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Application of the Low-Valent Titanium Reductive Elimination of 1,6-Dibenzoate-2,4-dienes to the Total Synthesis of 6(E)-5(S)-12(R)-Leukotriene B_4

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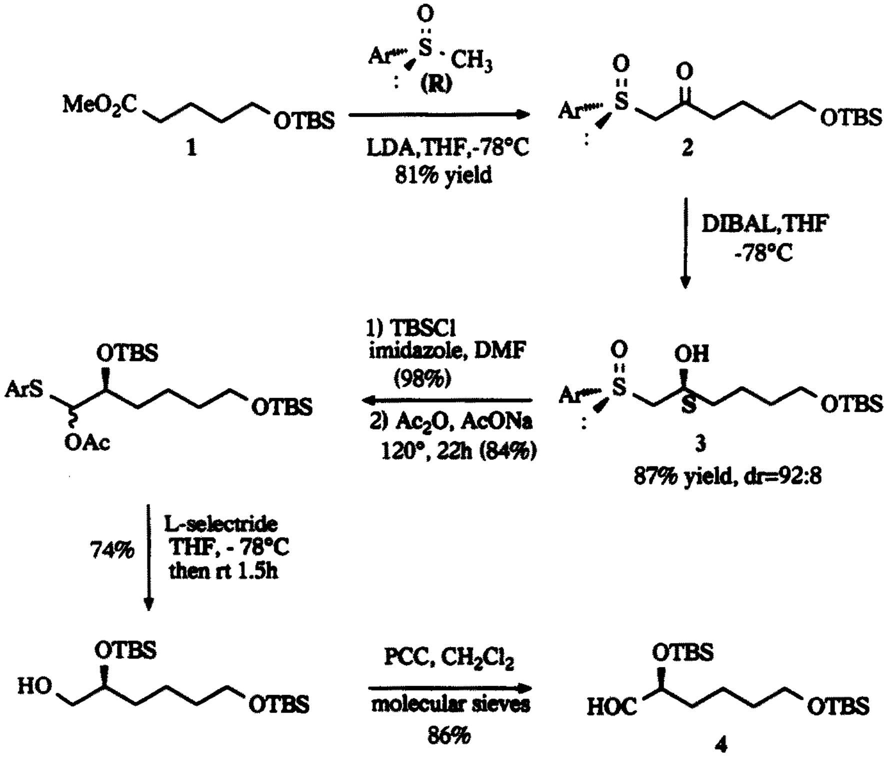
Abstract: A stereoselective synthesis of 6(E)-5(S)-12(R)-leukotriene B_4 is described in this paper, using a novel reaction, the low-valent titanium induced reductive elimination of a 1,6-dibenzoate-2,4-diene, for the selective synthesis of the trans-triene moiety.

In most syntheses of leukotrienes[1], the conjugated triene moiety was prepared by consecutive Wittig reactions. Usually the 6-7 double bond was made in the last step as a mixture of 6E and 6Z isomers in ratios ranging from 1/5 to 1/3. In a unique paper[2] describing a stereospecific synthesis of 6E-LTB$_4$ 10, the last two steps were the introduction of the 6,8-diene unit in a 50% isolated yield followed by a Wittig olefination to create the 10-11 double bond in 25% isolated yield. In the preceeding communication[3], we report our discovery of a new method for the stereoselective synthesis (higher than 95% trans) of conjugated trienes in almost quantitative yields via the low-valent titanium reductive elimination[4] of 1,6-dibenzoate-2,4-dienes. In this paper we wish to report the stereoselective total synthesis of 6E-LTB$_4$ in which the conjugated triene unit is prepared quantitatively in one step using this novel reaction.

The synthesis is based on the condensation of the two chiral aldehydes 4 and 5 with diacetylene followed by reduction of the triple bonds to a 1,6-diol-2,4-diene. Protection of the alcohols with benzoate esters followed by low-valent Ti reductive elimination lead to the isolation of the trienic compound 8 in a quantitative yield (Scheme 2) with no sign of the 7 other possible double bond isomers.

The optically active aldehyde 4 was prepared by an asymmetric synthesis as shown in Scheme 1. The condensation of 1 with (+)-(R)-methyl-p-tolylsulfoxide yielded 2 in a 81% yield. DIBAL reduction[5] gave (+)-[(S)R, 2S] β-hydroxysulfoxide 3 in 87% yield in a 92:8 ratio of diastereomers as determined from the ^{1}H NMR of the crude product. Finally, the aldehyde 4 was obtained from 3 via a Pummerer rearrangement of the *t*-butyldimethylsiloxy derivative followed by reduction (L-selectride) and subsequent oxidation (PCC) of the corresponding alcohol.

The diol 6 (Scheme 2) was prepared as a mixture of diastereomers by condensation of the two aldehydes 4 and 5[6] with diacetylene[7] in two high yield steps. The diyne was then reduced to the 1,3-diene with activated zinc[8] in 79% yield. The diol was subsequently benzoylated to give 7. Following our recent discovery[4], the dibenzoate 7 was treated with a suspension of Ti(0) for 20 minutes giving the triene 8 as the sole product and in quantitative yield. By ^{1}H NMR and spin decoupling it was possible to show the Z geometry of the C_{14-15} double bond (J_{14-15} = 11 Hz) and the E geometry for the C_{6-7} and C_{10-11} double bonds ($J_{6-7} = J_{10-11}$ = 15.5 Hz). The E geometry for the C_{8-9} double bond was established using compound 9 which was obtained after deprotection of the TBDMS groups and exposure of the triol to $RuCl_2(PPh_3)_2$[9] (via selective oxidation of the primary alcohol to the corresponding aldehyde followed by cyclization to the 6-membered lactol, subsequently oxidized to the lactone). From spin decoupling experiments, the ^1H NMR of 9 confirmed the stereochemistry of the C_{6-7}, C_{10-11}, and C_{14-15} double bonds: $J_{14-15} = 10.5$ Hz (Z), $J_{6-7} = J_{10-11} = 14.3$ Hz (E). By adding a stoichiometric amount of $Pr(FOD)_3$, the coupling constant $J_{8-9} = 14.9$ Hz was determined, attesting to the E configuration of the C_{8-9} double bond. In this manner the all-trans configuration of the triene was determined.



Scheme 1

Finally the lactone was opened with LiOH to give 6E-LTB_4[10] showing the reported[2] UV spectrum in MeOH [256nm (E 56900), 277nm (E 45200)].

Hence, this application shows the synthetic promise of the stereoselective trans-triene synthesis via low-valent titanium reductive elimination of 1,6-dibenzoate-2,4-dienes which are readily obtained in 2 steps from the corresponding 1,6-diol-2,4-diyne. The reaction is rapid and gives quantitative yield. We are currently investigating extension of this methodology towards higher polyenes as well as continuing our synthetic applications of this method.

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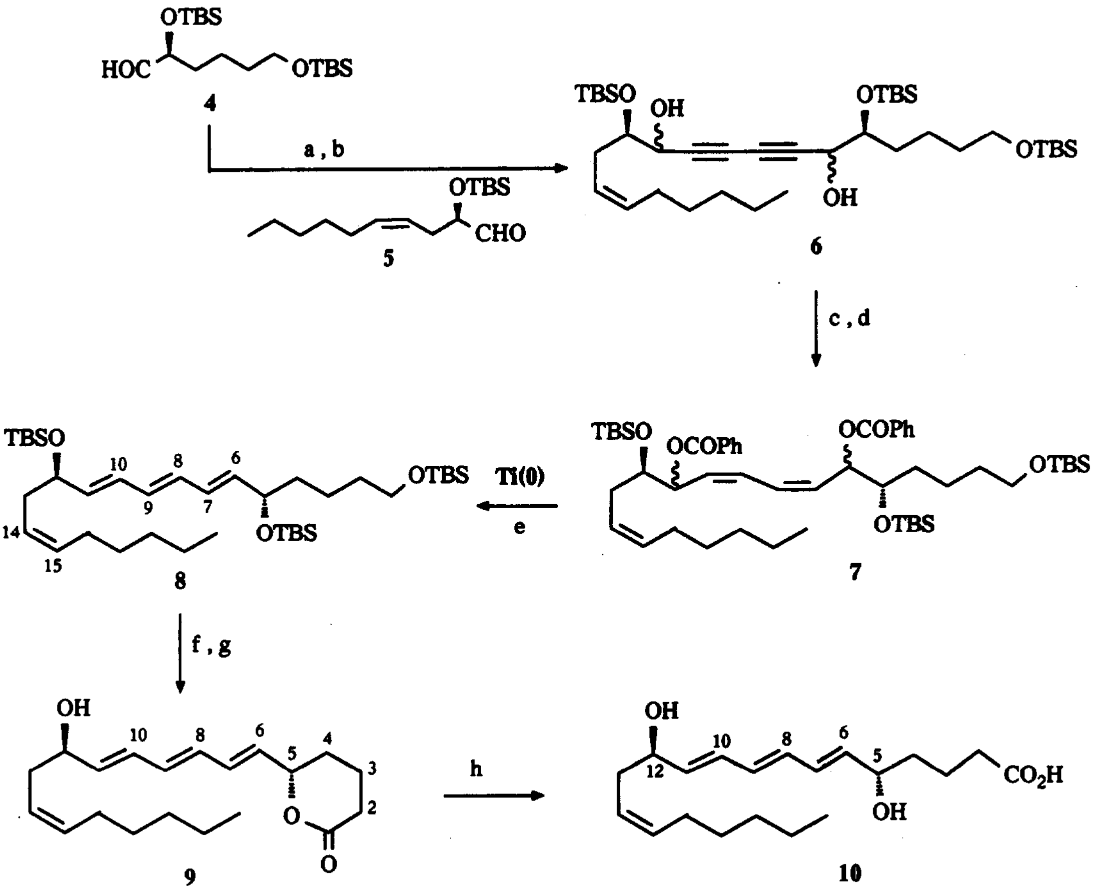

a). H—≡—≡—MgBr, THF, -78°C then 0° for 1h, 82%; b). EtMgBr, 0°C then 5, THF, 0°C, rt for 3h, 91%; c). Zn/Cu, MeOH-H_2O, rt 32h, 73%; d). PhCOCl, pyridine, rt 12h, 89%; e). Ti(0), 6 eq. (from $TiCl_3$ and $LiAlH_4$: 2/1), THF, 65°, 20min, 99%; f). TBAF, THF, 0°C, 75%; g). $RuCl_2(PPh_3)_2$, benzene, rt, 2h, 70%; h). LiOH, THF-H_2O, rt, 20min, 45%.

Scheme 2

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10. $[\alpha]_D$ +11.2 (c = 2, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ: 6.27 (m, 1 H, H-7), 6.21 (m, 3 H, H-8,9,10), 5.74 (m, 2 H, H-6,11, dd with J = 14.6 and 7.7 Hz upon decoupling at 4.19 ppm), 5.58 (m, 1 H, H-15, d with J = 11.0 Hz upon decoupling of m at 2.1 ppm), 5.34 (m, 1 H, H-14, dd with J = 10.6 Hz upon decoupling of m at 2.35 ppm), 4.19 (m, 1 H, H-5,12), 2.35 (m, 4 H, H-2,13),2.10 (m, 2 H, H-16), 1.65 (m, 4 H), 1.36 (m, 6 H), 0.09 (t, 3 H, J = 7.0 Hz).

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