has been synthesized where the overall scheme became simpler than that for **1** due to the lack of a *cis* double bond at C(14). Since the additional double bond at C(14) of LTB_4 is not responsible



LTB_4



10,11-dihydro-LTB_4 (**1**):
X = (*Z*)-CH=CH
10,11-dihydro-LTB_3 (**2**):
X = CH_2CH_2



10,11-dihydro-12-oxo-LTB_4 (**3**):
X = (*Z*)-CH=CH

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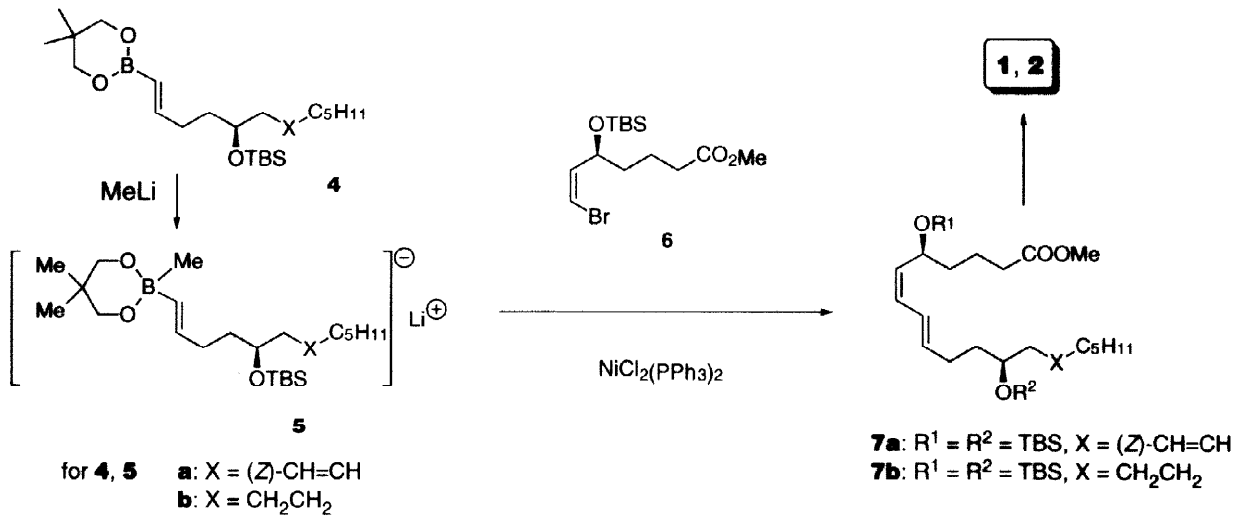
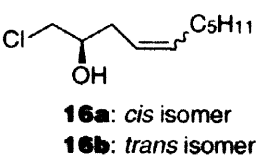


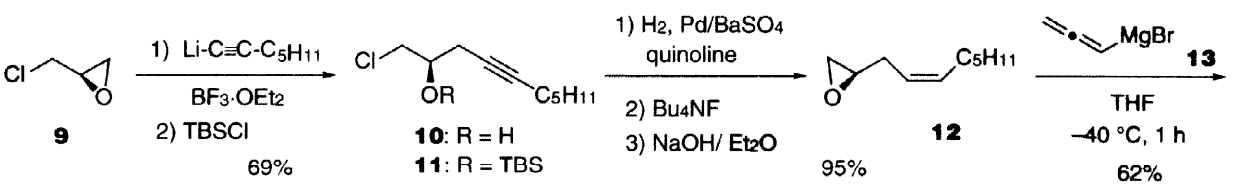
Scheme 1

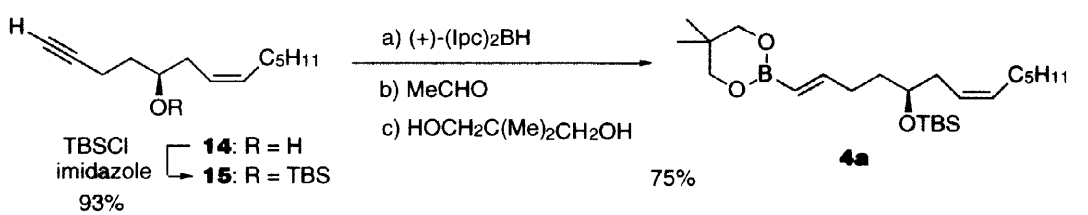
for the biological activity,[9] **2** should serve the purpose as equally well as **1**. Herein we would like to report the synthesis of **1**, **2**, and 10,11-dihydro-12-oxo-LTB_4 (**3**).[10]

The key step eventually producing **1** and **2** is shown in Scheme 1. Stereo- and enantioselective synthesis of the C(1)-C(7) segment **6** (>99% ee) has been established in the synthesis of LTB_4 by us.[11] Consequently, our initial investigation focused on finding an efficient method to obtain the pure boronate esters **4a** and **4b**. Among the reported methods, we applied the following protocols: (1)[12] hydroboration of the corresponding acetylene with Br_2BH followed by hydrolysis and esterification with 2,2-dimethyl-1,3-propanediol; (2)[13] hydroboration of the acetylene with $(Ipc)_2BH$ followed by oxidation and esterification; (3)[14] $CrCl_2$-mediated reaction of the aldehyde with the dichloromethaneboronic ester **8** (structure, see ref 15). Among them, the second method was found to be successful as illustrated in Schemes 2 and 3 (**15** → **4a**, **18** → **4b**). Detailed sequences to **15** and **18** and the subsequent hydroboration are described below.

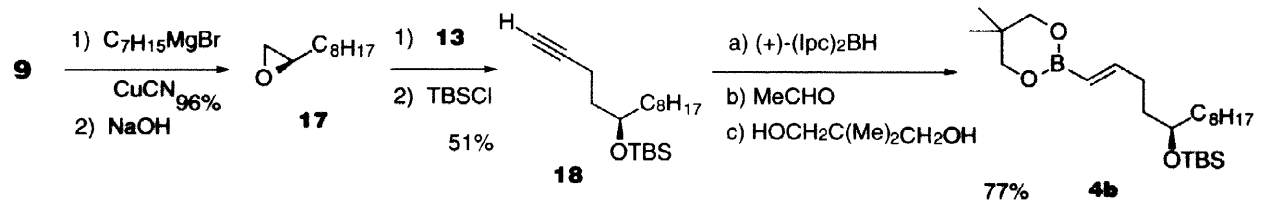
(*R*)-Epichlorohydrin (**9**) of 98.8% ee was transformed into alcohol **10** by the Yamaguchi method.[15] Initial attempts to convert **10** into *cis* olefin **16a** produced a mixture of *cis* and *trans* isomers (**16a** and **16b**) in varying ratios of 8 : 1 ~ >20 : 1. Thus, the hydroxyl group of **10** was protected as the TBS ether and reduction was successfully carried out to afford stereospecifically the TBS ether of **16a** in 99% yield. Desilylation of the TBS ether was effected by Bu_4NF and subsequent treatment of **16a** with NaOH afforded







Scheme 2

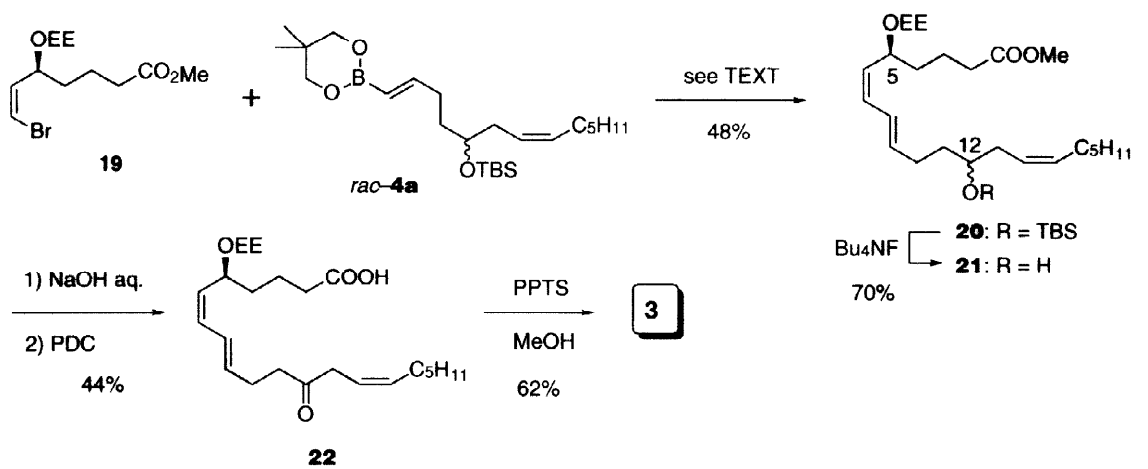


Scheme 3

epoxide **12** in good yield. Epoxide ring-opening of **12** with the allenylmagnesium bromide (**13**), prepared from propargyl bromide and Mg in the presence of $HgCl_2$,[16] afforded a mixture of **14** and the corresponding bromohydrin. Without separation, the mixture was treated with NaOH to afford **14** and **12** in 62% and 20% yields, respectively, after chromatography on silica gel. Silylation of **14** furnished acetylene **15**. As mentioned above, transformation of the acetylene part of **15** to the alkenyl boronate ester group was accomplished by using the protocol of Suzuki and Miyaura.[13] Thus, hydroboration of **15** with (+)-$(Ipc)_2BH$ followed by reaction with excess MeCHO at 40 °C overnight furnished the diethyl boronate ester, which upon ligand exchange with 2,2-dimethyl-1,3-propanediol gave **4a** in 75% yield from **15**. In a similar manner, reaction of epoxide **9** and $C_7H_{15}MgBr$ followed by a similar transformation as described above afforded acetylene **18**, which upon hydroboration furnished **4b** in good yield (Scheme 3).

For the coupling of **4a** and **6**, MeLi was added to a mixture of **4a** and $NiCl_2(PPh_3)_2$ (10 mol%) in THF to generate borate **5a** and a Ni(0) species, to which bromide **6** was added and the reaction was carried out at room temperature overnight to furnish stereoselectively **7a**[17] in 77% yield.[18] Finally, treatment of **7a** with excess Bu_4NF ensued desilylation and hydrolysis to afford **1** in 83% yield. Similarly, coupling of **4b** and **6** afforded **7b**[19] and reaction with Bu_4NF gave **2** in 58% yield.

Using the coupling strategy, 10,11-dihydroxy-12-oxo-LTB_4 (**3**) was synthesized. To differentiate the two hydroxyl groups at C(5) and C(12), the ethoxyethyl ether **19** was chosen as the C(1)-C(7) intermediate. Thus, coupling reaction of **19** (>99% ee) with the racemic boronate ester (*rac*-**4a**) (MeLi, $NiCl_2(PPh_3)_2$ (10 mol%), rt, overnight), furnished stereoselectively the product **20**, which upon desilylation afforded alcohol **21**. After hydrolysis, the crucial oxidation was carried out successfully by using PDC to furnish ketone **22**. Finally, deprotection of the EE group at C(5) completed the synthesis of **3**. The ^1H NMR spectrum of **3** thus prepared indicated no double bond migration at C(14) to the stable position of C(13) and is in good agreement with that reported.[10]



Scheme 4

In summary, we have established the synthesis of the dihydro-LTB_4 metabolites. The synthesis is convergent and highly stereoselective. Thus the present synthesis should provide a valuable access to the biological study of LTB_4. In addition, we were able to synthesize, for the first time, 10,11-dihydro-LTB_3.

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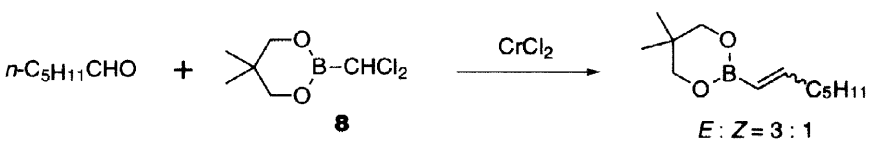
(b) Although the reaction with the pinacol boronate esters is highly stereoselective giving *trans* olefins, reaction of *n*-$C_5H_{11}CHO$ and the boronate ester **8**,[14c] in which propanediol is attached as the ligand, gave a 3 : 1 mixture of *trans* and *cis* olefins. For the coupling reaction, the pinacol esters are not good reagents. (c) Wuts, P. G. M.; Thompson, P. A. *J. Organometal. Chem.* **1982**, *234*, 137-141.



8 $E : Z = 3 : 1$

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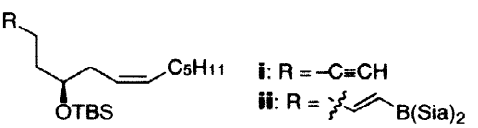
17. ^1H NMR (300 MHz, $CDCl_3$) of **7a**: δ 0.01, 0.04, 0.049, 0.052 (4s, 12 H), 0.87 (s, 9 H), 0.88 (t, *J* = 7 Hz, 3 H), 0.89 (s, 9 H), 1.2-1.8 (m, 12 H), 2.01 (q, *J* = 7 Hz, 2 H), 2.07-2.25 (m, 4 H), 2.31 (t, *J* = 7 Hz, 2 H), 3.66 (s, 3 H), 3.62-3.74 (m, 1 H), 4.52 (dt, *J* = 9, 6 Hz, 1 H), 5.23 (dd, *J* = 11, 9 Hz, 1 H), 5.32-5.50 (m, 2 H), 5.68 (dt, *J* = 15, 7 Hz, 1 H), 5.88 (t, *J* = 11 Hz, 1 H), 6.22 (dd, *J* = 15, 11 Hz, 1 H).
18. Palladium-catalyzed coupling reaction of **6** and organoborane **ii**, prepared from acetylene **i** and $(Sia)_2BH$, under forcing conditions (LiOH, THF-H_2O, reflux, 18 h) gave the acid of **7a** only in lower yields of <30%.



19. ^1H NMR (300 MHz, $CDCl_3$) of **7b**: δ 0.04 (s, 12 H), 0.87 (s, 9 H), 0.88 (t, *J* = 7 Hz, 3 H), 0.89 (s, 9 H), 1.2-1.8 (m, 20 H), 2.04-2.19 (m, 2 H), 2.31 (t, *J* = 7 Hz, 2 H), 3.66 (s, 3 H), 3.60-3.69 (m, 1 H), 4.55 (dt, *J* = 9, 6 Hz, 1 H), 5.23 (dd, *J* = 11, 9 Hz, 1 H), 5.68 (dt, *J* = 15, 7 Hz, 1 H), 5.89 (t, *J* = 11 Hz, 1 H), 6.22 (dd, *J* = 15, 11 Hz, 1 H).