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HIGHLY STEREOCONTROLLED, MULTIGRAM SCALE SYNTHESIS OF LEUKOTRIENE B_4

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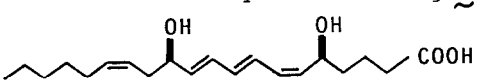
Summary: Leukotriene B_4 (1) is synthesized in quantity by combining the enyne 3 with the vinyl iodide 5 via the vinylborane. The two fragments 3 and 5 are prepared readily by using the kinetic resolution of the corresponding racemic alcohols dl-2 and dl-4 as a key step.

Leukotriene B_4 (LTB_4, 1) is biosynthesized from arachidonic acid via the 5-lipoxygenase pathway.[1] Studies on the biological properties of 1 have shown that 1 is powerfully chemotactic for macrophages and neutrophiles and therefore relevent to allergic and inflammatory states.[2] Due to the biological importance and the difficulty in isolating 1 in quantity from bio-

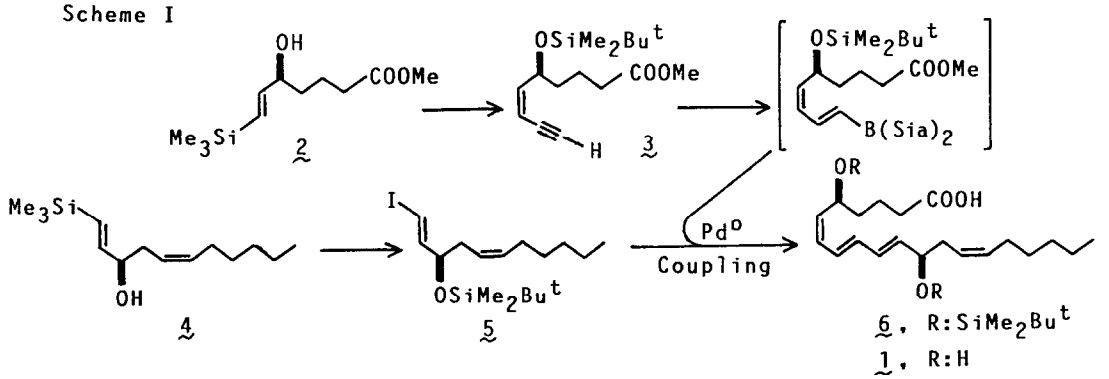


LTB_4 (1)

logical sourses, several groups have embarked on the synthesis of this compound.[3] The combining method of two hydroxy bearing chiral fragments has been employed frequently to prepare 1.[4] However, the stereoselectivity of the coupling reaction was not so high and, therefore, isolation of 1 by HPLC or repeated flash chromatography was required. Herein we wish to report a highly stereocontrolled synthesis of 1 in which HPLC separation is not necessary to purify the final product 1 or any intermediates, thus making it possible to prepare 1 in large quantity.

Our synthesis of 1 is outlined in Scheme 1. The conjugated triene unit of 1 is constructed specifically from the cis enyne 3 and the trans vinyl

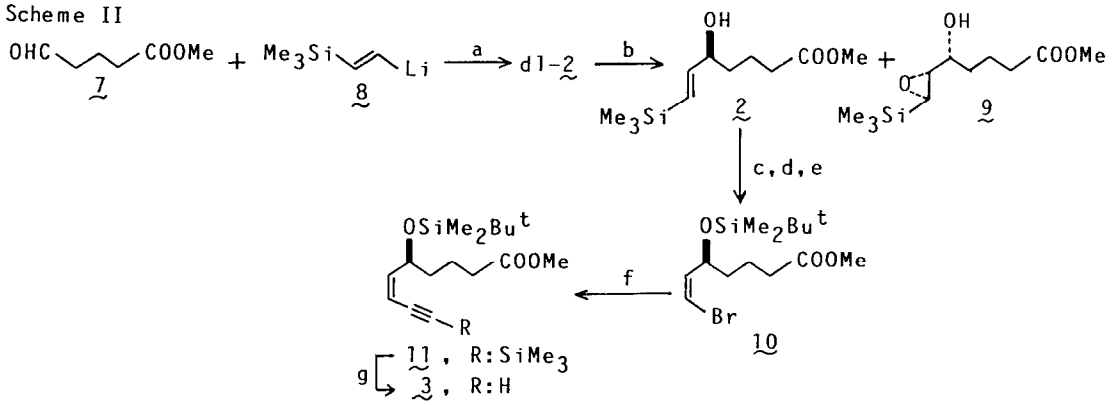
Scheme I



iodide 5 according to the procedure reported by Suzuki et al.[5] The fragments 3 and 5 are synthesized from the allylic alcohols 2 and 4, respectively, both of which can be readily prepared by using the kinetic resolution of the corresponding racemic alcohols by the Sharpless asymmetric epoxidation.[6]

Preparation of 3 is outlined in Scheme II. The alcohol dl-2 was prepared in 56% yield by the reaction of the aldehyde 7[7] with the lithium anion 8 derived from trans 1-tributylstannyl-2-trimethylsilylethene and ^{n}BuLi.[8] Kinetic resolution of dl-2 using TBHP, D(-)DIPT, and Ti($O^{i}Pr$)$_4$ at -21 °C for 20 h proceeded highly efficiently to give 2 ($[\alpha]_D^{25}$ +6.78° (c 1.15, $CHCl_3$)) and the epoxide 9 ($[\alpha]_D^{25}$ +6.74° (c 1.75, $CHCl_3$))in 43% and 45% yields, respectively. Optical purity of 2 and 9 was found to be >99%, respectively, by ^{1}H NMR spectroscopy of the corresponding MTPA esters. Noteworthy is the fact that the kinetic resolution of the ester bearing alcohol dl-2 proceeded with almost infinite rate difference between the two enantiomers as was observed in the case of the usual γ-trimethylsilyl allylic alcohols.[6] After separatrion of 2 and 9, 2 was transformed into the cis vinyl bromide 10 in 74% yield.[9] Coupling reaction of 10 and trimethylsilylacetylene using $Pd(PPh_3)_4$ and CuI as catalysts afforded 11 in 94% yield.[10,11] Liberation of the terminal acetylene was effected by treatment with KCN and $AgNO_3$[11] to afford 90% yield of 3 ($[\alpha]_D^{25}$ +49.6° (c 1.15, $CHCl_3$)), which was found to be homogeneous by ^{1}H and ^{13}C NMR spectroscopy.

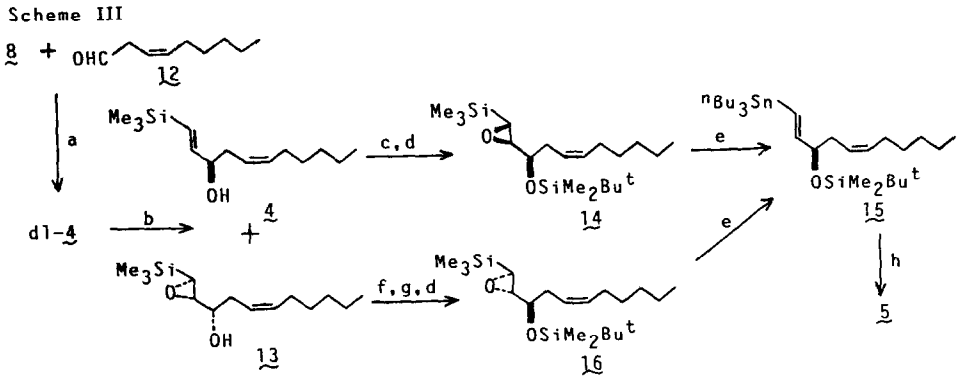
Scheme II



a, -78 °C, THF; b, TBHP (1.5 equiv), D(-)DIPT (1.2 equiv), Ti($O^{i}Pr$)$_4$ (1 equiv), CH_2Cl_2, -21 °C, 20 h; c, Br_2, CH_2Cl_2, 0 °C; d, $^{n}Bu_4NF$, THF, 0 °C; e, $ClSiMe_2Bu^t$, imidazole, DMF, 0 °C→20 °C; f, $Me_3SiC{\equiv}CH$ (3 equiv), $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), $^{n}PrNH_2$ (3 equiv), C_6H_6, 20 °C; g, KCN (7 equiv), $AgNO_3$ (4 equiv), EtOH-THF-H_2O (1 : 1 : 1), 0 °C.

The fragment 5 was prepared starting from the racemic alcohol dl-4, which was obtained by the reaction of the aldehyde 12[12] with 8 in 84% yield (Scheme III). Kinetic resolution of dl-4 using L(+)DIPT was also found to proceed highly efficiently to afford 4 (>99% ee, $[\alpha]_D^{25}$ +4.2° (c 1.15, $CHCl_3$)) and 13 (>99% ee, $[\alpha]_D^{25}$ +7.6° (c 1.40, $CHCl_3$)) in 44% and 43% yields, respectively.[6] After separation of 4 and 13, 4 was converted into

Scheme III



a, -78 °C, THF; b, TBHP (1.5 equiv), L(+)DIPT (1.2 equiv), $Ti(O^iPr)_4$ (1 equiv), CH_2Cl_2, -21 °C, 3.5 h; c, TBHP (1.5 equiv), D(-)DIPT (0.25 equiv), $Ti(O^iPr)_4$ (0.20 equiv), 3A molecular sieves, CH_2Cl_2, -21 °C, 3 h; d, $ClSiMe_2Bu^t$, imidazole, DMF ; e, $^nBu_3SnH$ (1.1 equiv), LDA (1.5 equiv), THF, 0 °C→25 °C, 3 h; f, DEAD (1.4 equiv), p-NO_2-C_6H_4COOH (1.5 equiv), PPh_3 (1.55 equiv), THF, 0 °C, 30 min; g, 2N NaOH aq. (2 equiv), THF-MeOH (1 : 1), 0 °C, 1 h; h, I_2 (1.2 equiv), Et_2O, 0 °C, 30 min.

15 via 14 in 84% yield.[9] The epoxide 13 was also converted into 15 via the Mitsunobu inversion[13] in 81% overall yield.[9] Finally, treatment of 15 with I_2 led to 5 ($[\alpha]_D^{25}$ +7.2° (c 2.03, $CHCl_3$) in 92% yield.[9,14]

The chiral segments 3 and 5 in hand, coupling reaction to give the silyl ether 6 was carried out as follows (Scheme I). After hydroboration of 3 using disiamylborane (1.5 equiv) in THF at 0 °C for 1 h, aqueous 2N NaOH (6 equiv), 5 (1.4 equiv), and $Pd(PPh_3)_4$ (0.05 equiv) were added successively and the resulting mixture was stirred at 50 °C for 16 h.[5] The mixture was poured into sat. NH_4Cl and extracted with ether several times.[15] The combined extracts were dried and concentrated to give an oil[16] which was chromatographed on silic gel using a mixture of deoxygenated hexane and ether as the eluent to afford 6 ($[\alpha]_D^{25}$ +4.3° (c 0.60, $CHCl_3$)) in 70% yield. The silyl ether 6 was found to be homogeneous by ^1H and ^{13}C NMR spectroscopy and also by TLC.[17] Finally, treatment of 6 with excess $^nBu_4NF$ (10 equiv, THF, 25 °C, 18 h) followed by deoxygenated column chromatography on silica gel afforded 80% yield of LTB_4 (1, $[\alpha]_D^{25}$ +13.1° (c 0.26, $CDCl_3$); lit.[3g] $[\alpha]_D^{25}$ +12.6° (c 0.46, $CDCl_3$)), the purity of which was found to be >95% by RP-HPLC analysis. Spectroscopic data (IR, ^1H NMR) of 1 thus synthesized were in good agreement with the reported one[3f,g] and the retention time of 1 on RP-HPLC was identical with that of an authentic LTB_4.

We succeeded the highly stereocontrolled synthesis of 1. In our synthesis, HPLC separation is not necessary at any stage of the synthesis: therefore, it is possible to synthesize 1 in large quantity. In fact, we prepared 1.16 g of the silyl ether 6 from 0.86 g of 3 and 1.67 g of 5.

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15. Oxidative work-up (H_2O_2, OH^-) caused decomposition of 6.
16. Amount of the disiamylborane residue in the oil was less than 5%, if any.
17. 500 MHz ^{1}H NMR ($CDCl_3$) δ 6.36 (dd, J = 12, 14 Hz, 1H), 6.19 (m, 2H), 5.96 (t, J = 12 Hz, 1H), 5.72 (dd, J = 7, 14 Hz, 1H), 5.44 (dt, J = 12, 7 Hz, 1H), 5.38 (m, 2H), 4.57 (q, J = 7 Hz, 1H), 4.18 (q, J = 7 Hz, 1H), 2.38-2.22 (m, 4H), 2.01 (q, J = 7 Hz, 2H), 1.78-1.23 (m, 10H), 0.91 (s, 9H), 0.88 (s, 9H), 0.88 (t, 3H), 0.07 (s, 3H), 0.05 (s, 6H), 0.02 (s, 3H); 22.5 MHz ^{13}C NMR ($CDCl_3$) δ 179.8, 137.8, 134.9, 133.8, 132.0, 129.3, 128.1, 127.1, 125.2, 73.3, 68.8, 37.8, 36.5, 34.1, 31.6, 29.4, 27.5, 26.0, 22.6, 20.7, 18.3, 18.2, 14.1, -4.1, -4.3, -4.7.

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