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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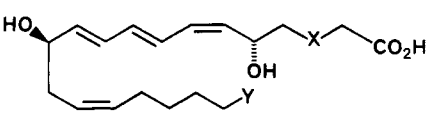
Derivatives of 4-[(methylsulfonyl)oxy]tetrahydro-2-furanacetate (e.g., **6**) when treated with base in aprotic solvent were readily transformed to (*E,E*)-1,3-dienes in retro-Michael reactions with concomitant elimination of the leaving group. When **6** was treated with DBU, elimination of the leaving 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



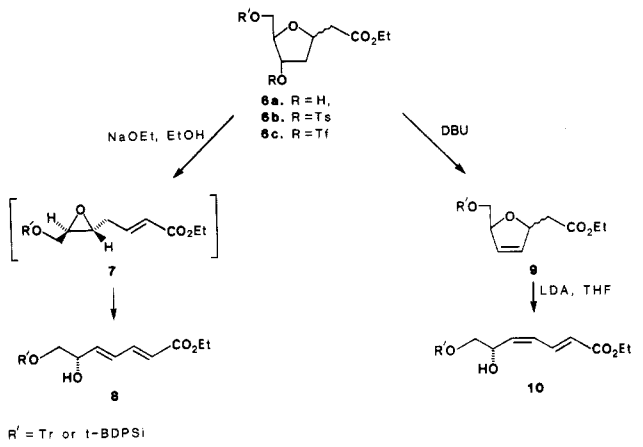
1. X = CH_2, Y = CH_3 : LTB_4
2. X = CH_2, Y = CH_2OH : 20-OH-LTB_4
3. X = CH_2, Y = CO_2H : 20-CO_2H-LTB_4
4. X = S, Y = CH_3 : 3-thia-LTB_4
5. X = S, Y = CF_3 : 3-thia-20-CF_3-LTB_4

(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

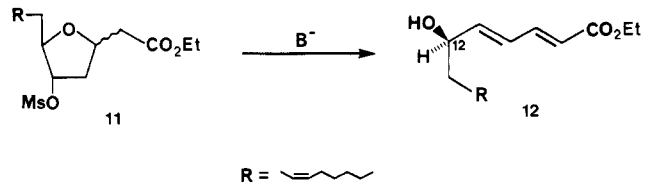
Scheme II



some in vivo models, in order to evaluate potential new drugs. Unfortunately, its chemical and metabolic instability has prevented its use in elaborating such models. This local hormone is rapidly oxidized in vivo first by hydroxylation at C-20 to give **2** (ω-oxidation), followed by oxidation to the diacid **3** and subsequent β-oxidation of the two acidic chains.[6] It is therefore desirable to have metabolically stable analogues[7] of LTB_4 to serve as probes in order to better understand the biological roles of this important mediator. We report herein a versatile approach to the total synthesis of LTB_4 and two such analogues, 3-thia-LTB_4 (**4**) and 3-thia-20,20,20-trifluoro-LTB_4 (**5**). We also describe in detail the use of tetrahydrofuran derivatives as common chiral precursors.

The synthesis of LTB_4 and its analogues is based on the concept of using chiral tetrahydrofurans such as **6a** as masked precursors of optically active (*Z,E*)- or (*E,E*)-dienes. It is of interest to have a precursor which is stable to nucleophiles and other conditions and yet able to be readily converted to the diene under mild conditions when needed. We have found that by appropriately placing a leaving group on the tetrahydrofuran ring, as in **6b**, one can perform a retro-Michael reaction with concomitant elimination of the leaving group, giving the (*E,E*)-diene **8**, presumably via the epoxide intermediate **7**[8] (Scheme II). In fact, epoxide **7** has been used for the synthesis of 5-*epi*-6-*epi*-LTA_4.[14a] Alternatively, initial elimination of the leaving group followed by retro-Michael reaction of the resulting dihydrofuran **9** gives only the (*Z,E*)-diene **10**. The dihydrofuran ring serves as a template to preserve the cis double bond geometry. However, many attempts to effect a one-pot transformation of **6c** directly to the pure (*Z,E*)-diene **10** failed. Some production of the (*Z,E*)-diene under kinetic condition (best ratio 1:1) was observed, but unfortunately no better ratio of **10** vs **8** was obtained by changing base, solvent, and temperature. It appears that pure (*Z,E*)-diene **10** can only be obtained from the cyclic olefins **9** under aprotic conditions (LDA or KHMDS in dry THF), while the treatment of pure **9**α or **9**β under protic conditions (EtO^-Na^+/EtOH) leads mainly to epimerization of the C-3 center. In all of these experiments, the resulting α,β-unsaturated ester of the diene is always in the *E* configuration.

Scheme III



Both derivatives **6a** and **9** are stable and the efficient opening of the tetrahydrofuran ring in either case underscores the versatility of this approach and confirms the synthetic utility of tetrahydrofurans as masked 1,3-dienes.[9]

Based on this observation, it was envisaged that replacement of the primary hydroxyl group in the tetrahydrofuran **6b** with an alkyl side chain (e.g. compound **11**, Scheme III) and subsequent treatment with base would give the corresponding C-14 chiral (*E,E*)-diene alcohol **12** bearing the desired 12R configuration of LTB_4. On the other hand, the (*Z,E*)-diene alcohol **10** after inversion of the chiral center would give a C-7 fragment bearing the 5*S* configuration that could be elaborated quite readily to the analogues of LTB_4.

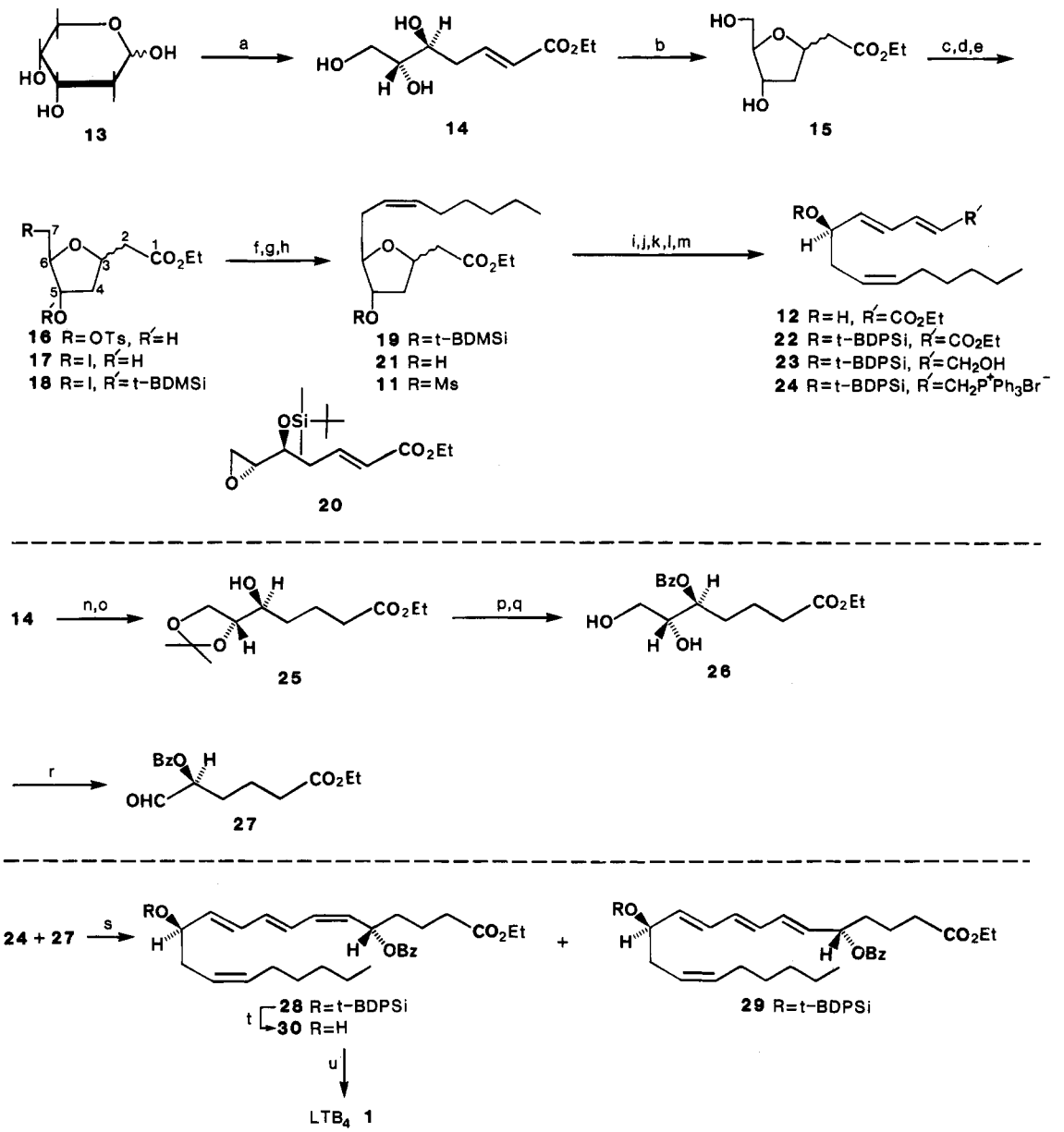
The common precursor **15** for the synthesis of both LTB_4 and its analogues was prepared from 2-deoxy-D-ribose (**13**) as reported.[8] Thus, reaction with (carbethoxymethylene)triphenylphosphorane in refluxing tetrahydrofuran gave the triol **14** in 80% yield. Treatment of **14** with a catalytic amount of sodium ethoxide in ethanol gave the tetrahydrofuran **15** as a mixture of α- and β-isomers in the ratio of 1:1 that were not separable by chromatography (Scheme IV).

For the synthesis of LTB_4, the primary alcohol of the tetrahydrofuran **15** was selectively transformed to the tosylate **16**. Displacement of the tosylate with sodium iodide followed by protection of the secondary alcohol **17** with *tert*-butyldimethylchlorosilane gave **18** in 63% overall yield.

The α- and β-isomers of **18** were readily separable and fully characterized. The anomeric configuration of the β-isomer was determined by using nuclear Overhauser effect difference NMR spectroscopy (NOEDS).[10] Displacing the iodide **18** with lithium (3,3-dimethyl-1-butynyl)-1-heptenylcuprate[11] reagent in the presence of HMPA

(3) Borgeat, P.; Samuelsson, B. *J. Biol. Chem.* **1979**, *254*, 2643.
(4) (a) Guindon, Y.; Zamboni, R.; Lau, C. K.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 739. (b) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 2631. (c) Rokach, J.; Adams, J. *Acc. Chem. Res.* **1985**, *18*, 87. (d) Nicolaou, K. C.; Zipkin, R. E.; Dolle, R. E.; Harris, B. D. *J. Am. Chem. Soc.* **1984**, *106*, 3548. (e) Kaye, A. D.; Pattenden, G. *Tetrahedron Lett.* **1986**, *27*, 2033. (f) LeMerrer, Y.; Gravier, C.; Languin-Micas, D.; Depezay, J. C. *Tetrahedron Lett.* **1986**, *27*, 4161. (g) Pianetto, P.; Rollin, P.; Pougny, J. R. *Tetrahedron Lett.* **1986**, *27*, 5833. (h) Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1986**, *27*, 5857.
(5) See, for example: (a) Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. *J. Am. Chem. Soc.* **1980**, *102*, 7984. (b) Corey, E. J.; Marfat, A.; Monroe, J.; Kim, K. S.; Hopkins, P. B.; Brion, F. *Tetrahedron Lett.* **1981**, *22*, 1077. (c) Sih, C. J.; Han, C. Q.; Ditullio, D.; Wang, Y. F. *J. Org. Chem.* **1986**, *51*, 1253.
(6) (a) Harper, T. W.; Carrity, M. J.; Murphy, R. C. *J. Biol. Chem.* **1986**, *261*, 5414. (b) Soberman, R. J.; Harper, T. W.; Murphy, R. C.; Austen, K. F. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 2292. (c) Nadeau, M.; Fruteau De Laclos, B.; Picard, S.; Braguet, P.; Corey, E. J.; Borgeat, P. *Can. J. Biochem. Cell Biol.* **1984**, *62*, 1321. (d) Sirois, P.; Roy, S.; Borgeat, P.; Picard, S.; Corey, E. J. *Biochem. Biophys. Res. Commun.* **1981**, *99*, 385. (e) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 4751. (f) Nicolaou, K. C.; Chung, Y. S.; Hernandez, P. E.; Taffer, I. M.; Zipkein, R. E. *Tetrahedron Lett.* **1986**, *27*, 1881.
(7) For other leukotriene analogues, see: (a) Marfat, A.; Corey, E. J. *Adv. Prostaglandin, Thromboxane Leukotriene Res.* **1985**, *14*, 220. (b) Tolstikov, G. A.; Miftakhov, M. S.; Tolstikov, A. G. *Tetrahedron Lett.* **1985**, *26*, 3867. (c) Hanzawa, Y.; Inazawa, K.; Kon, A.; Aoki, H.; Kobayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 659.
(8) Rokach, J.; Zamboni, R.; Lau, C. K.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 2759.
(9) A procedure for obtaining the (*Z,E*)-diene by using Wittig reaction on pseudoglucal were recently reported: Tulshian, D. B.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1981**, *103*, 474.
(10) Bernstein, M. A.; Morton, H. E.; Guindon, Y. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1155.
(11) House, H. O.; Umen, M. *J. Org. Chem.* **1973**, *38*, 3893.
(12) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 6456.

Scheme IV[a]



[a] (a) $Ph_3P{=}CHCO_2Et$, THF; (b) NaOEt, EtOH; (c) TsCl, pyr; (d) NaI, acetone; (e) *t*-BDMSiCl, CH_2Cl_2; (f) (+≡+Cu⟨═ C_5H_{11}) Li, ether, HMPA, CuBr·Me_2S; (g) *n*-Bu_4NF, THF; (h) MsCl, Et_3N; (i) NaOEt, EtOH; (j) *t*-BDPSiCl, Et_3N, CH_2Cl_2; (k) AlH_3, THF; (l) CBr_4, Ph_3P (m) Ph_3P, CH_3CN; (n) H_2, Pd/C; (o) DMP, acetone, *p*-TsOH; (p) BzCl, Et_3N, CH_2Cl_2; (q) 1 N HCl, MeOH; (r) $Pb(OAc)_4$, CH_2Cl_2; (s) BuLi, THF; (t) *n*-Bu_4F, THF; (u) K_2CO_3, MeOH–H_2O.

and excess cuprous bromide–dimethyl sulfide complex gave 36% isolated yield of the desired product **19** together with 25% recovered starting material. It is also of interest to note that the yield of the coupling reaction is independent of whether the α- or β-anomer of **18** is used. When a 1:1 mixture of the isomers was used, a 1:1 mixture of the product isomer resulted.

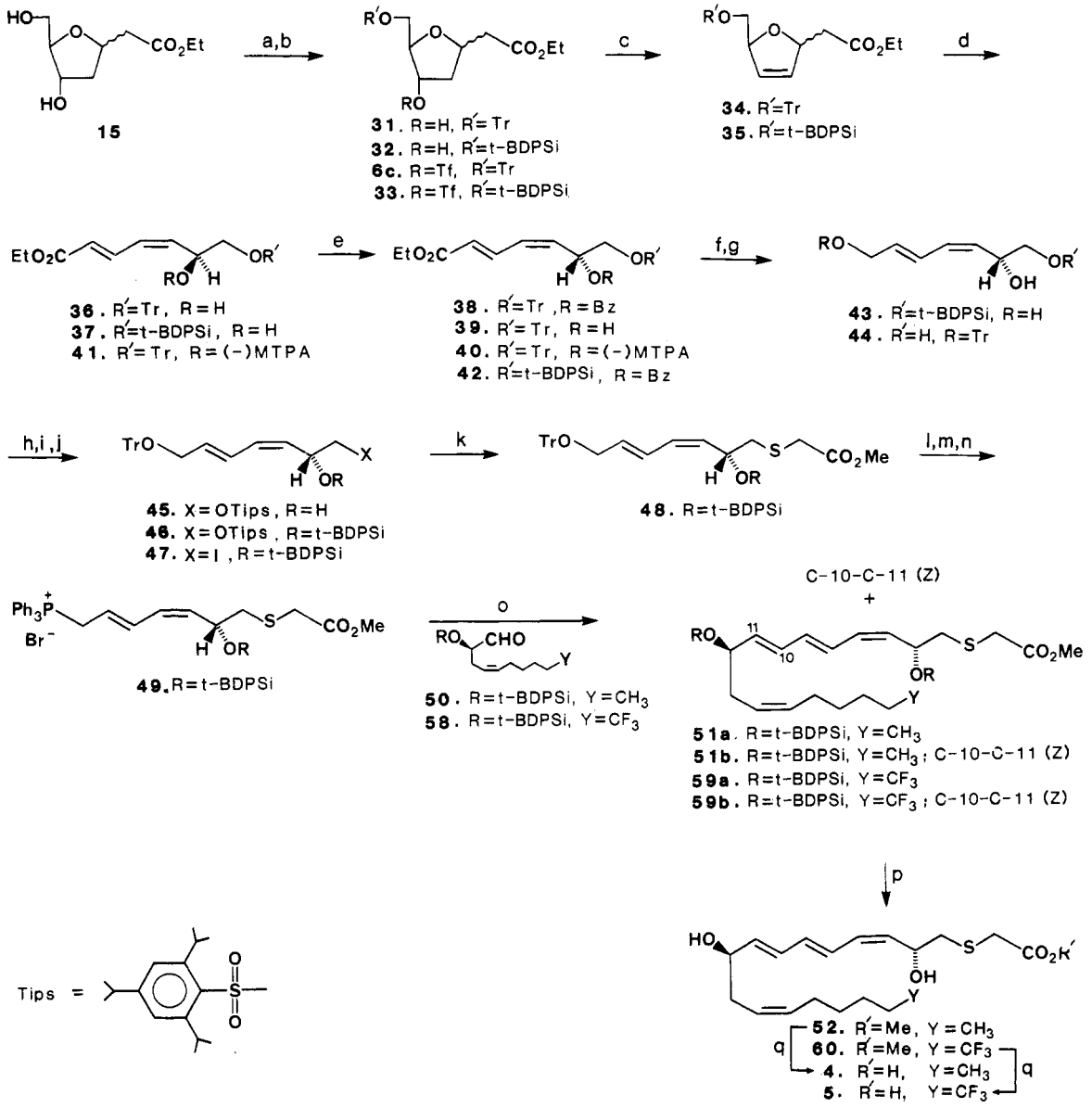
The silyl group of **19** was removed, and subsequent mesylation of the resulting alcohol **21** gave the key intermediate **11** in 71% yield. Treatment of **11** with sodium ethoxide in ethanol led cleanly to the (*E,E*)-diene alcohol **12**, in 90% yield. Again, there is no difference in yield whether the α- or β-anomer of **11** is used. Protection of the alcohol with *tert*-butyldiphenylchlorosilane followed by reduction of the ester with aluminum hydride gave the primary alcohol **23**, in 92% yield. The alcohol was transformed to the corresponding bromide, which was then displaced by triphenylphosphine to give the Wittig reagent **24** bearing the C-7 to C-20 segment of LTB_4.

Since the stereochemistry of C-3 of the starting sugar **13** was identical with that at C-5 of LTB_4, the synthesis of the C-1 to C-6 segment of LTB_4 was done by using the same intermediate.

Hydrogenation of the α,β-unsaturated ester **14** and formation of the kinetically favored acetonide[8] gave the alcohol **25** in good yield. Benzoylation of **25** and a subsequent treatment with 1 N HCl in MeOH gave in 50% yield the corresponding diol **26**. Oxidative cleavage of the vicinal diol with lead tetraacetate gave the aldehyde **27** in 65% yield.

The synthesis of LTB_4 was then completed as follows. Reaction of the phosphonium ylide generated from **24** with aldehyde **27** in the presence of 6.6 equiv of HMPA gave a mixture of the olefinic isomers **28** (48% yield) and **29** (9% yield). In the absence of HMPA, the ratio of **28** to **29** was only 3:1. Treatment of **28** with tetra-*n*-butylammonium fluoride gave **30** in 80% yield. Hydrolysis of the ester and the benzoate gave LTB_4 in 60% yield. UV

Scheme V[a]



[a] (a) See ref 16a; (b) *t*-BDPSiCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2, or TrCl, pyr; (c) Tf_2O, pyr, CH_2Cl_2, then DBU; (d) LDA, THF, 0 °C; (e) Ph_3P, benzoic acid, DEAD, THF; (f) DIBAH, toluene; (g) TrCl, pyr, then *n*-$Bu_4N^+F^-$, THF; (h) 2,4,6-triisopropylbenzenesulfonyl chloride, Et_3N, CH_2Cl_2; (i) *t*-BDPSiCl, CH_2Cl_2, *i*-Pr_2NEt; (j) NaI, MEK; (k) methylthioglycolate, NaH, THF; (l) 20% aqueous TFA, CH_2Cl_2; (m) CBr_4, DIPHOS, CH_2Cl_2; (n) Ph_3P, CH_3CN; (o) LiHMDS, THF, −78 °C then 23 → 0 °C; (p) Bu_4NF, AcOH, THF, then CH_2N_2, then K_2CO_3, MeOH; (q) NaOH, MeOH.

(max) CH_3OH: 260, 270.5, 281 nm.

For the synthesis of the two analogues of LTB_4 the C-furanosides **31** (α and β) were prepared from the same intermediate **15** (Scheme V). The endocyclic olefins **34** (α and β) were obtained in 78% yield through the formation of a secondary triflate ester[13] **6c** followed by treatment in the same reaction mixture with DBU.

The efficient opening of either α- or β-isomer **34** by LDA in dry THF at 0 °C led cleanly and exclusively to the optically active (*Z*,*E*)-diene ester **36**, $[\alpha]_D$ +79.4° (*c* 1.11, $CHCl_3$), in very high yield.[14]

The allylic alcohol in **36** was to become the hydroxyl group at C-5 of our LTB_4 analogues, so that an inversion of configuration at this center was necessary. This was achieved by using a well-known procedure (DEAD, triphenylphosphine, benzoic acid)[15] to give the benzoate **38** in 89% yield, $[\alpha]_D$ +76.8° (*c* 1.65, $CHCl_3$). The extent of the inversion of the allylic alcohol **36** has been verified in the following way. The benzoate **38** was treated with sodium ethoxide to give the corresponding cyclic α- and β-tetrahydrofuran derivatives followed by LDA, which effected the opening of the cycle and gives the allylic alcohol **39**, $[\alpha]_D$ −77.2° (*c* 1.55, $CHCl_3$), as opposed to $[\alpha]_D$ + 79.4° (*c* 1.11, $CHCl_3$) for **36**. Also both Mosher ester[16] of alcohols **36** and **39** were made and the ^1H NMR analysis indicated that **38** was obtained with 97% inversion.

We decided to change the trityl either group for a more

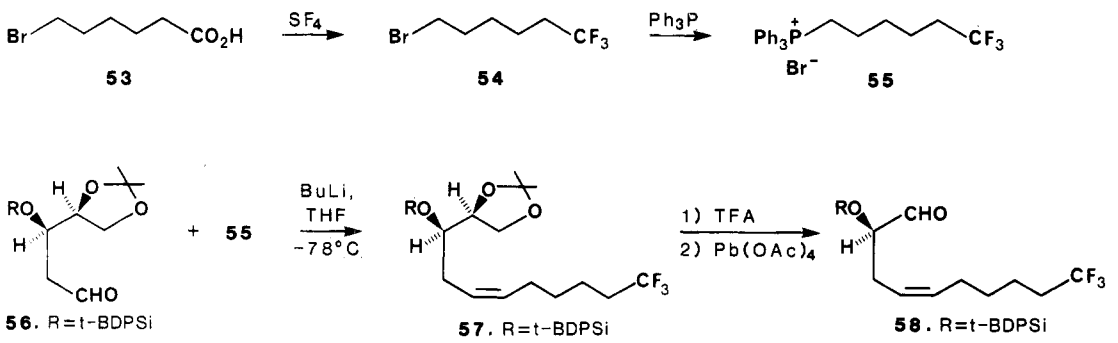
(13) Binkley, R. W.; Ambrose, M. G.; Hehemann, D. G. *J. Org. Chem.* **1980**, *45*, 4387.

(14) For precedent LDA-induced retro-Michael reaction, see: (a) Rokach, J.; Lau, C. K.; Zamboni, R.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 2763. (b) Grubbs, R. H.; Stille, J. R. *J. Am. Chem. Soc.* **1986**, *108*, 855.

(15) (a) Grynkiewicz, G.; Burzynska, H. *Tetrahedron Lett.* **1976**, *32*, 2109. (b) Mitsunobu, O. *Synthesis* **1981**, 1.

(16) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Scheme VI



stable one in acidic condition since we encountered difficulty to hydrolyze the trityl ether in the presence of allylic *tert*-butyldiphenylsilyl ether. So the same reaction sequence was done with *t*-BDPSi ether[17] derivative **32**, which was transformed via intermediates **33**, **35**, and **37** to **42**. DiBAH reduction[18] of both esters in **42** led to the diene diol **43**. The resulting primary alcohol was then tritylated, followed by desilylation using $Bu_4N^+F^-$ in dry THF, affording **44** in 61% yield from **42**. Selective primary sulfonylation of **44** with triisopropylbenzenesulfonyl chloride[19] in the presence of triethylamine was then followed by protection of the secondary alcohol as *tert*-butyldiphenylsilyl ether to give **46** in 87% yield. Successive displacement of the sulfonate **46** with sodium iodide in 2-butanone gave the primary iodide **47** followed by the sodium thiolate of methyl thioglycolate in THF at 50 °C for 4 h gave the C-1–C-10 unit **48** in 80% yield.

Completion of the synthesis of 3-thia-LTB_4 was then realized in the following way. Regeneration of the primary hydroxyl group from **48** was achieved with 20% aqueous trifluoroacetic acid[20] in CH_2Cl_2. The resulting allylic alcohol was converted to the corresponding bromide (CBr_4, DiPHOS, CH_2Cl_2) in 82% yield and to the phosphosium salt **49** by treatment with triphenylphosphine in acetonitrile. Formation of the ylide of **49** at −78 °C (THF) using LiHMDS as base followed by the addition of aldehyde **50** and warming of the reaction mixture to 0 °C gave trienes **51a** and **51b** in a 1:1 ratio. Removal of both silyl ether using $Bu_4N^+F^-$ in the presence of acetic acid followed by separation of the isomers using HPLC led to the 3-thia-LTB_4 methyl ester **52**. Subsequent saponification gave the 3-thia-LTB_4 (**4**).

The introduction of a metabolically stable group such as trifluoromethyl (CF_3) at C-20 of 3-thia-LTB_4 (**4**) was then realized as follows. Treatment of 6-bromohexanoic acid (**53**) with sulfur tetrafluoride[21] gave the trifluoro derivative **54** (Scheme VI).

The corresponding phosphonium salt **55** was treated with butyllithium in dry THF followed by addition of aldehyde **56**[22] to afford the (*Z*)-olefin **57**. Selective removal of the acetonide and cleavage of the resulting diol with lead tetraacetate in presence of potassium carbonate gave the aldehyde **58** in 87% yield.

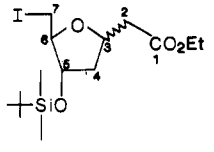
The aldehyde **58** was then coupled with the same ylide derived from **49** (C-1–C-10 unit) as described previously (Scheme V) to give a mixture of trienes **59a** and **59b** in 68% yield. Removal of silyl ethers followed by separation of the resulting diol gave 3-thia-20,20,20-trifluoro-LTB_4 methyl ester **60**. Saponification (NaOH, MeOH) gave 3-thia-20,20,20-trifluoro LTB_4 (**5**). Both analogues **4** and **5** were shown to be biologically active in a PMN aggregation assay[23] with similar potency to LTB_4 itself. Functional effects and in vivo activity will be reported elsewhere.

In conclusion, the potential usefulness of optically active tetrahydrofurans as masked stable precursors of stereochemically well defined 1,3-dienes, has been illustrated in the synthesis of LTB_4, 3-thia-LTB_4, and 3-thia-20,20,20-trifluoro-LTB_4.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Hexamethylphosphoramide (HMPA) and methylene chloride were distilled from CaH_2 and stored under a nitrogen atmosphere. All other solvents were of reagent grade from freshly opened bottles. Flash chromatography refers to the procedure described by Still et al.[24] NMR spectra were recorded on a Bruker AM 250 (250 MHz), a Bruker WH400 (400 MHz), or a Varian EM 390 (90 MHz) instrument. IR spectra were obtained with a Perkin-Elmer 681 spectrophotometer. UV spectra were recorded on a Perkin-Elmer Lambda 5 instrument. Optical rotations were obtained with the indicated solvent and concentration in a 1-dm cell by using a Perkin-Elmer 481 polarimeter. Mass spectrometric (MS, 70 eV) measurement were performed by Morgan Schaffer (Montreal, Quebec, Canada) using a Hitachi Perkin-Elmer RMU-6D mass spectrometer. High-resolution mass spectra were obtained at the McGill University Mass Spectrometry Unit on a ZAB-HS spectrometer. All reactions were monitored by thin-layer chromatography (TLC). TLC was performed with E. Merck 60F-254 precoated silica (0.2 cm) on glass.

The chemical names are given following IUPAC rules. To facilitate the notation of ^1H NMR data in the Experimental Section and the supplementary material, an unofficial numbering is adopted; i.e., the numbering of the tetrahydrofuranacetate was the same as if the furan ring had been opened up starting from the ester carbon as shown, for example, for 18.



Ethyl Tetrahydro-4(*S*)-[(*tert*-butyldimethylsilyl)oxy]-5-(*S*)-(iodomethyl)-2-furanacetate (18). A 1:1 mixture of α- and β-isomers of iodide **17** (40 g, 0.127 mol), *tert*-butyldimethylchlorosilane (28.7 g, 0.19 mol), (*N*,*N*-dimethylamino)pyridine (7.74

(17) Hanessian, S.; Lavallée, P. *Can. J. Chem.* **1975**, *53*, 2975.
(18) For a recent study on DIBAH reagent, see: Yoon, N. M.; Gyoung, Y. S. *J. Org. Chem.* **1985**, *50*, 2443.
(19) Lohrmann, R.; Khorana, H. G. *J. Am. Chem. Soc.* **1966**, *88*, 829.
(20) For an example, see: Prugh, J. D.; Rooney, C. S.; Deana, A. A.; Ramjit, H. G. *J. Org. Chem.* **1986**, *51*, 648.
(21) (a) Hasek, W. R.; Smith, W. C.; Engelhardt, V. A. *J. Am. Chem. Soc.* **1960**, *82*, 543. (b) Hasek, W. R. *Org. Synth.* **1961**, *41*, 104.
(22) (a) Wong, M. Y. H.; Gray, G. R. *J. Am. Chem. Soc.* **1978**, *100*, 3548. (b) See ref 2b.
(23) Evans, J.; Nathaniel, D.; Charleson, S.; Leveillé, C.; Zamboni, R.; Leblanc, Y.; Frenette, R.; Fitzsimmons, B. J.; Leger, S.; Hamel, P.; Ford-Hutchinson, A. W. *Prostaglandins, Leukotrienes Med.* **1986**, *23*, 167.
(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

g, 0.06 mol), and triethylamine (35.6 mL, 0.254 mol) was stirred at room temperature in dichloromethane (150 mL) for 18 h. Water (200 mL) was added, and the resulting mixture was extracted with ether (3 × 700 mL). After normal workup the resulting brown oil was chromatographed on silica gel (eluted with 95:5 hexane-/ethyl acetate) to give 25 g each of the β- and α-C-glycosides **18a** and **18b** (91% yield). The β-isomer **18a** exhibited $[\alpha]_D$ +11.38° (*c* 1.23, $CDCl_3$): ^1H NMR (250 MHz, $CDCl_3$) δ 0.0915 (s, 3 H, $SiCH_3$), 0.1073 (s, 3 H, $SiCH_3$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 1.84 (ddd, 1 H, H-4β $J(\alpha,\beta)$ = 13 Hz, $J(3,4\beta)$ = 9.3 Hz, $J(4\beta,5)$ = 5.88 Hz), 1.98 (ddd, 1 H, H-4α, $(J\alpha,\beta)$ = 13 Hz, $J(3,4\alpha)$ = 5.81 Hz, $J(4\alpha,5)$ = 2.67 Hz), 2.53 (dd, 1 H, CH_2CO_2Et, $J(2,2')$ = 15.4 Hz, $J(3,2)$ = 6 Hz), 2.67 (dd, 1 H, CH_2CO_2Et, $J(2,2')$ = 15.4 Hz, $J(3,2)$ = 6 Hz), 3.128 (dd, 1 H, CH_2I, $J(7,7')$ = 10.3 Hz, $J(6,7)$ = 6.6 Hz), 3.227 (dd, 1 H, CH_2I, $J(7,7')$ = 10.4 Hz, $J(6,7)$ = 4.27 Hz), 3.74 (m, 1 H, H-6), 4.16 (q, 2 H, CH_2CH_3, *J* = 7.3 Hz), 4.20 (m, 1 H, H-5), 4.57 (m, 1 H, H-3); decoupling experiment, irradiate H-3, each CH_2CO_2Et collapsed to a doublet J = 15.4 Hz, also H-4α collapsed to a doublet, $J(\alpha,\beta)$ = 13 Hz, irradiate H7,7',H-6 collapsed to a doublet, $J(5,6)$ = 1.17 Hz; the β-configuration at C-1 was confirmed by NOEDS[10] (irradiation time, 5 s),

irradiated protons	obsd NOE
H-6	H-7,7'
	H-5
	H-3

HRMS, calcd for $C_{14}H_{26}O_4SiI$ 413.0642, found 413.0646 ($M^+ - CH_3$).

The α-isomer **18b** exhibited $[\alpha]_D$ +20.11° (*c* 1.85, $CDCl_3$): ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (t, 3 H, methyl, *J* = 7.1 Hz), 1.748 (ddd, 1 H, H-4α, $J(\alpha,\beta)$ = 12.9 Hz, $J(3,4\alpha)$ = 6 Hz, $J(4\alpha,5)$ = 5.2 Hz), 2.35 (dt, 1 H, H-4β, $J(\alpha,\beta)$ = 13.1 Hz, $J(3,4\beta)$ = $J(4\beta,5)$ = 6.64 Hz), 2.58 (dd, 1 H, CH_2COEt, $J(2,2')$ = 15.62 Hz, $J(3,2)$ = 7.14 Hz), 2.78 (dd, 1 H, CH_2CO_2Et, $J(2,2')$ = 15.6 Hz, $J(3,2)$ = 6.9 Hz), 3.13–3.24 (m, 2 H, CH_2I), 3.79 (m, 1 H, H-6), 4.14 (q, 2 H, $CO_2CH_2CH_3$, *J* = 7.1 Hz), 4.24 (m, 1 H, H-5), 4.56 (ddd, 1 H, H-3, $J(3,4)$ = 6.6 Hz); HRMS, calcd for $C_{15}H_{29}O_4SiI$ 428.0877, found 428.0854 (M^+).

Ethyl Tetrahydro-4(*S*)-[(*tert*-butyldimethylsilyl)oxy]-5-(*R*)-(2-octenyl)-2-furanacetate (19). To a cold (−78 °C) stirring solution of (*Z*)-1-bromo-1-heptene[12] (6.22 g, 35 mmol) in ether (40 mL) was added a hexane solution of *tert*-butyllithium (31.8 mL, 2.2 M solution, 70 mmol). The resulting mixture was allowed to stir at −78 °C for 3 h. Meanwhile, to a cold (−78 °C) ether (40 mL) solution of 3,3-dimethyl-1-butyne (3.13 g, 38 mmol) was added dropwise a solution of *n*-butyllithium in hexane (21 mL, 35 mmol). The mixture was warmed to 0 °C for 0.5 h and then transferred to a stirring slurry of copper bromide–dimethyl sulfide complex (7.1 g, 35 mmol) in ether (80 mL) at 0 °C. The resulting light orange solution of 3,3-dimethyl-1-butynyl copper was cooled to −78 °C. To this solution was then transferred the above-mentioned (*Z*)-1-heptenyllithium reagent prepared earlier. The resulting mixture was stirred at −78 °C for 0.5 h. More copper bromide–dimethyl sulfide complex (2.3 g, 11.5 mmol) in 10 mL of dimethyl sulfide was added. The resulting mixture was stirred at −78 °C for another 0.5 h. Hexamethylphosphoramide (12 mL, 72 mmol) was then added dropwise followed by the addition of an ether (5 mL) solution of the iodide **18** (2.928 g, 6.84 mmol). The mixture was stirred at −78 °C for 1 h and then warmed to −10 °C for 4 h. Acetic acid (5 mL) was added. A grayish granular precipitate resulted. The clear solution was filtered through a short column of Florisil and eluted with ether. The eluant was concentrated under reduced pressure to give a light brown oil, which was chromatographed (silica gel, 3% ethyl acetate in hexane as eluant) to give the alkylated product **19** (903 mg, 36% yield) and some starting material **18** (731 mg, 25%). Product **19** was characterized in the next step after removal of the silyl group.

Ethyl Tetrahydro-4(*S*)-hydroxy-5(*R*)-(2-octenyl)-2-furanacetate (21). To the silyl ether **19** (1.4 g, 3.5 mmol) was added at room temperature with stirring a solution of tetra-*n*-butylammonium fluoride (7 mL, 1 M THF solution). The mixture was stirred at room temperature for 20 min. The resulting mixture was chromatographed on silica gel (eluted with 7:3 hexane/ethyl acetate) to give the corresponding alcohol **21** (825 mg, 75% yield). When only the α-C-glycoside **19b** was employed, only the α-C-glycoside **21b** was obtained: $[\alpha]_D$ +20.74° (*c* 1,48, $CDCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.89 (t, 3 H, H-14, $J(14,13)$ = 6.6 Hz), 1.26 (t, 3 H, $CO_2CH_2CH_3$), 1.3 (m, 3 H, H-11–13), 1.79 (ddd, 1 H, H-4α, $J(\alpha,\beta)$ = 13.4 Hz, $J(4\alpha,5)$ = 3.9 Hz, $J(4\alpha,3)$ = 5.9 Hz), 2.03 (dt, 1 H, H-10, $J(10,11)$ = 6.8 Hz), 2.20 (ddd, 1 H, H-7', $J(7',8)$ = 6.2 Hz), 2.27 (ddd, 1 H, H-7, $J(7,7')$ = 14 Hz, $J(7,8)$ = 6.2 Hz), 2.46 (ddd, 1 H, H-4β, $J(4\beta,5)$ = 6.3 Hz, $J(4\beta,3)$ = 7.8 Hz), 2.65 (dd, 1 H, H-2', $J(2',3)$ = 6.3 Hz), 2.74 (dd, 1 H, H-2, $J(2,2')$ = 15.9 Hz, $J(2,3)$ = 6.0 Hz), 3.92 (ddd, 1 H, H-6, $J(6,7)$ = $J(6,7')$ = 7.0 Hz), 4.1 (ddd, 1 H, H-5, $J(5,6)$ = 3.2 Hz), 4.35 (q, 2 H, $CO_2CH_2CH_3$, *J* = 7.1 Hz), 4.43 (m, 1 H, H-3), 5.40 (m, 1 H, H-8, $J(8,9)$ = 11.0 Hz, $J(8,10)$ = 0.7 Hz), 5.53 (m, 1 H, H-9, $J(9,10)$ = 6.8 Hz, $J(9,7)$ = $J(9,7')$ = 1.0 Hz); HRMS, calcd for TMS derivative $C_{19}H_{36}O_4Si$ 356.2382, found 356.2376 (M^+).

The β-C-glycoside **21a** exhibited the following: ^1H NMR (90 MHz, $CDCl_3$) δ 2.56 (m, 2 H, CH_2CO_2Et), 3.76 (m, 1 H, methine), 3.93–4.2 m (m, 1 H, methine), 4.13 (q, 2 H, ethyl CH_2, *J* = 7.5 Hz), 4.16–4.7 (m, H, methine), 5.43 (m, 2 H, olefinic).

The stereochemistry of the C-glycoside linkage was determined by 2D chemical shift correlated spectroscopy (COSY) and 2D NOE spectroscopy (NOESY).

Ethyl 6(*R*)-Hydroxy-2(*E*),4(*E*),8(*Z*)-tetradecatrienoate (12). To a solution of the mesylate **11** (1.02 g, 2.8 mmol) in 5 mL of dry ethanol at room temperature was added a solution of sodium ethoxide in ethanol (7 mL, 1 M solution, 2.5 mmol). The resulting mixture was stirred at room temperature for 0.5 h. Saturated ammonium chloride solution (15 mL) was added. The ethanol was removed under reduced pressure. The residual aqueous solution was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate. Concentration of the extract under reduced pressure gave a yellow oil, which was chromatographed on silica gel (eluted with 25% ethyl acetate in hexane) to give the trienol **12** (633 mg, 85% yield): $[\alpha]_D$ +11.4° (*c* 1.31, $CDCl_3$); HRMS, calcd for TMS derivative $C_{18}H_{31}O_3Si$ 323.2042, found 323.2041 ($M^+ - CH_3$).

6(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-2(*E*),4(*E*),8(*Z*)-tetradecatrien-1-ol (23). To a cold (0 °C) solution of ester **22** (827 mg, 1.64 mmol) in dry tetrahydrofuran (5 mL) was added a tetrahydrofuran solution of AlH_3·$^1/_3H_2O$ (6 mL, 0.55 M, 3.28 mmol). The resulting mixture was stirred at 0 °C for 1 h. Phosphate buffer solution (pH 7) (10 mL) was added. The mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine and dried over anhydrous magnesium sulfate. Concentration of the organic extracts gave a light yellow oil, which after chromatography (silica gel, 25% ethyl acetate in hexane) gave the alcohol **23** as a colorless oil (697 mg, 92% yield): $[\alpha]_D$ +22.1° (*c* 1.49, $CDCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.85 (m, 3 H), 1.05 (s, 9 H), 1.1–1.3 (m, 6 H), 1.7–1.9 (m, 2 H), 2.1–2.3 (m, 2 H), 4.1 (d, 2 H), 4.2 (m, 1 H), 5.2 (m, 2 H), 5.4–6.2 (m, 6 H), 7.1–7.8 (m, 10 H).

1-Bromo-6(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-2(*E*),4(*E*),8(*Z*)-tetradecatriene. To a solution of CBr_4 (1 g, 3.0 mmol) and Ph_3P (1 g, 3.8 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added alcohol **23** (0.5 g, 1.1 mmol). The mixture was stirred 5 min. The reaction mixture was passed through SiO_2 column by using 5% ethyl acetate/hexane. Evaporation of the eluent under vacuum afforded the bromide (0.6 g, 100% yield): ^1H NMR (90 MHz, $CDCl_3$) δ 0.9 (m, 3 H), 1.05 (s, 9 H), 1.1–1.3 (m, 6 H), 1.8 (m, 2 H), 2.25 (m, 2 H), 3.9 (d, 2 H), 4.15 (q, 2 H), 5.2 (m, 2 H), 5.4–6.2 (m, 6 H), 7.2–7.4 (m, 6 H), 7.5–7.8 (m, 4 H).

[6(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-2(*E*),4(*E*),8(*Z*)-tetradecatrien-1-yl]triphenylphosphonium Bromide (24). To the bromide (0.6 g, 1 mmol) in CH_3CN (10 mL) was added Ph_3P (1 g, 3.8 mmol). The reaction was stirred 2 h at room temperature and evaporated. Chromatography of the residue on SiO_2 using a gradient from 1% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2 afforded the phosphonium salt **24** (0.8 g, 88% yield) as a foam: ^1H NMR (90 MHz, $CDCl_3$) δ 0.9 (m, 3 H), 1.1 (s, 9 H), 1.2 (m, 6 H), 1.75 (m, 2 H), 2.2 (m, 2 H), 4.15 (m, 1 H), 4.7 (dd, 2 H), 5.2 (m, 2 H), 5.4–6.3 (m, 6 H), 7.0–8.3 (m, 25 H).

Ethyl 5(*S*)-(Benzoyloxy)-12(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-6(*Z*),8(*E*),10(*E*),14(*Z*)-eicosatetraenoate (28) and the 6*E* Isomer (24). To a solution of the phosphonium salt **24** (0.8 g, 1.0 mmol) in THF (12 mL) at −78 °C was added *n*-BuLi (0.6 mL, 0.96 mmol) dropwise over 10 min. The dark red ylide

was stirred 15 min at −78 °C, and then HMPA (1.2 mL, 6.6 mmol) was added. After 5 min the aldehyde **27** (270 mg, 1 mmol) in 2 mL of THF was added dropwise. The reaction mixture was stirred 20 min at −78 °C and 20 min at −40 °C and quenched with 50 mL of 20% NH_4OAc in H_2O. The mixture was extracted with ether. The ether phase was washed with H_2O and saturated NaCl, dried, and evaporated. The residue was first purified by passage through a pad of SiO_2 by using 10% ethyl acetate and 5% triethylamine in hexane to afford 520 mg of the trienes **28** and **29** as a 5.5:1 mixture of isomers. Final purification on a Waters Prep 500 using 6% ethyl acetate and 1% triethylamine in hexane afforded 320 mg (48%) of the desired isomer **28** and 53 mg of **29**.

For **28**: $[\alpha]_D$ +202° (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.9 (m, 3 H), 1.05 (s, 9 H), 1.2–1.3 (m, 6 H), 1.25 (t, 3 H), 1.8–1.95 (m, 6 H), 2.15–2.25 (m, 2 H), 2.35 (m, 2 H), 4.1 (q, 2 H), 4.2 (m, 1 H), 5.2–5.4 (m, 2 H), 5.45 (t, J = 10 Hz, 1 H), 5.7 (dd, J_1 = 6 Hz, J_2 = 15 Hz), 5.9 (m, 1 H), 5.9–6.05 (m, 1 H), 6.1–6.2 (m, 2 H), 6.5 (m, 1 H), 7.2–7.7 (m, 13 H), 8.1 (d, 2 H).

For **29**: $[\alpha]_D$ +106° (*c* 0.5, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.9 (m, 3 H), 1.05 (s, 9 H), 1.2–1.3 (m, 6 H), 1.25 (t, 3 H), 1.7–1.95 (m, 6 H), 2.1–2.35 (m, 2 H), 2.35 (m, 2 H), 4.1 (q, 2 H), 4.2 (m, 1 H), 5.2–5.4 (m, 2 H), 5.55 (m, 1 H), 5.62–5.72 (m, 2 H), 5.9–6.2 (m, 2 H), 6.35 (q, 2 H), 7.3–7.7 (m, 13 H), 8.10 (d, 2 H).

Ethyl 5(*S*)-(Benzoyloxy)-12(*R*)-hydroxy-6(*Z*),8(*E*),10-(*E*),14(*Z*)-eicosatetraenoate (30). To the **28** isomer (54 mg) in THF (1 mL) was added tetra-*n*-butylammonium fluoride solution (1 M) (1 mL). The solution was stirred at room temperature for 3 h. The reaction mixture was applied directly to a SiO_2 column. Elution with 25% ethyl acetate and 3% Et_3N in hexane afforded 29 mg of the alcohol (79% yield): $[\alpha]_D$ 260° (*c* 1.0, $CHCl_3$); ε 49 000 (271 nm); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.9 (m, 3 H), 1.2–1.3 (m, 6 H), 1.25 (t, 3 H), 1.6–1.7 (m, 5 H), 1.9 (m, 1 H), 2.05 (m, 2 H), 2.3–2.4 (m, 4 H), 4.1 (q, 2 H), 4.25 (m, 1 H), 5.35–5.45 (m, 1 H), 5.45 (t, J = 10 Hz, 1 H), 5.55–5.65 (m, 1 H), 5.8 (dd, J_1 = 6 Hz, J_2 = 15 Hz), 5.9–5.95 (m, 1 H), 6.15–6.4 (m, 3 H), 6.60 (dd, J_1 = 16 Hz, J_2 = 12 Hz), 7.4–7.5 (m, 2 H), 7.5–7.6 (m, 1 H), 8.05 (m, 1 H).

5(*S*),12(*R*)-Dihydroxy-6(*Z*),8(*E*),10(*E*),14(*Z*)-eicosatetraenoic Acid (LTB_4, 1). To the ester **30** (25 mg) in MeOH (3 mL) and H_2O (0.7 mL) was added K_2CO_3 (50 mg). The reaction mixture was stirred overnight at room temperature. Most of the MeOH was removed on a rotary evaporator, and AcOH (160 μL) was added. A little MeOH was then added in order to obtain a clear solution. HPLC on a Waters C_{18} μ-Bondapak column was performed with CH_3CN (40%), H_2O (20%), and 0.02% AcOH. The fractions containing LTB_4 were combined, and excess K_2CO_3 (≃20 mg) was added. The fractions were evaporated to ∼2 mL and applied to a XAD-8 column. Elution with H_2O removed the excess salts. Elution with MeOH afforded LTB_4 (1) as a potassium salt: 11 mg (63% yield); ^1H NMR (DMSO-d_6, 400 MHz) δ 0.9 (m, 3 H), 1.3–1.4 (m, 6 H), 1.5–1.7 (m, 5 H), 1.8 (m, 1 H), 2.0–2.1 (m, 4 H), 4.1 (m, 1 H), 4.45 (m, 1 H), 4.95 (m, 1 H), 5.4 (t, J = 10 Hz, 1 H), 5.45–5.55 (m, 2 H), 5.80 (dd, J_1 = 6 Hz, J_2 = 15 Hz), 6.05 (t, J = 10 Hz, 1 H), 6.25–6.45 (m, 2 H), 6.60 (t, J = 12 Hz, 1 H); UV (CH_3OH) (max) 260, 270.5, 281 nm.

Ethyl Tetrahydro-4(*S*)-hydroxy-5(*R*)-[((triphenylmethyl)oxy)methyl]-2(*R*)-furanacetate (31β) and Ethyl Tetrahydro-4(*S*)-hydroxy-5(*R*)-[((triphenylmethyl)oxy)methyl]-2(*S*)-furanacetate (31α). The mixture of diol **15** (3.7 g, 18.14 mmol) was dissolved in 20 mL of pyridine, and 0.37 g (0.17 equiv, 3.03 mmol) of (dimethylamino)pyridine was added followed by 6.1 g (1.2 equiv, 21.8 mmol) of triphenylmethyl chloride at room temperature. The resulting mixture was stirred for 18 h. The mixture was poured into 50 mL of ice–water and extracted with dichloromethane (4 × 60 mL), and after normal workup, purification by flash chromatography (40% ethyl acetate in hexanes) gave 6.5 g (80%) of a mixture of trityl ether. Separation of both isomers by flash chromatography (25% ethyl acetate in hexanes) gave **31β** and **31α**.

For **31β**: $[\alpha]_D$ +6.76° (*c* 2.66, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.85 (m, 1 H, H-4), 2.07 (m, 1 H, H-4′), 2.52 (dd, 1 H, J(2,3) = 6.3 Hz, J(2,2′) = 15 Hz, H-2′), 2.67 (dd, 1 H, J(2,3) = 6.3 Hz, H-2), 3.06 (dd, 1 H, J(7,7′) = 9 Hz, J(6,7) = 6.3 Hz, H-7), 3.23 (dd, 1 H, J(6,7′) = 5 Hz, H-7′), 3.95 (m, 1 H, H-6), 4.13 (q, 2 H, J = 7 Hz, CH_2CH_3), 4.33 (m, 1 H, H-5), 4.57 (m, 1 H, H-3), 7.2–7.5 (m, 15 H, 3 Ph). Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.30; H, 6.78. Found: C, 75.10; H, 6.98.

For **31α**: $[\alpha]_D$ +8.76° (*c* 5.5, $CHCl_3$); ^1H NMR (250 MHz, acetone-d_6) δ 1.23 (t, 3 H, J = 7.1 Hz, CH_3CH_2), 1.72 (ddd, 1 H, J(4α,4β) = 12.7 Hz, J(4α,5) = 6.6 Hz, H-4α), 2.38 (ddd, 1 H), J(4β,5) = 6.2 Hz, H-4β), 2.62 (dd, 1 H, J(2′,3) = 5.9 Hz, H-2′), 2.72 (dd, 1 H, J(2,2′) = 15.3 Hz, J(2,3) = 7.5 Hz, H-2), 3.10 (m, 2 H, H-7,7′), 4.0 (m, 1 H, J(6,7) = 4.5 Hz, H-6), 4.12 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 4.20 (d, 1 H, OH), 4.33 (m, 1 H, J(5,6) = 4.0 Hz, H-5), 4.55 (quint, 1 H, J(3,4α) = 5.1 Hz, J(3,4β) = 6.2 Hz, H-3), 7.2–7.6 (m, 15 H, 3 Ph). NOE experiment (irradiation time 2–5 s),

irradiated protons	obsd NOEs, %
H-4α	H-4β = 9.0; H-5 = 0.7
H-4β	H-4α = 11.8; H-5 = 2.8; H-3 = 4.0

Ethyl 3,4-Dihydro-5(*R*)-[((triphenylmethyl)oxy)-methyl]-2(*R*)-furanacetate (34α). To a solution of 0.07 mL (2.2 equiv 0.99 mmol) of pyridine in 2 mL of dichloromethane at −10 °C was added dropwise 0.15 mL (2 equiv, 0.89 mmol) of trifluoromethanesulfonic anhydride. After the mixture was stirred for 15 min a solution of alcohol **31α** (200 mg, 0.45 mmol) in 2 mL of dichloromethane was added dropwise, and the resulting mixture was stirred for 10 min; then 0.4 mL of DBU (2.68 mmol) was added, and the red clear solution was stirred for 3 h. The reaction mixture was diluted with 100 mL of dichloromethane and treated in usual manner. Purification by flash chromatography (10% ethyl acetate in hexanes) gave 146 mg (76%) of the desired olefin **34α**: $[\alpha]_D$ −129° (*c* 0.56, $CHCl_3$); ^1H NMR (250 MHz, acetone-d_6) δ 1.24 (t, 3 H, J = 7 Hz, CH_3CH_2O), 2.51 (dd, 1 H, J(2′,3) = 7.4 Hz, H-2′), 2.60 (dd, 1 H, J(2,2′) = 15.2 Hz, J(2,3) = 5.7 Hz, H-2), 3.05 (dd, 1 H, J(6,7′) = 4.5 Hz, H-7′), 3.10 (dd, 1 H, J(7,7′) = 9.4 Hz, H-7), 4.13 (q, 2 H, J = 7.1 Hz, OCH_2CH_3), 5.02 (m, 1 H, J(6,7) = 5.1 Hz, H-6), 5.27 (m, 1 H, J(3,4) = 1.1 Hz, J(3,5) = 1.8 Hz, J(3,6) = 5.8 Hz, H-3), 5.97 (m, 1 H, J(5,6) = 1.1 Hz, H-5), 6.03 (m, 1 H, J(4,5) = 6.2 Hz, J(4,6) = 1.8 Hz, H-4), 7.2–7.6 (m, 15 H, 3 Ph); NOE experiment (irradiation time 2–5 s),

irradiated protons	obsd NOEs, %
H-2,2′	H-3 = 3.3; H-6 = 0.6; H-4 = 1.5; H-5 = ca. 0.2
H-7,7′	H-6 = 11.0; H-3 = 1.1; H-5 = 2.2; H-4 < 0.4

The same reaction on β product **31β** gave **34β**: $[\alpha]_D$ −41.9° (*c* 0.86, $CHCl_3$); ^1H NMR (250 MHz, acetone-d_6) δ 1.20 (t, 3 H, J = 7.1 Hz, CH_3), 2.60 (d, 2 H, J(2,3) = 6.6 Hz, H-2), 3.07 (dd, 1 H, J(6,7′) = 4.1 Hz, H-7′), 3.13 (dd, 1 H, J(7,7′) = 9.7 Hz, H-7), 4.10 (q, 2 H, J = 7.1 Hz, CH_2CH_3), 4.95 (m, 1 H, J(6,7) = 5.1 Hz, H-6), 5.17 (m, 1 H, J(3,4) = 1.5 Hz, J(3,5) = 1.8 Hz, J(3,6) = 3.6 Hz, H-3), 5.90 (m, 1 H, J(5,6) = 1.1 Hz, H-5), 6.00 (m, 1 H, J(4,5) = 5.8 Hz, J(4,6) = 2.2 Hz, H-4), 7.2–7.6 (m, 15 H, 3 Ph); NOE experiment (irradiation time 2–5 s),

irradiated protons	obsd NOEs, %
H-2,2′	H-3 = 5.0; H-4 = 2.2; H-5 = 0.3; H-7,7′ = ca. 0.2
H-7,7′	H-6 = 12.2; H-5 = 2.3; H-4 = 0.3; H-2,2′ = 0.4

Ethyl 7-*O*-(Triphenylmethyl)-6(*R*),7-dihydroxy-2(*E*),4-(*Z*)-heptadienoate (36). To a stirred solution of **34** (890 mg, 2.08 mmol) in dry THF (10 mL) at 0 °C was slowly added (5 mL, 1.7 equiv, 3.54 mmol) of 0.71 M LDA solution in dry THF. After being stirred for 15 min the reaction mixture was quenched at 0 °C by the addition of 1 mL of saturated aqueous ammonium chloride and diluted with 100 mL of dichloromethane. After the usual treatment and flash chromatography (20% ethyl acetate in hexanes), 620 mg (70%) of the diene **36** was obtained: $[\alpha]_D$ +79.4° (*c* 1.11, $CHCl_3$); IR (neat) 3450, 2920, 1710, 1640, 1610 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.32 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.48 (d, 1 H, OH), 3.21 (m, 2 H, CH_2OTr), 4.23 (q, 2 H, J = 7 Hz, CH_2CH_3), 4.70 (m, 1 H, CHOH), 5.73 (dd, 1 H, J = 11 Hz, J = 8 Hz, H-5), 5.90 (d, 1 H, J = 15 Hz, H-2), 6.18 (t, 1 H, J = 11 Hz, H-4), 7.2–7.5 (m, 15 H, 3 Ph), 7.50 (dd, 1 H, J = 11 Hz, J = 15 Hz, H-3).

Ethyl 6-*O*-Benzoyl-7-*O*-(triphenylmethyl)-6(*S*),7-dihydroxy-2(*E*),4(*Z*)-heptadienoate (38). To a stirred solution of 300 mg (0.701 mmol) of alcohol **36**, 102 mg (1.2 equiv, 0.841

mmol) of benzoic acid and 220 mg (1.2 equiv) of triphenylphosphine in dry THF (5 mL) was added dropwise (0.13 mL, 1.2 equiv) of diethyl azodicarboxylate at room temperature. After the mixture was stirred for ca. 15 min, the solvent was evaporated, and the residue was diluted with 200 mL of dichloromethane and treated in the usual manner. The residue was purified by flash chromatography (7% ethyl acetate in hexanes) to give 330 mg (89%) of benzoate **38**: $[\alpha]_D$ +76.8° (*c* 1.65, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.3 (t, 3 H, J = 7 Hz, CH_2CH_3), 3.4 (ddd, 2 H, J = 11, 6.3, 5 Hz, H-7,7'), 4.2 (q, 2 H, J = 7 Hz, CH_2CH_3), 5.9 (t, 1 H, H-5), 5.95 (d, 1 H, J = 15 Hz, H-2), 6.15 (m, 1 H, H-6), 6.3 (t, 1 H, J = 11 Hz, H-4), 7.75 (dd, 1 H, J = 15, 11 Hz, H-3), 7.2, 7.4 (m, 18 H, Ph), 8.1 (d, 2 H, Ph).

Ethyl 7-*O*-(Triphenylmethyl)-6(*S*),7-dihydroxy-2(*E*),4-(*Z*)-heptadienoate (39). To a solution of benzoate **38** (97 mg, 0.182 mmol) in dry ethanol (2 mL) was added 0.06 mL of 1 M sodium ethoxide ethanol solution at room temperature. The reaction was followed by TLC (20% ethyl acetate in hexanes), and two less polar products appeared, which corresponded to the cyclic tetrahydrofurans derivatives. After the addition of more sodium ethoxide solution, the reaction mixture was acidified with HCl (1 N) and then extracted with dichloromethane (2 × 30 mL). After normal workup the residue was dried under vacuum before being dissolved in 1 mL of dry THF and cooled to 0 °C. A solution of LDA (0.30 M), 0.94 mL (1.5 equiv, 0.28 mmol) was added dropwise to effect the ring opening, and then the reaction mixture was quenched with saturated aqueous ammonium chloride, extracted with dichloromethane, and treated in usual manner. Purification of the residue by flash chromatography (20% ethyl acetate in hexanes) gave 35 mg of alcohol **39**, which correspond to the enantiomer of **36**: $[\alpha]_D$ −77.2° (*c* 1.55, $CHCl_3$); Anal. Calcd for $C_{28}H_{28}O_4$: C, 78.47; H, 6.59. Found: C, 77.17; H, 6.84.

7-*O*-(*tert*-Butyldiphenylsilyl)-2(*E*),4(*Z*)-heptadiene-1,6-(*S*),7-triol (43). To a stirred solution of diester **42** (1.6 g, 3.03 mmol) in dry toluene (30 mL) at −10 °C was slowly added (8 mL, 4 equiv) of a 1.5 M DIBAH solution in toluene. After complete addition the cooling bath was removed, and the mixture was stirred at room temperature for 3 h. Methanol (0.3 mL) was added dropwise at 0 °C, and the reaction mixture was transferred to a vigorously stirred ethyl acetate–ice–water mixture. After acidification with 1 N aqueous HCl, the aqueous phase was extracted with ethyl acetate (3 × 50 mL) and worked up as usual. Purification by flash chromatography (50% ethyl acetate in hexanes) afforded 920 mg (79%) of the diol **43**: $[\alpha]_D$ −42.0° (*c* 1.24, $CHCl_3$); IR (neat) 3600, 2930, 2860 cm^{-1}; mass spectrum, *m/e* 325 ($M^+ - (CH_3)_3C$), 307 ($M^+ - (CH_3)_3C - H_2O$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.08 (s, 9 H, $(CH_3)_3$), 2.61 (m, 1 H, OH), 3.60 (ddd, 2 H, J = 11, 8, 4.2 Hz, $SiOCH_2$), 4.17 (m, 2 H, CH_2OH), 4.67 (m, 1 H, CHOH), 5.37 (dd, 1 H, J = 11 Hz, J = 8 Hz, H-5), 5.83 (dt, 1 H, J = 14.7 Hz, J = 6.3 Hz, H-2), 6.08 (t, 1 H, J = 11 Hz, H-4), 6.37 (dd, 1 H, J = 14.7 Hz, J = 11 Hz, H-3), 7.37–7.70 (m, 10 H, 2 Ph). Anal. Calcd for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.91. Found: C, 72.21; H, 8.08.

7-*O*-(Triphenylmethyl)-3(*Z*),5(*E*)-heptadiene-1,2(*S*),7-triol (44). Compound **43** (2.3 g, 6.0 mmol) was treated as previously described for **31**. The crude mixture was dissolved in dry THF (20 mL), and then 6 mL (1.2 equiv, 3.12 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF was slowly added at room temperature and followed by TLC (60% ethyl acetate in hexanes). After 30 min the solvent was removed and the crude mixture was applied to the top of a flash chromatography column. The diol **44** was eluted with 80% ethyl acetate in hexanes to give 1.4 g (61%): $[\alpha]_D$ +12.4° (*c* 1.35, $CHCl_3$); IR (neat) 3400, 3090, 3060, 3020, 2920, 2860 cm^{-1}; mass spectrum, *m/e* 143 ($M^+ - Ph_3C$); ^1H NMR (250 MHz, $CDCl_3$) δ 2.10 (br s, 2 H, 2 OH), 3.58 (m, 2 H, CH_2OH), 3.70 (d, 2 H, J = 6.3 Hz, CH_2OTr), 4.70 (br s, 1 H, CHOH), 5.40 (dd, 1 H, J = 11 Hz, J = 8 Hz, H-3), 5.88 (dt, 1 H, J = 14.7 Hz, J = 6.3 Hz, H-6), 6.17 (t, 1 H, J = 11 Hz, H-4), 6.60 (dd, 1 H, J = 14.7 Hz, J = 11 Hz, H-5), 7.20–7.47 (m, 15 H, 3 Ph). Anal. Calcd for $C_{26}H_{26}O_3$: C, 80.79; H, 6.73. Found: C, 77.99; H, 6.79.

2-*O*-(*tert*-Butyldiphenylsilyl)-1-*O*-[(2,4,6-triisopropylphenyl)sulfonyl]-7-*O*-(triphenylmethyl)-3(*Z*),5(*E*)-heptadiene-1,2(*S*),7-triol (46). Compound **45** (594 mg, 0.92 mmol) was treated as previously described for **22**. Flash chromatography (5% ethyl acetate in hexanes) gave 620 mg of the silyl ether **46** and 71 mg of recovery starting alcohol **45**: 87% yield based on recovery of alcohol; $[\alpha]_D$ −9.7° (*c* 1.48, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.03 (s, 9 H, $(CH_3)_3$), 1.20 (2 d, 18 H, 2 $CH(CH_3)_2$), 2.88 (septet, 1 H, J = 6.3 Hz, $CH(CH_3)_2$), 3.43 (d, 2 H, J = 5.4 Hz, CH_2OTr), 3.90 (ddd, 2 H, J = 8 Hz, J = 4.2 Hz, CH_2OSO_2), 4.02 (septet, 2 H, J = 6.3 Hz, 2 $CH(CH_3)_2$), 4.75 (m, 1 H, CHOSi), 5.32 (dd, 1 H, J = 11 Hz, J = 8 Hz, H-3), 5.80 (dt, dd, t, 3 H, H-4–6), 7.15–7.63 (m, 27 H, 5 Ph and $ArSO_2$). Anal. Calcd for $C_{57}H_{66}O_5SiS$: C, 76.82; H, 7.47. Found: C, 77.37; H, 6.99.

6-*O*-(*tert*-Butyldiphenylsilyl)-7-iodo-1-*O*-(triphenylmethyl)-2(*E*),4(*Z*)-heptadiene-1,6(*S*)-diol (47). To a stirred solution of sulfonate **46** (620 mg, 0.698 mmol) in 5 mL of methyl ethyl ketone was added 630 mg (6 equiv, 4.19 mmol) of sodium iodide, and the resulting mixture was warmed to 70 °C for 18 h. Another 420 mg (4 equiv, 2.79 mmol) of sodium iodide was added; after 4 h the reaction was dissolved with 100 mL of dichloromethane and treated as previously described for **17**. Flash chromatography (3% ethyl acetate in hexanes) give 358 mg of the desired iodo **47** as a syrup and 100 mg of starting material (83%, based on recovery sulfonate). For **47**: $[\alpha]_D$ +39.8° (*c* 0.96, $CHCl_3$); HRMS, calcd for $C_{19}H_{19}O_2Si$ 307.1154, found 307.1154 ($M^+ - (CH_3)_3C - H_2O$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.07 (s, 9 H, $(CH_3)_3$), 3.15 (ddd, 2 H, J = 9.4 Hz, J = 6.3 Hz, J = 5 Hz, CH_2I), 3.48 (d, 2 H, J = 5 Hz, CH_2OTr), 4.52 (m, 1 H, CHOSi), 5.38 (dd, 1 H, J = 11 Hz, J = 6.3 Hz, H-5), 5.80 (m, 3 H, H-2–4), 7.2–7.68 (m, 25 H, 5 Ph).

Methyl 5-*O*-(*tert*-Butyldiphenylsilyl)-10-*O*-(triphenylmethyl)-3-thia-5(*S*),10-dihydroxy-6(*Z*),8(*E*)-decadienoate (48). To a suspension of sodium hydride 234 mg (10 equiv, 4.88 mmol) in dry THF (10 mL) was added dropwise at 0 °C 0.22 mL (5 equiv, 2.44 mmol) of methyl thioglycolate in dry THF (2 mL). After the mixture was stirred at room temperature for 1 h, the iodo derivative **47** (358 mg, 0.488 mmol) in dry THF was added dropwise at 0 °C. After complete addition the cooling bath was removed and the reaction mixture warmed to 50–55 °C for 4 h. The reaction was allowed to cool to room temperature and transferred slowly to a saturated aqueous ammonium chloride solution. The resulting mixture was extracted with dichloromethane (3 × 30 mL) and treated as usual. Purification by flash chromatography (5% ethyl acetate in hexanes) give 344 mg (96%) of **48** as a colorless oil: $[\alpha]_D$ +25.0° (*c* 2.0, $CHCl_3$); IR (neat) 3060, 3020, 2950, 2930, 2860, 1740 cm^{-1}; HRMS, calcd for $C_{41}H_{39}O_4SiS$ 655.2338, found 655.2375 ($M^+ - (CH_3)_3C$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.04 (s, 9 H, $(CH_3)_3$), 2.78 (d, 2 H, J = 6.3 Hz, SCH_2), 3.05 (AB, 2 H, J = 14.7 Hz, $OCCH_2S$), 3.48 (d, 2 H, J = 5.9 Hz, CH_2OTr), 3.61 (s, 3 H, CO_2Me), 4.68 (m, 1 H, CHOSi), 5.44 (br t, 1 H, J = 8 Hz, H-6), 5.68 (m, 1 H, H-9), 5.90 (m, 2 H, H-7,8), 7.20–7.68 (m, 25 H, 5 Ph).

Methyl 5(*S*),12(*R*)-Bis[(*tert*-butyldiphenylsilyl)oxy]-3-thia-6(*Z*),8(*E*),10(*E*),14(*Z*)-eicosatetraenoate (51a) and the 10*Z* Isomer (51b). To a stirred solution of the ylide generated by treatment of the bromide **49** (100 mg, 0.119 mmol) with a solution of LiHMDS (0.34 M; 0.46 mL, 1.3 equiv, 0.155 mmol) in THF (3 mL) at −78 °C for 20–30 min was added a solution of the aldehyde **50** (73 mg, 1.5 equiv, 0.179 mmol) in dry THF (1.5 mL). After being stirred at −78 °C for 30 min, the reaction mixture was allowed to warm slowly to 0 °C. After 2 h the reaction was quenched with a saturated aqueous solution of ammonium chloride (0.5 mL), diluted with dichloromethane (50 mL) and treated in the usual way. Flash chromatography of the residue (5% ethyl acetate in hexanes) gave 59 mg (56%) of a 1:1 mixture of Wittig products **51a** and **51b**.

Methyl 5(*S*),12(*R*)-Dihydroxy-3-thia-6(*Z*),8(*E*),10(*E*),14-(*Z*)-eicosatetraenoate (3-Thia-LTB$_4$ Methyl Ester, 52). To a stirred solution of the 1:1 mixture of 10,11-*cis*- and 10,11-*trans*-**51**, (30 mg, 0.034 mmol) in dry THF (1 mL) at −10 °C were added 8 μL (4 equiv, 0.135 mmol) of acetic acid and 0.5 mL (15 equiv, 0.567 mmol) of a solution of tetra-*n*-butylammonium fluoride in THF (1 M). The cooling bath was removed, and the resulting mixture was stirred for 8 h. Then 0.17 mL (5 equiv) of tetra-*n*-butylammonium fluoride was added, and the reaction was stirred overnight. It was diluted with dichloromethane (50 mL) and treated in usual manner. The residue was dissolved in dichloromethane (2.1 mL) and treated with excess etherial diazomethane for 15 min. The solvent was removed, and then 2 mL of dry methanol was added followed by a few milligrams of po-

tassium carbonate. After the heterogenous mixture was stirred for 15 min, 1 mL of 25% ammonium acetate was added and diluted with 50 mL of dichloromethane.

After normal workup, purification and separation of the residue by standard-phase HPLC (Waters μ-Porasil column; 30% ethyl acetate in hexanes) gave 2 mg of 10,11-cis methyl ester and 2 mg of 10,11-trans methyl ester **52** (32%). For **52**: UV (MeOH) (max) 271 nm. ^{1}H NMR (250 MHz, acetone-d_6) δ 0.90 (t, 3 H, J = 7 Hz, CH_3), 1.32 (m, 6 H), 2.32 (m, 2 H, H-13), 2.79 (m, 2 H, CH_2S), 3.41 (s, 2 H, SCH_2CO), 3.71 (s, 3 H, CO_2Me), 4.18 (m, 1 H, H-12), 4.80 (m, 1 H, H-5), 5.47 (m, 3 H, H-6, H-14, H-15), 5.83 (dd, 1 H, J = 14.6 Hz, J = 6.3 Hz, H-11), 6.10 (t, 1 H, $J_{6,7} = J_{7,8}$ = 11 Hz, H-7), 6.33 (m, 2 H, H-9,10), 6.61 (t, 1 H, $J_{8,9}$ = 12.5 Hz, H-8).

5(*S*),12(*R*)-Dihydroxy-3-thia-6(*Z*),8(*E*),10(*E*),14(*Z*)-eicosatetraenoic Acid (3-Thia-LTB$_4$, 4). To a solution of methyl ester **52** (1 mg, 2.7 μmol) in 50 μL of methanol at 0 °C was added a solution of aqueous sodium hydroxide (1 N; 60 μL, excess). The resulting mixture was allowed to warm to room temperature and stirred for 4 h. The pH was adjusted to 3 by the addition of 1 N aqueous HCl and the mixture extracted with ether (20 mL). The combined organic phases were washed with saturated aqueous sodium chloride (5 mL) and dried over anhydrous sodium sulfate, and the solvent was removed at reduced pressure to give the desired acid **4** (700 μg, 72%): UV (MeOH) (max) 271 nm.

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Supplementary Material Available: Experimental procedures and characterization data for compounds **8**, **11**, **14–17**, **22**, **25–27**, **32α/β**, **35α/β**, **37**, **40–42**, **45**, **49**, **55**, and **57–60** and some unnumbered intermediates (15 pages). Ordering information is given on any current masthead page.

Organotin Phosphate Condensates as a Catalyst of Selective Ring-Opening of Oxiranes by Alcohols

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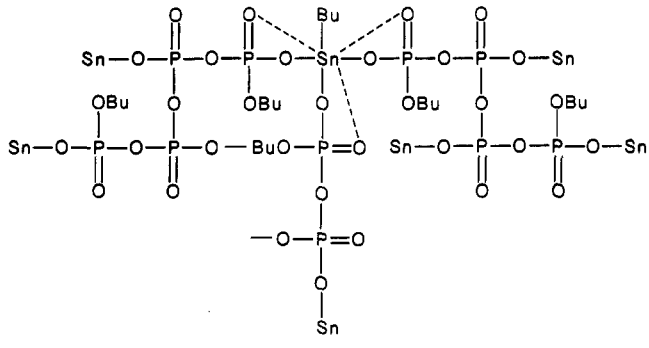
The highly regioselective alcoholysis of oxiranes is catalyzed by organotin phosphate condensates, providing a variety of β-alkoxy alcohols in good yields. The selectivity of the nucleophilic attack is dependent on the structures of epoxides. The *gem*-dialkyloxiranes are cleaved on the tertiary carbon, while β,γ-epoxy alcohols and their derivatives gave C-3 attack products. The anti stereoisomers are solely produced in the latter case. Thus the catalysis is both acidic and coordinative. Of practical importance is the recycled use of the catalyst without any appreciable decrease in the activity and the selectivities.

Organotin phosphate condensates (Sn-P Cat.) are thermolysis products of organotin oxides or chlorides in the presence of di- or trialkyl phosphates at 200–250 °C and catalyze polymerization of various epoxides, providing high polymers with high crystallinity.[1] The fact suggests that the polymerization proceeds in a stereospecific manner. We have revealed the actual active species to be associated with the unique seven-coordinate monoalkyltin tris(diphosphate) as shown below.[2] The stereospecificity of the polymerization is ascribable to the three-dimensional rigid network involving alternating tin diphosphate units on which the highly orientated coordination of epoxide monomers occurs.



Ring-opening of epoxides by alcohols is useful for preparing protected *vic*-diols if the reaction proceeds with high selectivities. To this end various efforts have been devoted with limited satisfaction.[3] Most promising and versatile among them is the alumina-catalyzed reaction disclosed by Psner et al.[4] Despite its wide applicability, this method occasionally suffers from the poor regioselectivity with unsymmetrical epoxides: the ratio of the two regioisomers varies between 6/1 and 1.5/1. In addition, no application to functionalized epoxides has been reported. More recently, Caron and Sharpless have reported the titanium tetraisopropoxide mediated reaction of β,γ-epoxy alcohols with up to 100/1 preference of nucleophilic attack at C-3 over C-2.[5] Furthermore, the exclusive C-3 attack also has been achieved for β,γ-epoxy esters with $AlPO_4$–Al_2O_3.[6]

We report here that Sn-P Cat. is quite effective for the selective cleavage of oxiranes by alcohols.[7]

Results

In a typical run, a mixture of an epoxide (5 mmol) and an alcohol (5–15 mmol) except methanol (vide infra) in an

(1) Nakata, T. *Coordination Polymerization*; Price, C. C., Vandenberg, E. J., Eds.; Plenum Press: New York, 1983; p 55.
(2) Otera, J.; Yano, T.; Kunimoto, E.; Nakata, T. *Organometallics* **1984**, *3*, 426.
(3) Smith, J. *Synthesis* **1984**, 629.
(4) Posner, G. H.; Rogers, D. Z.; Kinzig, C. M.; Gurria, G. M. *Tetrahedron Lett.* **1975**, 3597. Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8028 and 8214. Posner, G. H.; Hulce, M.; Rose, R. K. *Synth. Commun.* **1981**, *11*, 737.
(5) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.
(6) Riego, J.; Costa, A.; Saa, J. M. *Chem. Lett.* **1986**, 1565.
(7) For a preliminary report: Otera, J.; Yoshinaga, Y.; Hirakawa, K. *Tetrahedron Lett.* **1985**, *26*, 3219.

0022-3263/88/1953-0275$01.50/0