Synthesis of (*S*,5*Z*,8*E*,10*E*)-12-Hydroxyheptadeca-5,8,10-trienoic Acid (12*S*-HHT) and its Analogues

Toshifumi Tojo,[a] Qian Wang,[a] Toshiaki Okuno,[b] Takehiko Yokomizo,[b] Yuichi Kobayashi*[a]

[a] Department of Bioengineering, Tokyo Institute of Technology, Box B52, Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan
Fax +81(45)9245789; E-mail: ykobayas@bio.titech.ac.jp

[b] Department of Biochemistry, Juntendo University School of Medicine, Hongo 2-1-1, Bunkyo-ku, Tokyo 113-8421, Japan

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Abstract: Natural 12S-HHT and its analogues were synthesized for study of structure and activity relationship toward the BLT2 receptor. The Suzuki–Miyaura coupling was used for construction of the 8*E*,10*E*-diene moiety of 12*S*-HHT and analogues of (12*R*)- and 12-keto-types, whereas Wittig reaction was used for the synthesis of (8*Z*)- and (8*Z*,12*R*)-isomers.

Key words: asymmetric synthesis, cross-coupling, HHT, Wittig reaction, Suzuki–Miyaura coupling

LTB_4 is a highly potent natural inducer of inflammatory responses through binding to the receptors.[1] Existence of two subtypes of the receptors had been suggested on the basis of the binding assay, and later the subtypes were identified as BLT1 and BLT2 by Yokomizo and Shimizu.[2] Among the subtypes BLT1 binds LTB_4 more strongly than BLT2, and the low affinity of BLT2 led to discovery of that 12(*S*)-hydroxyheptadeca-5*Z*,8*E*,10*E*-trienoic acid (12*S*-HHT) binds strongly to BLT2 at 10^{-9} M.[3] Biological function has been disclosed recently and, due to the pharmaceutical interest, artificial agonist and antagonist of BLT2 with different structures have been discovered.[4] On the other hand, structural requirement of **1**, though being the prime concern, is not yet investigated probably due to the fact that 12*S*-HHT (**1**) was discovered as a by-product of the pathway leading to thromboxane A_2 (TXA_2) from PGH_2, a metabolite of cyclooxaganeses.[5] We envisioned that natural 12*S*-HHT (**1**) and analogues **2**–**5** delineated in Figure 1 would be a series of compounds for the purpose. We did not select possible 10*Z*-isomers because of our speculation that drastic change near the 12-hydroxyl group would decrease the activity. Up to now, several syntheses of 12*S*-HHT have been published.[6] The syntheses, however, suffer from low stereoselectivity or low efficiency. Among the analogues, ketone **5** is isolated from hHL-60 leukemia cells,[7] whereas (8*Z*)-isomer is synthesized in the synthesis of 12*S*-HHT.[6e]

We have published total synthesis of the lipoxygenase metabolites of several fatty acids,[8] in which Wittig reaction and Suzuki–Miyaura coupling were utilized to combine the alcoholic key intermediates to construct the required conjugated olefins, while the key intermediates were prepared by using the Sharpless asymmetric epoxidation (AE) of γ-silylallylic alcohol[9] or the Noyori asymmetric hydrogen transfer of the corresponding γ-silylacetylenic ketone.[10] With these inventions in mind, we envisaged methods to afford the compounds listed in Figure 1.

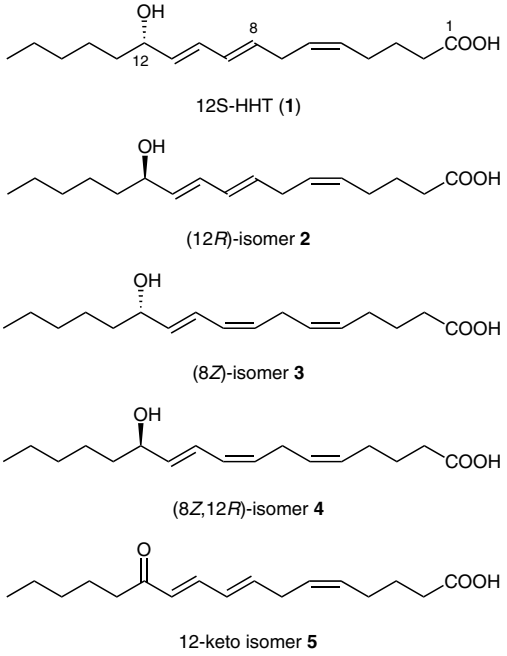

Figure 1 12*S*-HHT and its isomers

The synthesis of 12*S*-HHT (**1**) is summarized in Scheme 1, in which Suzuki–Miyaura coupling[11] of iodide (*S*)-**6** with vinyl borane **9** was envisaged to afford the conjugated olefin moiety of **1**. This iodide is easily available by the kinetic resolution of the racemic iodide *rac*-**6** by using the Sharpless asymmetric epoxidation.[12] This time the iodide (>99% ee by ^{1}H NMR spectroscopy of the MTPA ester) was converted to TBDPS ether (*S*)-**7** in 83% yield.[13] Vinyl borane **9**, the coupling partner, was synthesized by hydroboration of acetylene **8** with $(Sia)_2BH$ in THF. Coupling of (*S*)-**7** with **9** (1.2 equiv) was carried out in the presence of a catalytic amount of $Pd(PPh_3)_4$ and excess NaOH in aqueous THF at room temperature for three hours. The crude diene **10** containing a residual by-product(s) probably derived from excess **9** was subjected to deprotection with TBAF (1.1 equiv) to produce alcohol **11** in 50% yield from (*S*)-**7**. Iodide **12** was derived from alco-

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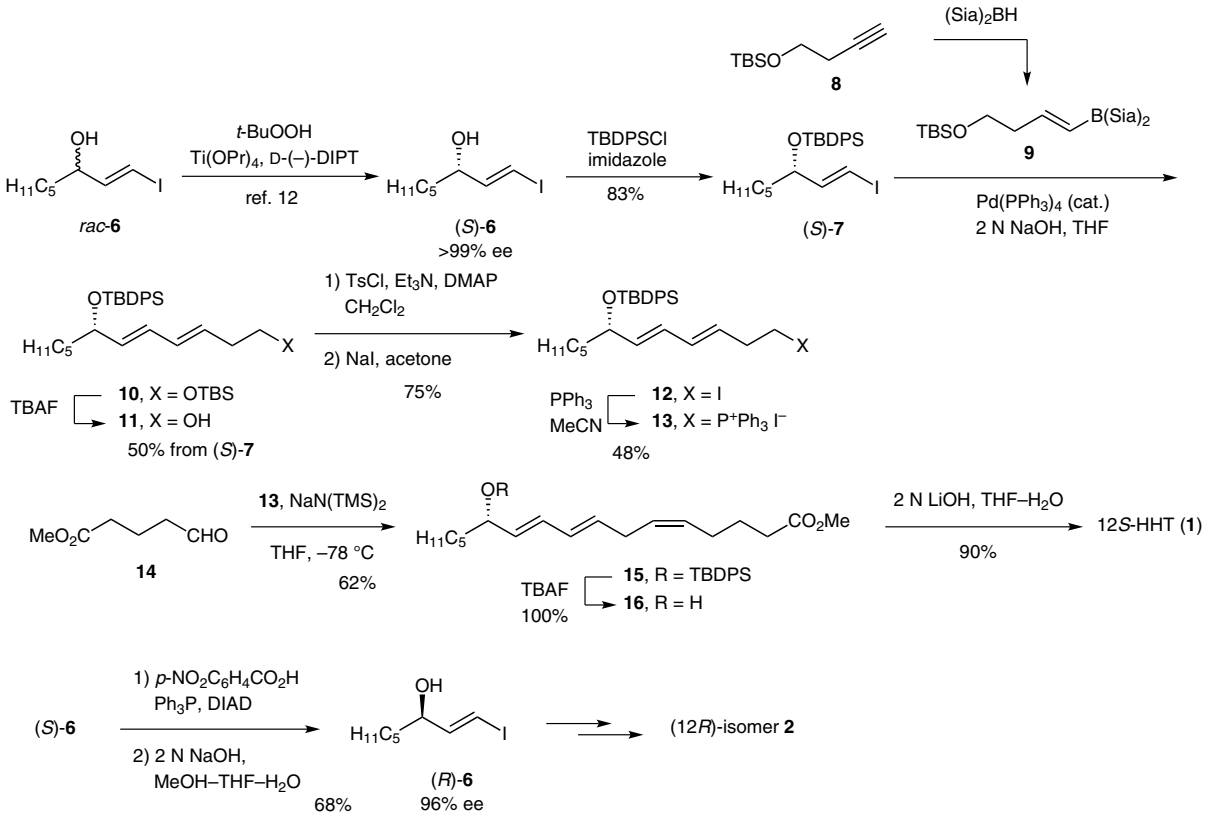

Scheme 1 Syntheses of 12*S*-HHT (**1**) and (12*R*)-isomer **2**

hol **11** by tosylation followed by substitution with NaI in acetone, whereas an attempted direct conversion of **11** to **12** with I_2 and PPh_3 was unsuccessful. Finally, iodide **12** was converted to the phosphonium salt **13** in 48% yield after Et_2O wash, which was a required purification for the next Wittig reaction. Aldehyde **14** derived from the δ-lactone in 91% yield in two steps [(1) K_2CO_3 (0.1 equiv), MeOH; (2) PCC] was subjected to Wittig reaction with an anion derived from **13** and $NaN(TMS)_2$ at –78 °C in THF to afford **15** stereoselectively (by ^{1}H NMR analysis). Deprotection of the TBDPS group afforded **16** quantitatively {$[\alpha]_D^{20}$ +14 (*c* = 0.06, acetone); lit.[6e] $[\alpha]_D^{25}$ +9 (*c* = 0.34, acetone)}, and the ^{1}H NMR spectrum of **16** was identical to that reported.[6a,b,e,f] Finally, hydrolysis of **16** furnished 12*S*-HHT (**1**) in a good yield.[14]

Synthesis of (12*R*)-enantiomer **2** was carried out as well (Scheme 1). Although the necessary alcohol (*R*)-**6** is synthesized by using the Sharpless epoxidation/kinetic resolution,[12] Mitsunobu inversion was applied to the above alcohol (*S*)-**6** for our convenience to afford (*R*)-**6**, which was obtained in 96% ee by ^{1}H NMR spectroscopy of the derived MTPA ester.

This reaction sequence was repeated with racemic alcohol *rac*-**6** to produce racemic 12-HHT (*rac*-**1**), which upon oxidation with Dess–Martin periodinane produced 12-keto isomer **5** in good yield.[14]

For the synthesis of (8*Z*)-isomer **3**, Wittig reaction of aldehyde **23** with phosphonium salt **21** to afford **24** was conceived as a key step (Scheme 2). The phosphonium reagent **21** was synthesized according to the literature method[15] except that the carboxylic acid end was left as 'CH_2OR' in order to furnish this moiety at a later stage of the synthesis. In brief, the TBS ether **17** was converted to alcohol **19** through reaction with ethylene oxide followed by Linder hydrogenation. Alcohol **19** was then converted to iodide **20** in 91% yield, which upon reaction with PPh_3 afforded the phosphonium reagent **21** efficiently. Vinyl iodide (*S*)-**7**, prepared above in 96% ee, was transformed to aldehyde **23** by reaction with CuCN followed by DIBAL reduction in 83% yield. Wittig reaction of the aldehyde with anion derived from **21** and $NaN(TMS)_2$ was conducted at –78 °C in THF to produce **24** stereoselectively by ^{1}H NMR spectroscopy. Selective deprotection of the silyl group in **24** afforded alcohol **25**, which upon oxidation with PCC followed by the Pinnick oxidation gave acid **26** in 42% yield. Finally, deprotection of the TBDPS group with TBAF afforded **3** in good yield: $[\alpha]_D^{23}$ +7 (*c* = 0.15, acetone).[14]

Similarly, TBDPS ether (*R*)-**7** derived from (*R*)-**6** was transformed to (8*Z*,12*R*)-isomer **4**: $[\alpha]_D^{23}$ +8 (*c* = 0.17, acetone).

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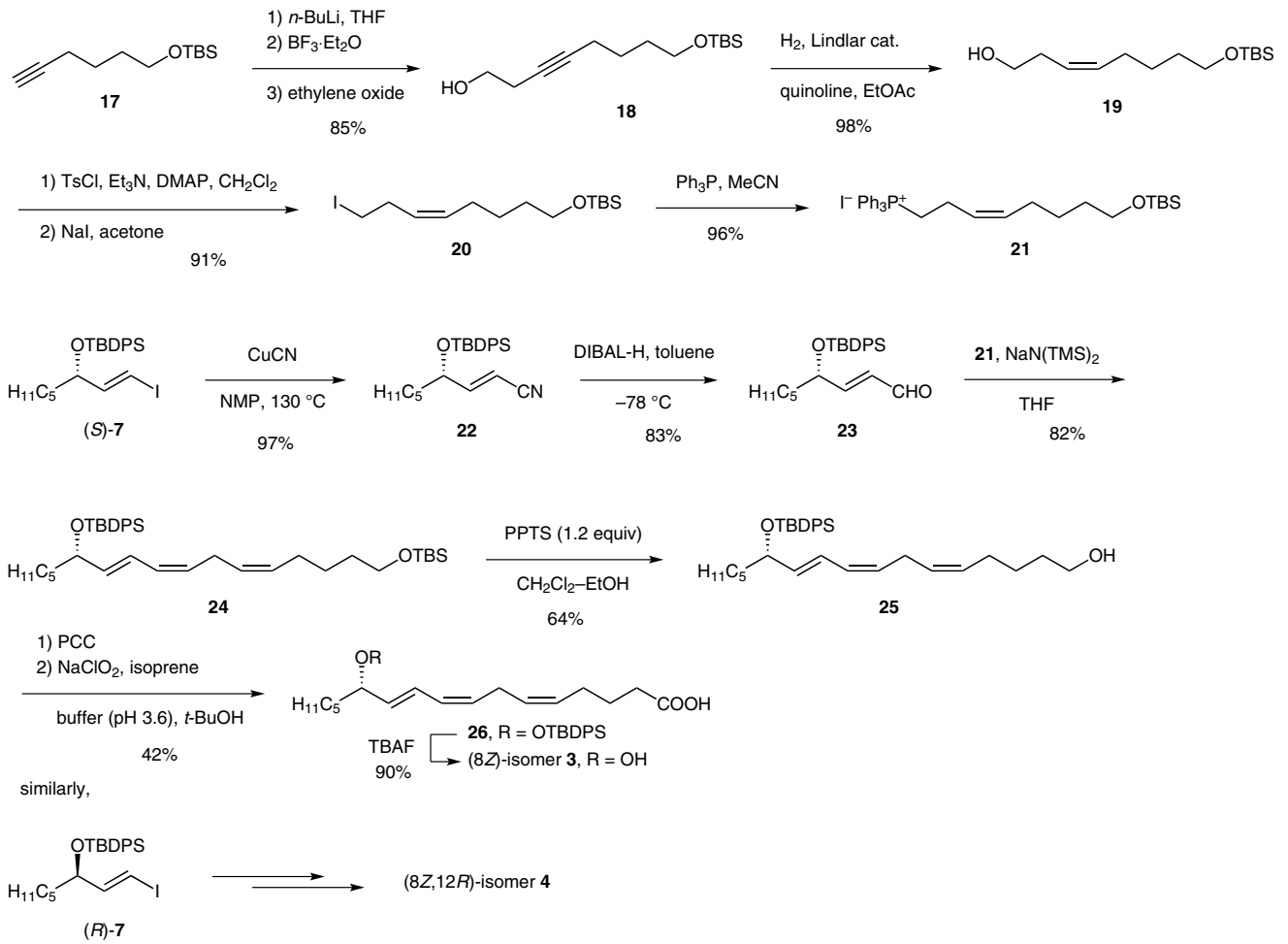

Scheme 2 Syntheses of (8*Z*)-isomer **3** and (8*Z*,12*R*)-isomer **4**

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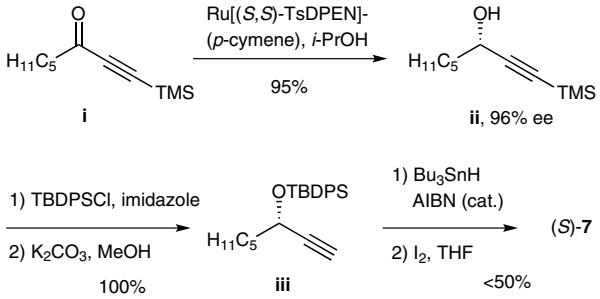
(13) The Noyori reduction of acetylene ketone **i** afforded alcohol **ii** with 96% ee by chiral HPLC of the derived benzoate. However, hydrostannation of the TBDPS ether **iii** under

radical- (AIBN) or $PdCl_2(PPh_3)_2$-catalyzed conditions followed by iodination gave a mixture of (*S*)-**7**, the *cis*-isomer, and the regioisomer (Scheme 3).



Scheme 3

(14) 12*S*-HHT (**1**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.0 Hz, 3 H), 1.14–1.80 (m, 10 H), 2.00–2.20 (m, 2 H), 2.37 (t, *J* = 7.5 Hz, 2 H), 2.83 (t, *J* = 6.0 Hz, 2 H), 2.60–4.00 (br s, 2 H), 4.12 (q, *J* = 6.0 Hz, 1 H), 5.30–5.52 (m, 2 H), 5.55–5.73 (m, 2 H), 6.04 (dd, *J* = 15.0, 10.5 Hz, 1 H), 6.18 (dd, *J* = 15.0, 10.5 Hz, 1 H).
(8*Z*)-Isomer **3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.0 Hz, 3 H), 1.18–1.81 (m, 10 H), 2.00–2.26 (m, 2 H), 2.36 (t, *J* = 7.0 Hz, 2 H), 2.87 (dt, *J* = 16.0, 7.0 Hz, 1 H), 3.03 (dt, *J* = 16.0, 7.0 Hz, 1 H), 3.20–4.00 (br s, 2 H), 4.26 (q, *J* = 6.0 Hz, 1 H), 5.32–5.52 (m, 3 H), 5.69 (dd, *J* = 15.0, 6.0 Hz, 1 H), 5.98 (t, *J* = 11.0 Hz, 1 H), 6.58 (dd, *J* = 15.0, 11.0 Hz, 1 H).
12-Keto isomer **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.0 Hz, 3 H), 1.23–1.42 (m, 5 H), 1.57–1.82 (m, 4 H), 2.08–2.22 (m, 2 H), 2.38 (t, *J* = 7.0 Hz, 2 H), 2.55 (t, *J* = 7.5 Hz, 2 H), 2.94 (t, *J* = 5.0 Hz, 2 H), 5.40–5.55 (m, 2 H), 6.05–6.26 (m, 3 H), 7.13 (dd, *J* = 16.0, 10.0 Hz, 1 H).

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