Synthesis of 5-*O*-Benzoyl-14,15-didehydroleukotriene B_4 (LTB_4) Ethyl Ester and 5-*O*-Benzoyl-14,15-didehydro-20-hydroxyleukotriene B_4 (LTB_4) Ethyl Ester: Direct Precursors of Labeled LTB_4s

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5-*O*-Benzoyl-14,15-didehydro-LTB_4 ethyl ester and 5-*O*-benzoyl-14,15-didehydro-20-hydroxy-LTB_4 ethyl ester, the direct precursors of isotopically labeled LTB_4's have been prepared. Their syntheses were accomplished by condensation of acetylenic anions on an epoxide in the presence of $BF_3{\cdot}Et_2O$. This epoxide in turn was prepared from 2-deoxy-D-ribose in five steps. The acetylenic linkage, in these compounds, allows the incorporation of tritium or deuterium at a late stage of the synthesis.

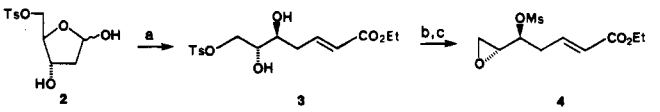
Over the past several years the lipoxygenase derivated metabolites of arachidonic acid have been the subject of extensive research. This research has in no small part been due to the biologically important nature of these molecules. The major pro-inflammatory product of the lipoxygenase pathway is leukotriene B_4 (LTB_4) and as such it is implicated in numerous disease states, such as psoriasis and inflammatory bowel disease.[1]

With many biological mediators the availability of isotopically labeled versions of the natural product and its metabolites has proven exceptionally useful in defining the physiological role of the molecule. Leukotriene B_4 is no exception with 14,15-[^{3}H]-LTB_4 playing a prominent role in the detection and purification of its receptors, the establishment of radioimmunological assays (RIA's) for the detection of the picomole amounts found in vivo, and in the study of its metabolism.[2] The 14,15-[^{3}H]-20-OH-LTB_4 has also proven useful in RIA development and metabolic studies. The 20-OH-LTB_4 is of particular interest since it is reported to be the major urinary metabolite of LTB_4,[3] thus making it a potential marker for LTB_4 production in vivo.

In addition 14,15-[^{2}H]-LTB_4 and 20-OH-LTB_4 have proven useful as the ideal internal standards for GC/MS-based analyses of biological samples for these molecules. Since these compounds are generally only available through total synthesis, an efficient strategy for their preparation is necessary.

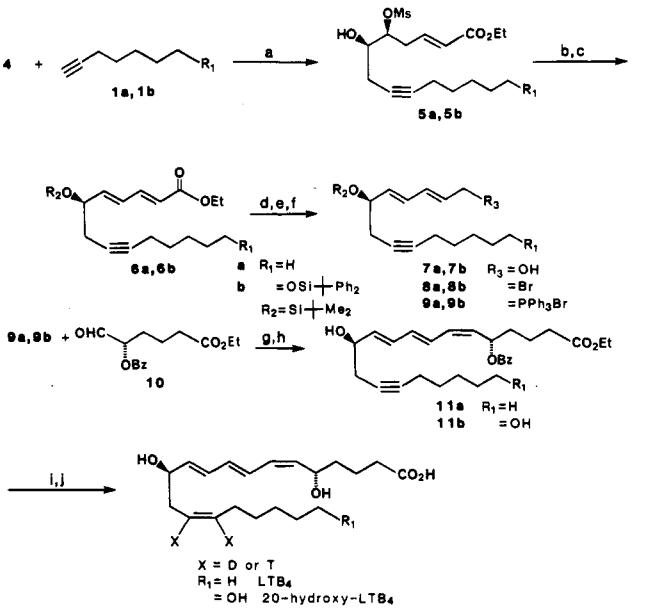
Herein a simple method to prepare 14,15-didehydro-LTB_4 (**11a**) and 14,15-didehydro-20-OH-LTB_4 (**11b**) is described. The presence of the acetylenic linkage between C_{14} and C_{15} in these compounds in place of the cis double bond of the natural product allows for the incorporation of two tritiums or deuteriums via a semihydrogenation at a late stage of the synthesis. In the original synthesis from these laboratories of LTB_4 a Wittig condensation between a dienic phosphorane and the α-benzoyloxy aldehyde **10** was employed to efficiently assemble the cis,trans,trans triene system.[4,5] Because of its straightforwardness it was

Scheme I[a]



[a] (a) $Ph_3P{=}CHCO_2Et$/THF/70 °C, 6 h; (b) K_2CO_3/EtOH/room temperature/3 h; (c) MsCl/Et_3N/CH_2Cl_2/−78 °C → room temperature.

Scheme II[a]



[a] (a) BuLi/$BF_3{\cdot}Et_2O$/THF, −78 °C, 1 h; (b) EtONa/EtOH/room temperature/1 h; (c) *t*-$BuMe_2SiCl$/Et_3N/DMAP/CH_2Cl_2/room temperature/24 h; (d) $AlH_3{\cdot}^1/_3Et_2O$/THF/0 °C/1 h; (e) CBr_4/DIPHOS/CH_2Cl_2/0 °C/0.5 h; (f) PPh_3/CH_3CN/room temperature/6 h; (g) BuLi/THF/HMPA/−78 °C → 0 °C/1 h; (h) *n*-Bu_4NF/THF/0 °C → room temperature/1 h.

decided to use this approach for the construction of the final carbon–carbon linkage in the present targets. Therefore the preparation of the phosphonium salts **9a** and **9b** having a C_{14}–C_{15} triple bond was considered (Scheme II).

Examining the structures **9**, it was recognized that these compounds could be obtained in a straightforward manner by the addition of an acetylenic anion representing C_{14}–C_{20} to an epoxide representing C_7–C_{13} of the final product. This epoxide in turn could be derived from 2-deoxy-D-

(1) Rae, S. A.; Smith, M. J. H. *J. Pharm. Pharmacol.* **1981**, *33*, 616–617. Greaves, M. W. *Br. J. Dermatol.* **1983**, *109*, 115–118. Barr, R. M.; Brain, S.; Camp, R. D. R.; Cilliers, J.; Greaves, M. W.; Mallet, A. I.; Misch, K. *Br. J. Dermatol.* **1984**, *111*, 23–28.

(2) Goldman, D. W.; Goetzl, E. J. *J. Immunol.* **1982**, *129*, 1600–1604. Goldman, D. W.; Goetzl, E. J. *J. Exp. Med.* **1984**, *159*, 1027–1041. Lin, A. H.; Ruppel, P. L.; Gorman, R. R. *Prostaglandins* **1984**, *28*, 837–849.

(3) Jubiz, W.; Radmark, O.; Malmsten, C.; Hansson, G.; Lindren, J. A.; Palmbald, J.; Liden, A. M.; Samuelsson, B. *J. Biol. Chem.* **1982**, *257*, 6106–6110. Nadeau, M.; Fruteau de laclos, B.; Picard, S.; Braquet, P.; Corey, E. J.; Borgeat, P. *Can. J. Biochem. Cell Biol.* **1984**, *62*, 1321–1326. Powell, W. S. *J. Biol. Chem.* **1984**, *259*, 3082–3089.

(4) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 2631–2634. Guindon, Y.; Zamboni, R.; Lau, C. K.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 739–742.

(5) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 4751–4754.

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ribose, thus providing the C_{12} hydroxylmethylene moiety stereochemically pure.

Condensation of 2-deoxy-5-*O*-tosylribofuranose[6] (**2**) (Scheme I) with (carbethoxymethylene)phosphorane (THF, 70 °C, 6 h) to effect a two-carbon homologation afforded the diol **3**. Treatment of this diol with potassium carbonate in dry ethanol gave the terminal epoxide, the remaining hydroxyl group was then mesylated to provide the epoxide **4** in 92% yield. Addition of the anion (3 equiv) derived from compound **1a** and **1b**[7,8] by treatment with *n*-BuLi to the epoxide **4** in the presence of $BF_3{\cdot}Et_2O$[9-11] gave the alcohols **5a** and **5b** in good yield (70% and 90%, respectively). Taking advantage of the acidity of the proton γ to the α,β-unsaturated ester, treatment of compounds **5a** and **5b** with sodium ethoxide in ethanol gave after silylation the diene esters **6a** and **6b** in 65% yield. Subsequently these esters **6a** and **6b** were reduced to the corresponding alcohols **7a** and **7b** by treatment with $AlH_3{\cdot}^1/_3Et_2O$.

The alcohols **7a** and **7b** were converted to the bromides **8a** and **8b**. The treatment of the bromides **8a** and **8b** with triphenyl phosphine afforded the phosphonium salts **9a** and **9b**. Condensation of the phosphoranes generated from these phosphonium salts (BuLi, THF, HMPA, −78 °C) with the aldehyde **10** furnished after desilylation[12] (*n*-Bu_4NF) and purification, the 5-(benzoyloxy)-14,15-didehydro-LTB_4 ethyl ester (**11a**) and corresponding 20-OH-LTB_4 derivative **11b** in 60% yield. These compounds are the direct precursors to the isotopically labeled LTB_4's and were converted to the desired compounds by semihydrogenation[13] and hydrolysis.[4,5,14]

In summary the above sequence for the preparation of 14,15-didehydro-LTB_4 and 20-OH-LTB_4 is simple, efficient, and allows access to the isotopically labeled analogues of these biologically important molecules in substantial quantities.

Experimental Section

NMR spectra were recorded on a Bruker AM 250 (250 MHz) spectrometer. Numbers in the spectral assignments refer to the position of the carbon in the final product. Optical rotations were obtained with the indicated solvent and concentration in a 1-dm cell using a Perkin-Elmer 481 polarimeter. High resolution mass spectra (HRMS) were performed by O. A. Mamer of McGill University.

Ethyl 1′(*S*)-[(Methylsulfonyl)oxy]-2(*R*)-oxirane-3′(*E*)-pentenoate (4). To a solution of the lactol[6] **2** (5 g, 17.3 mmol) in THF (50 mL) was added the (carbethoxymethylene)triphenylphosphorane (7.25 g, 20.7 mmol). The resulting solution was stirred at 60 °C for 3 h and the solvent was removed at reduced pressure. Flash chromatography of the residue (50% ethyl acetate in hexanes) gave the diol **3** (4.2 g, 70%).

To the diol (4.0 g, 11.6 mmol) in dry ethanol (100 mL) was added dry potassium carbonate (4.0 g). After 3 h the reaction was complete (TLC 50% ethyl acetate in hexanes) and THF was added; then the resulting mixture was evaporated at reduced pressure. Flash chromatography of the residue (50% ethyl acetate in hexanes) afforded the epoxy alcohol (1.9 g, 92%). The alcohol (1.9 g, 10.2 mmol) in CH_2Cl_2 (70 mL) at −78 °C was treated with Et_3N (2.13 mL, 1.5 equiv) and MsCl (948 μL, 1.2 equiv). The resulting mixture was stirred at −78 °C for 10 min and then allowed to warm to 20 °C. After 1 h an aqueous solution of 25% ammonium acetate was added and the resulting mixture was extracted with ether. After drying (Na_2SO_4), removal of the solvent and flash chromatography (40% ethyl acetate in hexanes) afforded the title product (2.9 g, 95%): $[\alpha]^{22}_D$ +3.2° (*c* 1.3, acetone); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 (t, 3 H, OCH_2CH_3), 2.70 (m, 2 H, $CH_2CH{=}CH$), 2.84 (m, 2 H, CH_2O), 3.02 (s, 3 H, CH_3SO_2), 3.12 (m, 1 H, CHO), 4.17 (q, 2 H, J = 7.2 Hz, OCH_2CH_3), 4.58 (m, 1 H, $CHOSO_2$), 5.94 (d, 1 H, J = 14.9 Hz, $CH{=}CHCO_2Et$), 6.90 (dt, 1 H, J = 7.2, 14.9 Hz, $CH{=}CHCO_2Et$); high resolution mass spectrum, m/z calcd for $C_{10}H_{17}O_6S$ $(M + H)^+$ 265.0747, found 265.0746.

Ethyl 6(*R*)-[(*tert*-Butyldimethylsilyl)oxy]-14-[(*tert*-butyldiphenylsilyl)oxy]-2(*E*),4(*E*)-tetradecadien-8-ynoate (6b). To the acetylene **1b** (400 mg, 1.14 mmol) in THF (1 mL) at −78 °C was added *n*-BuLi (1.14 mmol); then after 10 min $BF_3{\cdot}Et_2O$ (232 μL, 1.9 mmol) was added dropwise over a period of 5 min. After a further 5 min, the epoxide **4** (100 mg, 0.4 mmol) in THF (600 μL) was added, and the reaction mixture was stirred for 1 h. The reaction was quenched by the addition of 25% aqueous ammonium acetate (20 mL) and the resulting mixture was worked up with ethyl acetate in the usual manner. Flash chromatography of the residue (25% ethyl acetate in hexanes gave the alcohol **5b** (176 mg, 92%).

The alcohol **5b** in dry ethanol (1 mL) at room temperature was treated with sodium ethoxide (1.1 equiv) in dry ethanol (3 mL). After the resulting mixture had been stirred for 1 h at room temperature, an aqueous solution of 25% ammonium acetate was added (10 mL) and the mixture was extracted with ethyl acetate in the usual manner. Flash chromatography (20% ethyl acetate in hexanes) of the crude mixture afforded the desired diene alcohol (84 mg, 65%).

A solution of this alcohol in CH_2Cl_2 (500 μL) with triethylamine (1.5 equiv) was then treated with *tert*-butyldimethylsilyl chloride (38 mg, 1.2 equiv). The mixture was stirred overnight and aqueous 25% ammonium acetate was added and the resulting mixture was extracted with CH_2Cl_2 (2 × 20 mL). After drying (Na_2SO_4), removal of the solvent, and flash chromatography (10% ethyl acetate in hexanes) of the residue the compound **6b** was obtained as a colorless oil (95 mg, 95%): $[\alpha]_D$ −42.7° (*c* 0.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.05 and 0.07 (2 s, 6 H, $2CH_3$), 0.89 and 1.04 (2 s, 18 H, $2(CH_3)_3C$), 1.28 (t, 3 H, J = 7.3 Hz, OCH_2CH_3), 1.30 to 1.55 (m, 6 H), 2.11 (m, 2 H, $C{\equiv}CCH_2$), 2.33 (m, 2 H, $CHOCH_2C{\equiv}C$), 3.65 (t, 2 H, J = 6.3 Hz, CH_2O), 4.19 (q, 2 H, J = 7.0 Hz, OCH_2CH_3), 4.32 (m, 1 H, CHO), 5.86 (d, 1 H, J = 14.5 Hz, $CH{=}CHCH{=}CHCO_2$), 6.20 (dd, 1 H, J = 4.8, 15.1 Hz, $CH{=}CHCH{=}CHCO_2$), 6.33 (dt, 1 H, J = 15.1, 2.0 Hz, $CH{=}CHCH{=}CHCO_2$), 7.23 to 7.67 (m, 11 H, 2 Ph and $CH{=}CHCH{=}CHCO_2$); high resolution mass spectrum, m/z calcd for $C_{34}H_{47}O_4Si_2$ (M^+ − *t*-Bu) 575.3014, found 575.3013.

Ethyl 6(*R*)-[(*tert*-butyldimethylsilyl)oxy]-2(*E*),4(*E*)-tetradecadien-8-ynoate (6a): $[\alpha]^{22}_D$ −37.0° (*c* 1.0, acetone); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.03 and 0.06 (2 s, 6 H, $2CH_3$), 0.88 (m, 12 H, $(CH_3)_3C$ and CH_3), 1.27 (t, 3 H, J = 7.2 Hz, OCH_2CH_3), 1.28 to 1.45 (m, 6 H), 2.11 (bt, 1 H, J = 7.2 Hz, $C{\equiv}CCH_2$), 2.33 (m, 2 H, $CHOCH_2C{\equiv}C$), 4.18 (q, 2 H, J = 7.0 Hz, OCH_2CH_3), 4.31 (m, 1 H, $CHOCH_2C{\equiv}C$), 5.85 (d, 1 H, J = 15.4 Hz, $CH{=}CHCH{=}CHCO_2Et$), 6.16 (dd, 1 H, J = 5.0, 15.2 Hz, $CH{=}CHCH{=}CHCO_2Et$), 6.34 (bt, 1 H, J = 15.2, 2.0 Hz, $CH{=}CHCH{=}CHCO_2Et$), 7.26 (dd, 1 H, J = 10.6, 15.4 Hz, $CH{=}CHCH{=}CHCO_2Et$); high resolution mass spectrum, m/z calcd for $C_{22}H_{39}O_3Si$ $(M + H)^+$ 379.2667, found 379.2668.

Ethyl 5(*S*)-(benzoyloxy)-12(*R*),20-dihydroxy-6(*Z*),8(*E*),10(*E*)-eicosatrien-14-ynoate (11b). To a stirred solution

(6) Zamboni, R.; Milette, S.; Rokach, J. *Tetrahedron Lett.* **1984**, *25*, 5835–5838.
(7) Hommes, H.; Bransma, L. *Recl. Trav. Chim. Pays-Bas* **1977**, *96*, 160.
(8) Johnson, W. S.; Bailey, D. M.; Owyang, R.; Bell, A. R.; Janocques, B.; Crandall, J. K. *J. Am. Chem. Soc.* **1964**, *60*, 1959–1966.
(9) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947–959.
(10) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394.
(11) Belley, M.; Leger, S.; Zamboni, R., unpublished results.
(12) The 3/1 cis–trans mixtures at C_6–C_7 were separated by HPLC with 5% ethyl acetate in hexane (Waters μ-Porasil column) prior the desilylation.
(13) The semihydrogenations with tritium were performed by E. Do and G. Iles of the lipids Labs of New England Nuclear. Those with deuterium were carried out in house by J. Adams. General semihydrogenation procedure: 6 μmol of the acetylene derivative and 6 mg of Lindlar catalyst in 1 mL of 1% quinoline in ethyl acetate were stirred under an atmosphere of tritium (1 atm) for 30 min. At this time the reaction was filtered and solvent was removed under reduced pressure. Methanol was evaporated from the residue to remove any labile tritium; then the residue was purified by preparative HPLC. This yields material with a specific activity of approximately 40 Ci/mmol. The radiolabeled material prepared from these precursors is commercially available from NEN.
(14) In both cases the compounds were correlated by HPLC with LTB_4 standards.

of the phosphorane (0.2 mmol) generated by the treatment of the phosphonium salt **9b** (0.2 mmol) with 1 equiv of *n*-BuLi in dry THF (2 mL) containing HMPA (200 μL) at −78 °C was added a solution of the aldehyde **10** (60 mg, 1.2 equiv) in THF (1 mL). The resulting mixture was stirred at −78 °C for 1 h and then allowed to warm to 0 °C. After 0.5 h the reaction was quenched by the addition of 25% aqueous ammonium acetate (10 mL) and the resulting mixture was extracted with ether (2 × 50 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (20 mL) and dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure. Flash chromatography of the residue (10% ethyl acetate in hexanes) gave a mixture containing the desired product and the trans isomer (3/1). Subsequently the isomeric mixture was passed on HPLC (5% ethyl acetate in hexanes) to afford the cis isomer (65 mg, 45%) and the trans isomer (30 mg, 20%).

The cis product in THF (200 μL) at 0 °C was treated with tetra-*n*-butylammonium fluoride in THF (1 M) (140 μL, 4 equiv). After 2 h a 25% aqueous ammonium acetate solution was added and the resulting mixture extracted with CH_2Cl_2. After standard manipulations and flash chromatography (35% ethyl acetate in hexanes) the title product was obtained (33 mg, 99%): $[\alpha]^{22}_D$ +187.9° (*c* 1.0, acetone); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22 (t, 3 H, OCH_2CH_3), 1.40 to 2.46 (16 H, H-2 to H-4, H-13 and H-16 to H-19), 3.62 (bt, 2 H, H-20), 4.09 (q, 2 H, *J* = 7.0 Hz, OCH_2CH_3), 4.29 (m, 1 H, H-12), 5.42 (t, 1 H, *J* = 10.1 Hz, H-6), 5.77 (dd, 1 H, *J* = 6.0, 14.7 Hz, H-11), 5.91 (m, 1 H, H-5), 6.11 to 6.44 (m, 3 H), 6.67 (bt, 1 H, *J* = 14.0 Hz), 7.40, 7.52 and 7.99 (m, 5 H, Ph); high resolution mass spectrum, *m/z* calcd for $C_{29}H_{38}NO_4$ ($M + NH_4^+ - 2H_2O$) 464.2802, found 464.2800.

Ethyl 5(*S*)-(benzoyloxy)-12(*R*)-hydroxy-6(*Z*),8(*E*),10-(*E*)-eicosatrien-14-ynoate (11a): $[\alpha]^{22}_D$ +191.0° (*c* 1, acetone); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.86 (bt, 3 H, H-20), 1.21 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3), 1.29 to 2.44 (m, 16 H, H-2 to H-4, H-13 and H-16 to H-19), 4.09 (q, 2 H, *J* = 7.0 Hz, OCH_2CH_3), 4.28 (m, 1 H, H-12), 5.43 (t, 1 H, *J* = 10.1 Hz, H-6), 5.75 (dd, 1 H, *J* = 6.0, 14.6 Hz, H-11), 5.90 (m, 1 H, H-5), 6.11 to 6.44 (m, 3 H), 6.67 (bt, 1 H, *J* = 14.0 Hz), 7.40, 7.53, and 7.99 (m, 5 H, Ph); high resolution mass spectrum, *m/z* calcd for $C_{29}H_{42}NO_5$ ($M + NH_4^+$) 484.3063, found 484.3061.

Registry No. **1a**, 628-71-7; **1b**, 106027-21-8; **2**, 111998-96-0; **3**, 111998-97-1; **4**, 111998-98-2; **4** (epoxy alcohol), 79308-54-6; **5a**, 111999-02-1; **5b**, 111998-99-3; **6a**, 111999-03-2; **6b**, 111999-01-0; **6b** (R_2 = H), 111999-00-9; **7a**, 111999-10-1; **7b**, 111999-11-2; **8a**, 111999-09-8; **8b**, 112021-08-6; **9a**, 111999-08-7; **9b**, 111999-04-3; **10**, 82493-58-1; **11a**, 111999-07-6; **11b**, 111999-06-5; **11b** (12-$SiMe_2$Bu-*t*,20-$SiPh_2$Bu-*t* ether), 111999-05-4; *trans*-**11b** (12-$SiMe_2$Bu-*t*,20-$SiPh_2$Bu-*t* ether), 112021-07-5; $Ph_3P{=}CHCO_2Et$, 1099-45-2.

Total Synthesis of LTB_4 and Analogues

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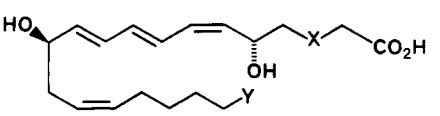
Derivatives of 4-[(methylsulfonyl)oxy]tetrahydro-2-furanacetate (e.g., **6**) when treated with base in aprotic solvent were readily transformed to (*E,E*)-1,3-dienes in retro-Michael reactions with concomitant elimination of the leaving group. When **6** was treated with DBU, elimination of the leaving group gave a dihydrofuran derivative which serves as a template to preserve the cis double bond geometry. Subsequent base-catalyzed retro-Michael opening reaction gave a (*Z,E*)-1,3 diene. The first approach was utilized to prepare LTB_4 by putting the C-14–C-20 segment onto the iodo derivative **18** via a cuprate displacement reaction. The C-1–C-6 segment was also constructed from 2-deoxy-D-ribose in six steps. Wittig reaction of **24** and **27** derived from the two fragments mentioned above gave LTB_4 after deprotection. To prepare 3-thia-LTB_4 (**4**) and 3-thia-20,20,20-trifluoro-LTB_4 (**5**) the latter approach was used. The C-5 alcohol of the (*Z,E*)-diene resulting from the opening of dihydrofuran **9** was inverted by using the Mitsunobu reaction. Thioglycolate displacement on the primary iodo **47** and Wittig reaction between the ylide generated from **49** and either aldehyde **50** or **58** furnished the two analogues **4** and **5**.

Introduction

In the last few years, the leukotriene "cascade" has attracted considerable attention in the scientific community. The leukotrienes (LTB_4, LTC_4, LTD_4, LTE_4) possess a formidable array of biological properties and have generated a massive involvement of the pharmaceutical industry in the search for new drugs that may offer new therapeutic intervention in disease states such as asthma, allergic diseases, inflammation etc.

LTB_4 (**1**; Scheme I) is an oxygenated product of arachidonic acid formed by the 5-lipoxygenase enzyme. It is one of the most potent chemotactic agents produced in man. Important roles in allergic, inflammatory,[1] and immunological reaction[2] have been attributed to LTB_4. The recent isolation,[3] characterization and synthesis[4,5] of LTB_4 has prompted us to study the action of that product in

Scheme I



1. X = CH_2, Y = CH_3 : LTB_4
2. X = CH_2, Y = CH_2OH : 20-OH-LTB_4
3. X = CH_2, Y = CO_2H : 20-CO_2H-LTB_4
4. X = S, Y = CH_3 : 3-thia-LTB_4
5. X = S, Y = CF_3 : 3-thia-20-CF_3-LTB_4

(1) (a) Ford-Hutchinson, A. W.; Bray, M. A.; Poig, M. V.; Shipley, M. E.; Smith, M. J. H. *Nature (London)*, **1980**, *286*, 264. (b) Simmons, P. M.; Salmon, J. A.; Moncado, S. *Biochem., Pharmacol.* **1983**, *32*, 1353. (c) Goetzl, E. J. *New Engl. J. Med.* **1980**, *303*, 822.

(2) Payan, D. G.; Missirian-Bastian, A.; Goetzl, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3501. Rola-Pleszczynski, M.; Borgeat, P.; Sirois, P. *Biochem. Biophys. Res. Commun.* **1982**, *108*, 1531.

0022-3263/88/1953-0267$01.50/0