7.26 (s, 1 H, H-3 Np), 5.33 (br s, 1 H, NH), 5.20 (s, 2 H, OCH_2S), 5.08 (d, J = 12 Hz, 1 H, $PhCH_2$), 4.98 (d, J = 12 Hz, 1 H, $PhCH_2$), 4.74 (d, J = 12 Hz, 1 H, H-5), 4.54 (d, J = 12 Hz, 1 H, H-6), 4.38 (dd, J = 8, 12 Hz, 1 H, H-4), 3.70 (t, J = 12 Hz, 1 H, H-3), 3.04 (d, J = 12 Hz, 1 H, OH), 2.22 (s, 3 H, SCH_3), 1.97 (s, 3 H, OAc), 1.88 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 183.9, 169.7, 144.2, 141.7, 136.1, 134.5, 134.1, 132.3, 131.9, 128.6, 128.2, 128.1, 127.0, 126.6, 74.8, 72.4, 70.9, 67.5, 65.3, 57.2, 20.8, 20.2, 14.9.

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Registry No. 1, 1404-15-5; 6, 137742-87-1; 6′, 137742-86-0; 7, 137820-56-5; 7′, 137742-85-9; 8, 33107-14-1; (*E*)-10, 137742-84-8; (*Z*)-10, 137742-83-7; 12, 137742-88-2; 12′, 137893-09-5; 13, 137742-89-3; 14, 137742-90-6; 15, 137768-16-2; 16, 137742-91-7; 17, 137742-92-8; 20, 137768-17-3; 21, 137742-93-9; 22, 137742-94-0; α-23, 137742-96-2; β-23, 137742-95-1; α-24, 137742-98-4; β-24, 137742-97-3; α-25, 137742-99-5; 1,2:5,6-Di-*O*-cyclohexylidene-D-mannitol, 76779-67-4; D-mannitol, 69-65-8; furan, 110-00-9.

Supplementary Material Available: IR and MS data for all compounds in the Experimental Section and the data for the X-ray crystallograpic structure determinations of structures 12 and 17 (14 pages). Ordering information is given on any current masthead page.

Stereocontrolled Total Synthesis of Leukotriene B_4

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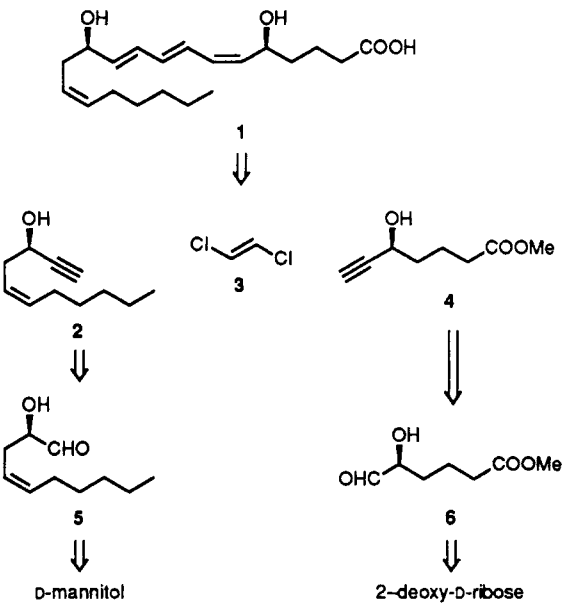
A stereocontrolled synthesis of leukotriene B_4 (1) is accomplished by assembly of the chiral synthons 2 and 4, prepared from D-mannitol and 2-deoxy-D-ribose, with (*E*)-dichloroethylene.

There is a great deal of current interest in hydroxylated eicosatetraenoic acids produced from arachidonic acid by the lipoxygenase pathway.[1] Leukotriene B_4 (LTB_4) has received attention due to its potent chemotactic properties toward macrophages and neutrophiles and its potential role in inflammation.[2] Due to the biological importance and the difficulty in isolating LTB_4 in quantity from biological material, several groups have developed strategies for synthesis of this compound[3] in which the coupling of two chiral building blocks by a Wittig reaction has frequently been employed. However, this coupling is usually not entirely stereoselective, and isolation of LTB_4 by HPLC is required.

Our approach to the synthesis of LTB_4 is based on the following retrosynthetic scheme:

The disconnection of C_7–C_8 and C_9–C_{10} leads to two chiral fragments C_1–C_7 and C_{10}–C_{20} and a single *E* olefin C_8–C_9. It has been shown[4] that the triene system having



a defined geometry can be efficiently generated by the palladium-catalyzed sequential substitution of dichloroethylenes *E* and *Z*. Thus, the sequential coupling of acetylenic alcohols 2 and 4 with (*E*)-dichloroethylene 3 and selective reduction of the triple bonds would give the desired molecule.

Results and Discussion

The α-hydroxy aldehyde 5 was prepared from D-mannitol according to Depezay.[3j] Compound 5 was then

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(4) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315; **1984**, *25*, 6001. Guillerm, D.; Linstrumelle, G. *Ibid.* **1985**, *26*, 3811; **1986**, *27*, 5857.

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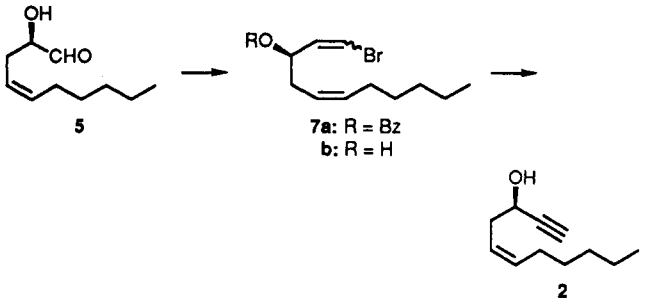
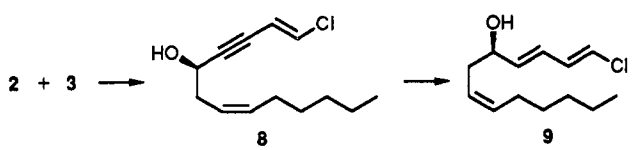
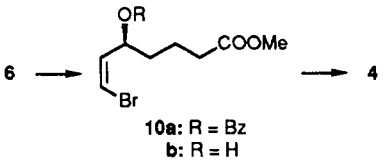
Scheme I



Scheme II



Scheme III



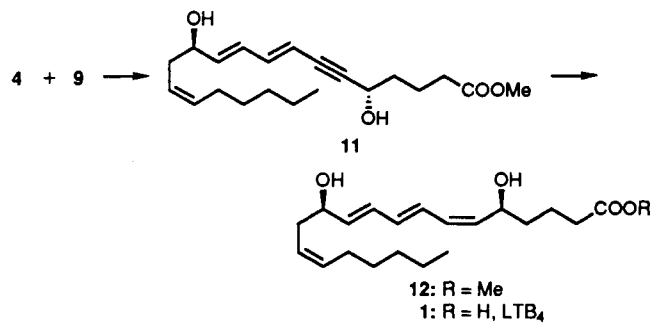
homologated to the terminal alkyne **2** according to the Matsumoto and Kuroda[5] method as modified by Pougny and Rollin:[6] treatment of **5** with (bromomethylene)triphenylphosphorane gave a mixture of (*Z*)- and (*E*)-bromo olefin **7a** in 73% yield. Debenzoylation with catalytic sodium methanolate in MeOH gave **7b** (*Z*/*E* ratio = 8:1) in 94% yield. Purification by flash chromatography gave the pure *Z* isomer **7b**. Dehydrohalogenation of the *Z* bromo alcohol **7b** by potassium *tert*-butoxide yielded the pure propargylic alcohol **2** in 86% yield (Scheme I).

Stereospecific coupling of the propargylic alcohol **2** with (*E*)-1,2-dichloroethylene in the presence of tetrakis(triphenylphosphine)palladium and copper iodide in benzene containing piperidine gave the hydroxy chloro enyne **8** in 80% yield (Scheme II). The *E,E* chloro diene **9** was prepared in 85% yield by reduction of **8** with lithium aluminium hydride in refluxing THF.[7] The dienic system was confirmed by analysis of the 300-MHz ^{1}H NMR spectrum: the coupling constants were J = 13.5 Hz and J = 15 Hz, respectively.

The chiral aldehyde **6**, synthetized from 2-deoxy-D-ribose according to Rokach,[3c] was treated with (bromomethylene)triphenylphosphorane in THF at −78 °C to give the bromo olefin **10a** (70%) as a mixture of inseparable *Z* and *E* isomers. After debenzoylation of **10a**, the alcohols **10b** (92%) (*E* + *Z* mixture) were treated with potassium *tert*-butoxide in THF. The *Z* isomer was dehydrohalogenated to give the propargylic alcohol **4** (70%) while the *E* isomer was recovered unchanged (Scheme III).

Stereospecific coupling of chloro diene **9** with the chiral propargylic hydroxy ester **4**, using tetrakis(triphenylphosphine)palladium, copper iodide in benzene containing *n*-butylamine, yielded the dienyne **11** (33%) (Scheme IV). Unreacted chloro diene **9** was recovered in 62% yield. The use of different catalysts ($PdCl_2$ $2PPh_3$, $Pd(dba)_2$, $PdCl_2(MeCN)_2$) in different solvents (THF, DMF, CH_3CN) gave lower yields of **11**. The 300-MHz ^{1}H NMR spectrum

Scheme IV



of this dienyne showed the presence of the *E,E* dienic system (J 15.5 Hz). Stereoselective reduction of the *E,E* conjugated dienyne **11** with activated zinc dust[8] in aqueous methanol produced the *E,E,Z* conjugated triene **12** in 70% yield.[9] The 300-MHz ^{1}H NMR spectrum of **12** again showed coupling constants (J = 15 Hz, J = 14.5 Hz, J = 11 Hz) which confirmed the *E,E,Z* trienic system of LTB_4.[10] The UV spectrum of **12** showed three characteristic bands at 259, 269, and 280 nm.

The ester **12** was saponified in 95% yield by potassium carbonate in methanol–water to give pure LTB_4 (**1**) having biological activity identical to those of the natural product.[11]

In conclusion, a total synthesis of LTB_4 has been developed using a strategy based on palladium(0)–copper(I) catalyzed technology and selective reduction to construct the carbon skeleton. This sequence is highly stereocontrolled, flexible, and convergent and makes available a number of useful stereoisomers of leukotrienes B.

Experimental Section

(1*Z*,3*R*,5*Z*)-3-(Benzoyloxy)-1-bromoundeca-1,5-diene (7a). To a suspension of (bromomethylene)triphenylphosphorane (2160 mg, 4.96 mmol) in dry THF (16 mL) at −78 °C was added potassium *tert*-butoxide (500 mg, 4.46 mmol). Stirring was maintained for 30 min until a yellow color persisted. The benzoate of **5** (680 mg, 2.48 mmol) in dry THF (4 mL) was then added dropwise at −78 °C under argon pressure. The suspension was allowed to warm to −20 °C and then diluted with ether (40 mL). The reaction mixture was filtered through silica gel (elution with hexane–ethyl acetate, 9:1) (80 mL). After concentration of the filtrate under vacuum, the residue was purified by flash chromatography (elution with hexane–ethyl acetate, 95:5). The *Z* and *E* isomers could not be separated, and only one product **7a** was obtained (630 mg, 73%): IR (NaCl film) 1720 (C=O), 1250 (O—C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{23}O_2Br$: C, 61.54; H, 6.6. Found: C, 61.37; H, 6.61.

(1*Z* and 1*E*,3*R*,5*Z*)-1-Bromoundeca-1,5-dien-3-ol (7b). To a solution of compound **7a** (600 mg, 1.7 mmol) in dry methanol (2 mL) was added at 0 °C sodium methanolate in methanol (1 M, 0.5 mL). After stirring for 3 h at room temperature, the mixture was diluted with anhydrous methanol and neutralized with Amberlite IR-120 (H^+). After filtration and concentration under vacuum, the residue was chromatographed on silica gel (elution with hexane–ethyl acetate, 9:1). The *E* isomer (59 mg, 14%) was first eluted followed by the *Z* isomer (400 mg, 94%).

(1*Z*,3*R*,5*Z*)-1-Bromoundeca-1,5-dien-3-ol (7bZ): $[\alpha]^{20}_D$ +65° (*c* 1.07, CCl_4); IR (NaCl film) 3600–3200 (OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (1 H, dd, J = 7 Hz, J = 1 Hz, H_1), 6.2 (1 H, dd, J = 7 Hz, H_2), 5.61 (1 H, dt, J = 10.5 Hz, J = 7 Hz, H_6), 5.41

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(11) We thank Dr. M. Delaforge and Dr. J. L. Boucher (University René Descartes, Paris) for biological analyses of these products.

(1 H, dt, J = 10.5 Hz, J = 7 Hz, H_5), 4.62 (1 H, qd, J = 7 Hz, J = 3.4 Hz, H_3), 2.4 (2 H, m, H_4), 2.07 (2 H, q, J = 7 Hz, H_7), 1.81 (1 H, d, J = 3.4 Hz, OH), 1.45–1.2 (6 H, m, aliphatic H), 0.88 (3 H, t, J = 6.6 H, CH_3-11). Anal. Calcd for $C_{11}H_{19}OBr$: C, 53.45; H, 7.75. Found: C, 53.66; H, 7.61. **(1*E*,3*R*,5*Z*)-1-Bromoundeca-1,5-dien-3-ol (7bE)**: $[\alpha]^{20}_D$ +35° (*c* 2.2, CCl_4); IR (NaCl) 3600–3200 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.35 (1 H, dd, J = 13.5 Hz, J = 1 Hz, H_1), 6.24 (1 H, dd, J = 13.5 Hz, J = 6.5 Hz, H_2), 5.61 (1 H, dt, J = 10.5 Hz, J = 7 Hz, H_6), 5.36 (1 H, dt, J = 10.5 Hz, J = 7 Hz, H_5), 4.15 (1 H, ddd, J = 7 Hz, J = 6.5 Hz, J = 4 Hz, H_3), 2.32 (2 H, t, J = 7 Hz, H_4), 2.02 (2 H, q, J = 7 Hz, H_7), 1.69 (1 H, d, J = 4 Hz, OH), 1.4–1.28 (6 H, m, aliphatic H), 0.88 (3 H, t, J = 6.6 Hz CH_3-11).

(3*R*,5*Z*)-Undec-5-en-1-yn-3-ol (2). Potassium *tert*-butoxide (265 mg, 2.36 mmol) was added to a solution of compound **7bZ** (290 mg, 1.18 mmol) dissolved in anhydrous DME. After being stirred overnight, the reaction mixture was neutralized with acetic acid (70 mL, 2.36 mmol), diluted with ether (10 mL), and filtered through silica gel (elution with ether). After evaporation of the filtrate under vacuum, the residue was purified by flash chromatography (elution with hexane–ethyl acetate, 8:2) to give propargylic alcohol **2** (168 mg, 86%): $[\alpha]^{20}_D$ +26° (*c* 2.2, CCl_4); IR (NaCl film) 3500–3300 (OH), 3300 (=CH), 2100 (C≡C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.64 (1 H, m, J = 10.5 Hz, J = 6 Hz, J = 1 Hz, H_6), 5.45 (1 H, m, J = 10.5 Hz, J = 7.5 Hz, J = 1.5 Hz, H_5), 4.38 (1 H, td, J = 7.5 Hz, J = 2 Hz, H_3), 2.45 (2 H, td, J = 7.5 Hz, J = 1 Hz, H_4), 2.4 (1 H, d, J = 2 Hz, H_1), 2.04 (2 H, qd, J = 6 Hz, J = 1.5 Hz, H_7), 1.4–1.26 (7 H, m, aliphatic H), 0.89 (3 H, t, J = 6.5 Hz, CH_3-11).

(1*E*,5*R*,7*Z*)-1-Chlorotrideca-1,7-dien-3-yn-5-ol (8). To a solution of (*E*)-dichloroethylene (0.77 mL, 10.1 mmol) in dry benzene (2 mL) at room temperature, under argon pressure, was added tetrakis(triphenylphosphine)palladium (24 mg, 0.02 mmol). Thirty minutes later a solution of compound **2** (168 mg, 1.01 mmol) in dry benzene (1 mL) was added under argon pressure. Then piperidine (0.2 mL, 2 mmol) and copper iodide (19 mg, 0.1 mmol) were successively added. After being stirred overnight at room temperature, the reaction mixture was hydrolyzed with a saturated aqueous solution of ammonium chloride (2 mL) and diluted with ether. The organic layer was extracted, dried over magnesium sulfate, and concentrated under vacuum. The orange oily product was purified by flash chromatography (elution with CH_2Cl_2) to give compound **8** (183 mg, 80%): $[\alpha]^{20}_D$ +29.5° (*c* 1.06, CCl_4); IR (NaCl film) 3400–3300 (OH), 3080 (=CH), 2200 (C≡C) cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.13 (1 H, dd, J = 13 Hz, J = 0.25 Hz, H_1), 5.71 (1 H, dd, J = 13 Hz, J = 2 Hz, H_2), 5.54 (1 H, m, J = 10.5 Hz, J = 6.7 Hz, H_8), 5.45 (1 H, m, J = 10.5 Hz, J = 7 Hz, H_7), 4.21 (1 H, m, H_5), 2.37 (2 H, t, J = 7 Hz, H_6), 1.95 (2 H, q, J = 6.7 Hz, H_9), 1.34–1.05 (7 H, m, aliphatic H and OH), 0.86 (3 H, t, J = 6.7 Hz, CH_3-13). Anal. Calcd for $C_{13}H_{19}OCl$: C, 68.86; H, 8.45. Found: C, 68.52; H, 8.5.

(1*E*,3*E*,5*R*,7*Z*)-1-Chlorotrideca-1,3,7-trien-5-ol (9). To a $LiAlH_4$ solution (56 mg, 1.47 mmol) in dry THF (2 mL) was injected a solution of enyne **8** (167 mg, 0.74 mmol) in dry THF (2 mL). After refluxing for 2 h under an argon atmosphere, the reaction mixture was allowed to cool to room temperature and was hydrolyzed by successive addition of water (0.06 mL), aqueous NaOH solution (15%, 0.06 mL), and water again (0.2 mL). After being stirred overnight, the mixture was diluted with ether and filtered through Celite 545. The filtrate was concentrated under vacuum and coevaporated with toluene (3 times). Flash chromatography (elution with methylene chloride) gave chloro diene **9** (145 mg, 85%): $[\alpha]^{20}_D$ +6.13° (*c* 1.01, CCl_4); IR (NaCl film) 3400–3300 (OH), 3080 (=CH), 1595 (C=C–C=C), 960(C=C *E*) cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.26 (1 H, dd, J = 13.5 Hz, J = 10.5 Hz, H_2), 5.78 (1 H, ddd, J = 15 Hz, J = 10.5 Hz, J = 1 Hz, H_3), 5.76 (1 H, dd, J = 13.5 Hz, J = 1 Hz, H_1), 5.51 (1 H, m, J = 10.5 Hz, J = 6.7 Hz, H_8), 5.39 (1 H, dd, J = 15 Hz, J = 6.5 Hz, H_4), 5.33 (1 H, m, J = 10.5 Hz, J = 7 Hz, H_7), 3.86 (1 H, m, H_5), 2.15 (2 H, m, J = 7 Hz, H_6), 1.96 (2 H, q, J = 6.7 Hz, H_9), 1.3–1.08 (7 H, m, aliphatic H and OH), 0.87 (3 H, t, J = 7 Hz, CH_3-13). Anal. Calcd for $C_{13}H_{21}OCl$: C, 68.26; H, 9.25. Found: C, 68.2; H, 9.43.

Methyl (5*S*,6*Z*)-5-(Benzoyloxy)-7-bromohept-6-enoate (10a). Compound **10a** was prepared by the same procedure used to synthesize compound **7a**. The benzoate of **6** (1.4 g, 5.3 mmol) in dry THF was added to the −78 °C solution of the ylide (prepared by potassium *tert*-butoxide addition (1.58 g, 14.2 mmol) to a (bromomethylene)triphenylphosphorane suspension (6.86 g, 15.75 mmol) in dry THF (110 mL) at −78 °C which been stirred for 30 min). When the reaction mixture had returned to room temperature, it was diluted with ether and the triphenylphosphine was precipitated. After filtrate concentration under vacuum and flash chromatography, compound **10a** (1.26 g, 70%) was obtained. The *Z* and *E* isomers could not be separated at this stage. Nevertheless ^1H NMR spectra gave the following values: ^1H NMR (300 MHz, $CDCl_3$) δ (*Z* isomer) 8.02 (2 H, m, *o*-H of benzoate), 7.62–7.09 (3 H, m, *m*-H and *p*-H of benzoate), 6.38 (1 H, d, J = 7.5 Hz, H_7), 6.23 (1 H, t, J = 7.5 Hz, H_6), 5.87 (1 H, m, H_5), 3.7 (3 H, s, OCH_3), 2.36 (2 H, t, J = 7 Hz, H_2), 1.8–1.5 (4 H, m, H_3 and H_4); (*E* isomer) 8.02 (2 H, m, *o*-H of benzoate), 7.62–7.09 (3 H, m, *m*-H and *p*-H of benzoate), 6.51 (1 H, d, J = 14 Hz, H_7), 6.25 (1 H, dd, J = 14 Hz, J = 7.2 Hz, H_6), 5.5 (1 H, m, H_5), 3.7 (3 H, s, OCH_3), 2.36 (2 H, t, J = 7 Hz, H_2), 1.8–1.5 (4 H, m, H_3 and H_4). Anal. Calcd for $C_{15}H_{17}O_4Br$: C, 52.80; H, 5.02. Found: C, 52.56; H, 4.97.

Methyl (5*S*,6*Z*)-7-Bromo-5-hydroxyhept-6-enoate (10b). Compound **10a** (1.098 g, 3.22 mmol) in dry methanol (10 mL) was debenzoylated at room temperature by the action of sodium methylate in methanol (1 M). After stirring for 5 h at room temperature, the mixture was diluted with methanol, neutralized with Amberlite IR-120 (H^+), and filtered. The filtrate was coevaporated with toluene to give compound **10b** (702 mg, 92%). The *Z* and *E* isomers could not be separated at this stage: IR (NaCl film) 3600–3400 (OH), 1730 (C=O) cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 6.36 (1 H, dd, J = 7.5 Hz, J = 1 Hz, J = 1 Hz, H_7), 6.15 (1 H, t, J = 7.5 Hz, H_6), 4.6 (1 H, m, H_5), 3.67 (3 H, s, OCH_3), 2.37 (2 H, t, J = 7 Hz, H_2), 1.91 (1 H, m, OH), 1.8–1.5 (4 H, m, H_3 and H_4). Anal. Calcd for $C_8H_{13}O_3Br$: C, 40.52; H, 5.52. Found: C, 40.57; H, 5.55.

Methyl (5*S*)-Hydroxyhept-6-ynoate (4).[3f] By a similar procedure used to prepare compound **2**, compound **10b** was treated by potassium *tert*-butoxide (661 mg, 5.9 mmol) in DME. After neutralization, the product was reesterified with diazomethane. Two compounds **4** and **10b** (*E* isomer) were separated after flash chromatography (elution with hexane–ethyl acetate, 7:3).

Compound 4: $[\alpha]^{20}_D$ −18.6° (*c* 1.01, CCl_4); IR (NaCl film) 3500–3300 (OH), 3400 (CH), 2100 (C≡C), 1730 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.45 (1 H, m, H_5), 3.67 (3 H, s, OCH_3), 2.5 (1 H, d, J = 2 Hz, H_7), 2.38 (2 H, t, J = 7.5 Hz, H_2), 1.9–1.7 (5 H, m, H_3, H_4, and OH); MS m/z 157 $(M + 1)^+$, 174 $(M + 18)^+$.

Compound 10b (*E* isomer): IR (NaCl film): 3600–3400 (OH), 1730 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.34 (1 H, dd, J = 13.5 Hz, J = 0.9 Hz, H_7), 6.21 (1 H, dd, J = 13.5 Hz, J = 6.5 Hz, H_6), 4.13 (1 H, q, J = 6.5 Hz, H_5), 3.67 (3 H, s, OCH_3), 2.35 (2 H, t, J = 7 Hz, H_2), 1.9–1.5 (5 H, m, H_3, H_4, and OH).

Methyl (5*S*,8*E*,10*E*,12*R*,14*Z*)-5,12-Dihydroxyeicosa-8,10,14-trien-6-ynoate (11).[3f] To a chloro diene **9** solution (116 mg, 0.5 mmol) in anhydrous benzene (2 mL), stirred at room temperature, was added tetrakis(triphenylphosphine)palladium (30 mg, 0.025 mmol); 30 min later, *n*-butylamine (0.5 mL, 5 mmol) and copper iodide (10 mg, 0.05 mmol) were added. Then alcohol **4** (132 mg, 0.84 mmol) diluted in anhydrous benzene (4 mL) was slowly injected under argon pressure. After being stirred overnight at room temperature, the reacting mixture was treated according to the same procedure used for compound **8** preparation. Flash chromatography (elution with hexane–ethyl acetate, 6:4) gave diol **11** (58 mg, 33%). Unreacted chloro diene **9** was also recovered (71 mg): $[\alpha]^{20}_D$ −3.97° (*c* 0.93, CCl_4); IR (NaCl film) 3400 (OH), 3000 (=CH), 2200 (C≡C), 1730 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.56 (1 H, dd, J = 15.5 Hz, J = 10.5 Hz, H_9), 6.27 (1 H, dd, J = 15.5 Hz, J = 10.5 Hz, H_{10}), 5.82 (1 H, dd, J = 15.5 Hz, J = 6 Hz, H_{11}), 5.6 (1 H, dd, J = 15.5 Hz, J = 2 Hz, H_8), 5.58 (1 H, m, J = 10.5 Hz, J = 7 Hz, H_{15}), 5.36 (1 H, m, J = 10.5 Hz, J = 7 Hz, H_{14}), 4.52 (1 H, m, H_5), 4.22 (1 H, q, J = 6 Hz, H_{12}), 3.67 (3 H, s, OCH_3), 2.34 (2 H, m, J = 7 Hz, H_{13}), 2.29 (2 H, m, H_4), 2.03 (2 H, q, J = 6 Hz, H_{16}), 1.79–1.72 (5 H, m, aliphatic H and OH), 0.86 (3 H, t, J = 6.5 Hz, CH_3-20).

Methyl (5*S*,6*Z*,8*E*,10*E*,12*R*,14*Z*)-5,12-Dihydroxyeicosa-6,8,10,14-tetraenoate (12).[3f] To a dienyne **11** solution (22 mg, 0.06 mmol) in a methanol–water mixture (9:7 v/v, 0.8 mL) was added 175 mg of activated zinc dust. This suspension was vig-

orously stirred overnight at room temperature and then diluted in methanol (2 mL). After filtration over Celite 545, the filtrate was evaporated under vacuum, diluted in ether, and then dried over magnesium sulfate. Flash chromatography (elution with methylene chloride–ethyl acetate, 65:35) gave the methyl ester LTB_4 **12** (41 mg; 70%): $[\alpha]^{20}_D$ +4.6° (*c* 0.39, CCl_4); IR (NaCl film) 3400 (OH), 3000 (=CH), 1730 (C=O), 1595 (C=C—C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.47 (1 H, dd, *J* = 14.5 Hz, *J* = 11 Hz, H_8), 6.3 (1 H, ddd, *J* = 15 Hz, *J* = 10.5 Hz, *J* = 1 Hz, H_{10}), 6.21 (1 H, dd, *J* = 14.5 Hz, *J* = 10.5 Hz, H_9), 6.07 (1 H, t, *J* = 11 Hz, H_7), 5.77 (1 H, dd, *J* = 15 Hz, *J* = 6.3 Hz, H_{11}), 5.55 (1 H, m, *J* = 10.5 Hz, *J* = 7 Hz, H_{15}), 5.54 (1 H, dd, *J* = 11 Hz, *J* = 9.5 Hz, H_6), 5.34 (1 H, m, *J* = 10.5 Hz, *J* = 7 Hz, H_{14}), 4.57 (1 H, m, *J* = 9.5 Hz, H_5), 4.2 (1 H, q, *J* = 6.3 Hz, H_{12}), 3.65 (3 H, s, OCH_3), 2.33 (4 H, m, H_4) and H_{13}), 2.02 (2 H, q, *J* = 6 Hz, H_{16}), 1.72–1.60 (5 H, m, aliphatics H and OH), 1.36–1.21 (7 H, m, aliphatics H and OH), 0.87 (3 H, t, *J* = 6.5 Hz, CH_3-20).

(5*S*,6*Z*,8*E*,10*E*,12*R*,14*Z*)-5,12-Dihydroxyeicosa-6,8,10,14-tetraenoic Acid (1). To a solution of methyl ester **12** (400 μg, 1.1 mmol) in methanol (320 μL) and water (80 μL) was added potassium carbonate (1.6 mg, 11 μmol). After the mixture was stirred for 18 h at room temperature under argon atmosphere, the methanol was evaporated by a stream of argon and the residue was purified on a C_{18}-Sep-Pak cartridge. Elutions with water (5 × 1 mL) removed the carbonate salts (pH = 8.9 to neutrality). Then, two elutions (2 × 2 mL) with methanol afforded leukotriene B_4 (360 μg, 95%). The methanol was removed under a stream of argon. The retention time of LTB_4 by HPLC analysis was identical with that of the natural product (column Spherisorb ODS C_{18}), eluent: 15–100% of CH_3CN/H_2O = 0.05% H_3PO_4, 35 min).

Registry No. 1, 71160-24-2; 2, 111137-93-0; 3, 156-60-5; 4, 90108-28-4; 5, 97579-36-7; 6, 76745-20-5; (*Z*)-7a, 111037-26-4; (*E*)-7a, 111037-35-5; (*Z*)-7b, 111037-27-5; (*E*)-7b, 111037-36-6; 8, 136693-10-2; 9, 136693-11-3; (*Z*)-10a, 111037-31-1; (*E*)-10a, 111037-37-7; (*Z*)-10b, 111037-32-2; (*E*)-10b, 106031-61-2; 11, 136693-12-4; 12, 83058-42-8; (bromomethylene)triphenylphosphorane, 39598-55-5.

Supplementary Material Available: ^1H NMR spectra for compounds 2, 4, 7bZ, 7bE, 8, 9, 10a, 10b, 10bE, 11, and 12 (11 pages). Ordering information is given on any current masthead page.

1,3-Dialkyl-3-acyltriazenes: Products and Rates of Decomposition in Acidic and Neutral Aqueous Solutions

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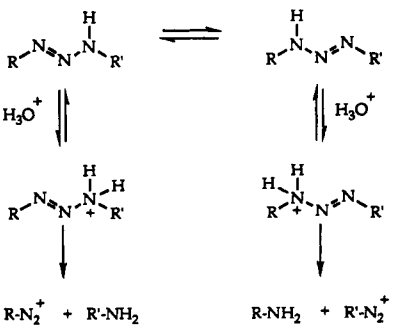
The products and mechanism of hydrolytic decomposition of a series of 1,3-dialkyl-3-acyltriazenes were studied in both acidic and neutral buffers. In the acidic region, the products are alkyl alcohols derived from the N(1) alkyl group and amides derived from the intact N(3) portion of the molecule. The solvent deuterium isotope effect (k_{H_2O}/k_{D_2O}) is less than 1.0. The mechanism is specific acid catalyzed, involving rapid reversible protonation of the 3-acyl group followed by scission of the N(2)–N(3) bond to generate an amide and an alkyl diazonium ion. The (2-hydroxyethyl)diazonium ion gives ethylene glycol and acetaldehyde, while the (2-chloroethyl)diazonium ion yields 2-chloroethanol. In the neutral region, the products are similar to those found in acidic buffers, alkyl alcohols, and amides. At this pH the (2-chloroethyl)diazonium ion produces ethylene glycol and acetaldehyde in addition to 2-chloroethanol. The solvent deuterium isotope effect (k_{H_2O}/k_{D_2O}) is greater than 1.0. The mechanism involves unimolecular heterolysis of the N(2)–N(3) bond to form an amide anion and an alkyldiazonium ion. The methyldiazonium ion leads to incorporation of deuterium in the methyl group of the products, indicating the existence of an equilibrium between the metastable methyldiazonium ion and diazomethane.

Introduction

The preparation[1] and proteolytic decomposition of 1,3-dialkyltriazenes[2] and 1,3,3-trialkyltriazenes[3] have been investigated in substantial detail. These simple alkyltriazenes decompose rapidly in aqueous solutions by an acid-catalyzed process which results in the formation of alkylamines and alkyl alcohols, the latter via an alkyldiazonium ion intermediate.[2] The situation is more complicated for unsymmetrical 1,3-dialkyltriazenes,[4] which exist in two rapidly equilibrating tautomeric forms and give rise competitively to two different pairs of alkyldiazonium ions and alkylamines (Scheme I). The rate of decomposition and product distribution for unsymmetrical 1,3-dialkyltriazenes is controlled by the stability of the two possible alkyldiazonium ions and the population and basicity of the two tautomeric forms. The intermediate formed in the rate-determining step of the hydrolytic

Scheme I



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