was chromatographed on 3 g of silica gel. Elution with ether afforded 8 mg (74%) of synthetic *dl*-quassin as a white crystalline solid. An analytical sample was prepared by recrystallization from ether: mp 189-190 °C; IR ($CHCl_3$) 3010, 2995, 2965, 2925, 2864, 1730, 1695, 1634, 1458, 1450, 1438, 1377, 1348, 1293, 1259, 1215, 1090, 1032, 980 cm^{-1}; ^1H NMR (220 MHz) ($CDCl_3$) δ 5.28 (d, 1 H, J = 2.5 Hz), 4.26 (br s, 1 H), 3.65 (s, 3 H), 3.56 (s, 3 H), 3.00 (dd, 1 H, J = 6.5, 18 Hz), 2.98 (s, 1 H), 1.86 (s, 3 H), 1.55 (s, 3 H), 1.18 (s, 3 H), 1.10 (d, 3 H, J = 7 Hz). Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.87; H, 7.21.

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A General and Stereocontrolled Total Synthesis of Leukotriene B_4 and Analogues

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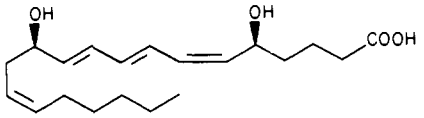
Abstract: A new, general, and stereocontrolled total synthesis of leukotriene B_4 (**1**) is disclosed. The application of the methodology to the synthesis of several novel analogues of leukotriene B_4 is also described.

Leukotriene B_4 (LTB_4, **1**) is an important metabolite of the 5-lipoxygenase arachidonic acid peroxidation pathway recently isolated by incubation with polymorphonuclear leukocytes.[1]



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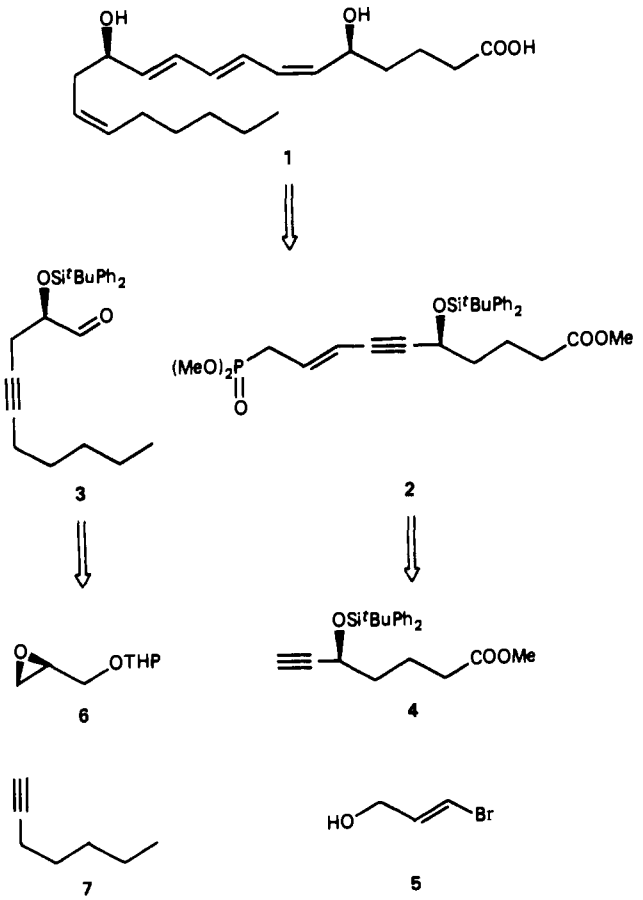
Implicated as a mediator in inflammation, this biomolecule exhibits potent chemotactic properties, facilitates adhesion of neutrophils to the endothelium, causes degranulation and release of lysosomal enzymes, increases the intracellular levels of calcium ions, and induces vascular permeability.[2] Due to its physiological importance and its low natural abundance, several syntheses of this compound have already appeared.[3-5] Despite their elegancy, however, these syntheses have limited value in the construction of certain novel analogues of LTB_4, and some of them suffer from low stereoselectivity and lengthy sequences. In this communication we wish to report a new general and efficient entry into the LTB_4 family that culminated in the total synthesis of the naturally occurring LTB_4 and of several novel structural analogues of it previously unavailable.

Scheme I outlines our retrosynthetic analysis of LTB_4, the advantages of which include (a) symmetrical disconnections leading first to two C_{10} fragments (C_1-C_{10}, **2** and C_{11}-C_{20}, **3**) and then to two C_3 fragments (**5** and **6**) and two C_7 fragments (**4** and **7**), (b) simultaneous generation of the two Z double bonds by controlled hydrogenation, (c) high degree of control of the geometry of the two E double bonds, (d) incorporation of chiral centers, and (e) flexibility to construct novel acetylenic and other LTB_4 analogues. This analysis led to a highly convergent and stereoselective strategy for the synthesis of LTB_4, the execution of which was carried out as described below.

Reaction of methyl 4-(chloroformyl)butyrate with bis(trimethylsilyl)acetylene in the presence of $AlCl_3$[6] (0 °C, CH_2Cl_2) led to the acetylenic ketone **8**[7] (60%) which was enantioselectively reduced to **9** (Scheme II) with ≥98% ee of (-)-9-pinanyl-BBN[8] (2 equiv of THF, 25 °C) in 85% chemical yield and ≥97:3 enantiomeric ratio.[9] Deprotection of the acetylene to afford **10**

Scheme I



(KF·$2H_2O$, DMF, 80%) was then followed by protection of the hydroxyl group leading to **11** (t-$BuPh_2SiCl$, imidazole, DMF,

† Fellow of the A. P. Sloan Foundation, 1979-1983, recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980-1984, and a J. S. Guggenheim Fellow, 1984.

(1) Borgeat, P.; Samuelsson, B. *J. Biol. Chem.* **1979**, *254*, 2643.
(2) Reviews: (a) Smith, M. J. H. *Gen. Pharmacol.* **1981**, *12*, 211. (b) Ford Hutchinson, A. W. *J. R. Soc. Med.* **1981**, *74*, 831. (c) Borgeat, P.; Sirois, P. *J. Med. Chem.* **1981**, *24*, 121. (d) Samuelsson, B. *Science (Washington, D.C.)* **1983**, *220*, 568. (e) Piper, P. J. *Trends Pharmacol. Sci.* **1983**, *4*, 75.

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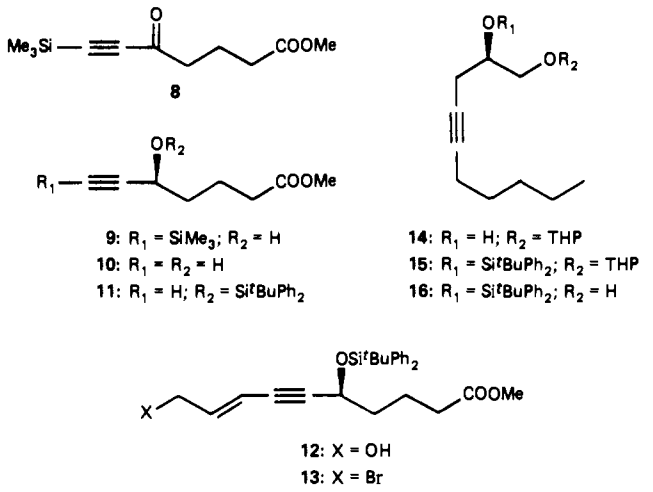
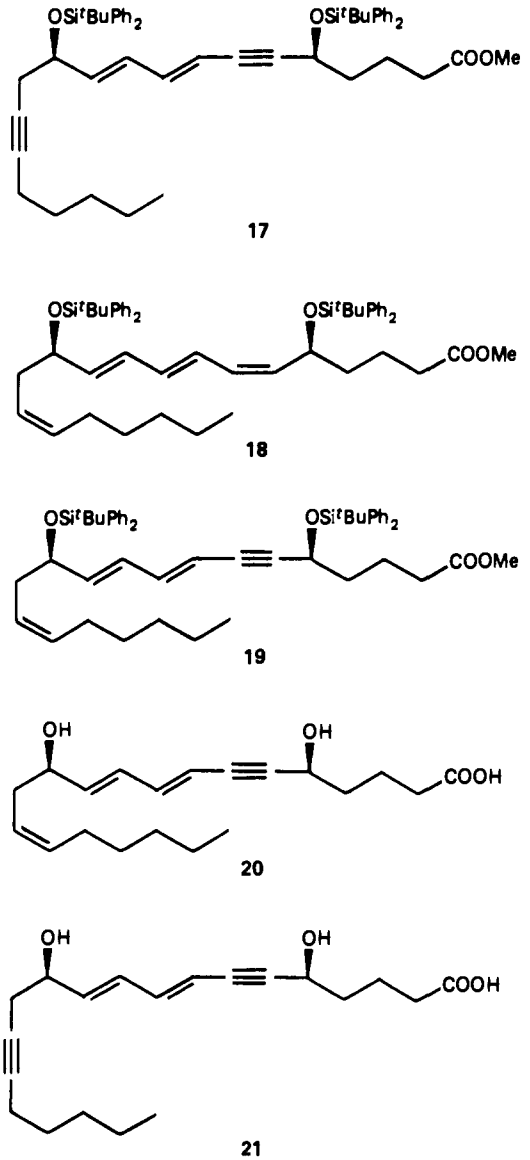
Scheme II



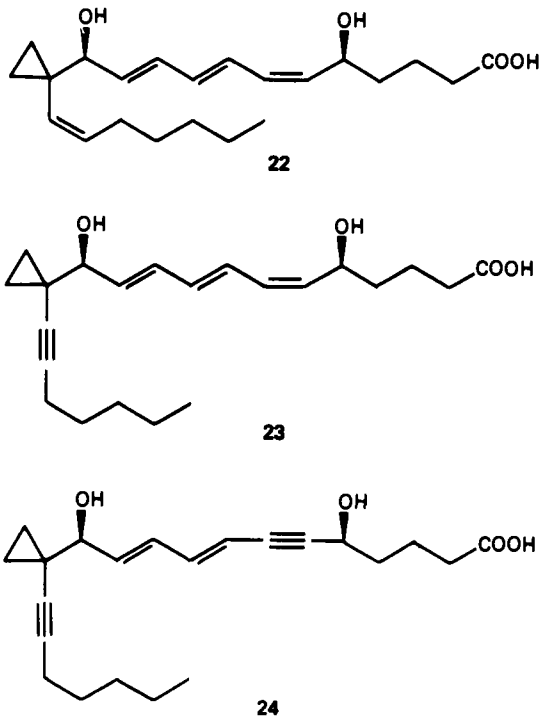
Scheme III



96%). Coupling[11] of **11** with the vinyl bromide **5**[12] (1.2 equiv) in Et_2NH at 25 °C in the presence of $Pd(PPh_3)_4$ (0.05 equiv) and

(3) (a) Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. *J. Am. Chem. Soc.* **1980**, *102*, 7984. (b) Corey, E. J.; Marfat, A.; Munroe, J.; Kim, K. S.; Hopkins, P. B.; Brion, F. *Tetrahedron Lett.* **1981**, *22*, 1077.

Scheme IV



CuI (0.06 equiv) proceeded smoothly to afford the alcohol **12** (93%), which was then converted to bromide **13** (1.3 equiv of PPh_3, 1.35 equiv of CBr_4 and CH_2Cl_2, −40–0 °C, 92%) from which the key intermediate C_1–C_{10} fragment **2** (R_f = 0.17, silica, 2% MeOH in ether) was produced (excess $P(OMe)_3$, 100 °C, 90%).

The optically active (*R*)-glycidol THP ether (**6**) readily available from ascorbic acid[13] was reacted (−78–25 °C) with 2 equiv of the anion of 1-heptyne (1.0 equiv of *n*-BuLi, 1.0 equiv of TMEDA and THF, −78 °C) to afford alcohol **14** (81%) which was then silylated to **15** (*t*-$BuPh_2SiCl$, imidazole, DMF, 96%) and depyranylated to **16** (AcOH:THF:H_2O, 3:2:2, 45 °C, 81%). Mild oxidation of **16** (10 equiv of CrO_3·2 pyr., Celite, and CH_2Cl_2, 0 °C) furnished the C_{11}–C_{20} fragment key intermediate aldehyde **3**[14] (75%, R_f = 0.20, silica, 5% ether in petroleum ether).

Generation of the anion of **2** (1.1 equiv of LDA and THF, −78 °C, 60 s) followed by addition of aldehyde **3** (1.0 equiv) (−78 °C, 8 h; −20 °C, 1 h; 0 °C, 1 h)[15] afforded, after workup and isolation, product **17** (Scheme III, 70%) as a 90:10 *E*:*Z* mixture of the newly generated double bond. Pure **17** (obtained after chromatographic separation) was subjected to controlled hydrogenation (Lindlar catalyst, $CHCl_2$, 25 °C) to afford **18** (60%), **19** (15%), and re-

(4) (a) Guindon, Y.; Zamboni, R.; Lau, C.-K.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 739. (b) Zamboni, R.; Rokach, J. *Ibid.* **1982**, *23*, 2631.
(5) Mills, L. S.; North, P. C. *Tetrahedron Lett.* **1983**, *24*, 409.
(6) Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45.
(7) All new compounds were characterized by full spectroscopic and analytical or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.
(8) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. For preparation of enantiomerically pure (−)pinene see: Brown, H. C.; Jadhav, P. K.; Desai, M. C. *J. Org. Chem.* **1982**, *47*, 4583.
(9) This enantiomer ratio was determined by preparing the Mosher[10] ester (alcohol + CF_3–CPh(OMe)COOH + DCC + DMAP catalyst, THF, 25 °C, 24 h) and by analyzing by ^1H NMR spectroscopy.
(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(11) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. Ratovelomana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917.
(12) Hatch, L. F.; Harwell, K. E. *J. Am. Chem. Soc.* **1953**, *75*, 6002.
(13) Takano, S.; Numata, H.; Ogasawara, K., *Heterocycles* **1982**, *19*, 237. Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure, D. E. *J. Org. Chem.* **1978**, *43*, 4876.
(14) ^1H NMR–Eu(hfc)$_3$ analysis of this compound revealed only one enantiomer present.
(15) Allowing the rapidly formed intermediate alkoxyphosphonate to decompose faster resulted in considerable loss of the stereoselectivity.

covered starting material (8%). The yield of the monoacetylene **19** could be increased to ca. 50% at ca. 50% conversion. Finally removal of all three protecting groups from **18** with excess *n*-Bu_4NF (10 equiv, THF, 25 °C) led to leukotriene B_4 (**1**)[16] directly, isolated by preparative thin-layer chromatography (silica, R_f = 0.18; 2% MeOH in ether) (70% yield). Similar treatment of **17** and **19** led to the diacetylenic and monoacetylenic leukotriene B_4 analogues **20** (72%) and **21** (73%), respectively. The facile hydrolysis of the methyl ester in these systems under these conditions is quite interesting and presumably is a consequence of internal assistance by the 5-hydroxy group.

To demonstrate further the generality of this new entry into the leukotriene B_4 family, the above technology was successfully applied to the synthesis of analogues **22–24** (Scheme IV) starting with phosphonate **2** and aldehyde III.[18]

The above convergent and flexible strategy to the leukotriene B series not only provides the naturally occurring substance LTB_4 (**1**) but also makes available a number of novel and potentially useful analogues previously unattainable. Biological investigations with these compounds are currently in progress.[21,22]

Experimental Section

General. ^1H NMR spectra were recorded on a Bruker WM-250 MHz spectrometer in $CDCl_3$ and are reported in δ from Me_4Si. IR spectra were recorded on Perkin-Elmer Model 281B or 781 infrared spectrophotometer, and the IR figures reported are ν_{max} in cm^{-1}.

All reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F-254) using UV light and 7% phosphomolybdic acid in ethanol–heat as developing agent. Preparative-layer chromatography was performed on 0.5-mm × 20-cm × 20-cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

All reactions were carried out under an argon atmosphere using dry freshly distilled solvents under anhydrous conditions unless otherwise noted. Ethereal solvents were dried and distilled under nitrogen from sodium benzophenone ketyl. Methylene chloride was distilled under nitrogen from calcium hydride. Amines were distilled under argon from calcium hydride. Reaction temperatures were externally measured. NMR multiplicities are reported by using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; J = coupling constant (Hz). Only the strongest and/or structurally most important peaks are reported for the IR. All yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials.

1-[(Tetrahydro-2*H*-pyran-2-yl)oxy]dec-4-yn-2(*R*)-ol (14). To a magnetically stirred solution of 1-heptyne (2.79 g, 29.0 mmol) and tetramethylethylenediamine (3.36 g, 29.0 mmol) in THF (8 mL) under argon was added a 1.6 M solution of *n*-butyllithium (18.1 mL, 29.0 mmol) at −78 °C. The reaction mixture was warmed to −20 °C and stirred at that temperature for 15 min. The reaction mixture was recooled to −78 °C and treated dropwise with a solution (*R*)-glycidol THP ether (**6**) (2.29 g, 14.5 mm in THF (3 mL). The reaction mixture was slowly warmed to 25 °C, stirred at that temperature for 16 h, and then quenched with a mixture of ice (100 g) and ether (150 mL). The organic phase was washed with 1 M $CuSO_4$ aqueous solution (2 × 50 mL), water (25 mL), and brine (50 mL), and dried ($MgSO_4$). Removal of the solvents followed by flash column chromatography (silica gel, 30% ether in petroleum ether, R_f = 0.12) afforded **14** (3.0 g, 81%) as a colorless oil: ^1H NMR (250 MHz, CDC Me_4Si) 20 δ 4.61 (bs, 1 H, OC*H*O), 4.00–3.49 (m, 5 H, CH_2O, C*H*OH, CH_2CH_2O), 3.29 (d, 0.5 H, CH_2OH, J = 4.0 Hz), 2.99 (d, 0.5 H, CH_2OH, J = 5.0 Hz), 2.50–2.37 (m, 2 H, H-3), 2.16 (bt, 2 H, H-6, J = 7.0 Hz), 1.93–1.70 (m, 2 H, CH_2), 1.68–1.44 (m, 6 H, CH_2), 1.42–1.25 (m, 4 H, CH_2), 0.91 (t, 3 H, H-10, J = 6.2 Hz); IR (thin film) ν_{max} (cm^{-1}) 3440 (m), 2940 (s), 2880 (s), 1456 (m), 1440 (m), 1382 (m), 1354 (m), 1325 (m), 1262 (m), 1202 (m), 1184 (m), 1130 (s), 1124 (s), 1075 (s), 1062 (s), 1032 (s), 972 (m), 908 (m), 870 (m), 810 (m).

Methyl 5(*S*)-(*tert*-Butyldiphenylsiloxy)-10-hydroxydec-8-en-6-ynoate (12). To a magnetically stirred solution of *trans*-3-bromoallyl alcohol (**5**) (2.29 g, 16.7 mmol) in degassed diethylamine (4.0 mL) was added $Pd(PPh_3)_4$ (96.0 mg, 0.083 mmol) under argon at ambient temperature and the mixture stirred for 10 min. A solution of terminal acetylene **11** (6.61 g, 16.7 mmol) was added in degassed diethylamine (7.0 mL) followed by CuI (200 mg, 1.0 mmol), and stirring was continued for 15 h). The reaction mixture was poured into ether (300 mL), washed with H_2O (5 × 30 mL) and brine (50 mL), and dried ($MgSO_4$). Removal of the solvent followed by flash column chromatography (silica gel, 40% ether in petroleum ether, R_f = 0.18) afforded **12** (7.05 g, 93%) as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$, Me_4Si) δ 7.75–7.66 (m, 4 H, aromatic), 7.45–7.32 (m, 6 H, aromatic), 5.99 (dt, 1 H, H-9, $J_{9,8}$ = 15.9 Hz, $J_{9,10}$ = 5.2 Hz), 5.59 (dd, 1 H, H-8, $J_{8,9}$ = 15.9 Hz, $J_{8,5}$ = 1.7 Hz), 4.46 (t, 1 H, H-5, J = 5.8 Hz), 4.13 (bs, 2 H, H-10), 3.65 (s, 3 H, OCH_3), 2.28 (t, 2 H, H-2, $J_{2,3}$ = 6.9 Hz), 1.86–1.66 (m, 4 H, H-3, H-4), 1.62 (bs, 1 H, OH), 1.08 (s, 9 H, *t*-Bu); IR (thin film). ν_{max} (cm^{-1}) 3420 (m), 3070 (m), 3040 (m), 2945 (s), 2925 (s), 2850 (s), 2200 (w), 1732 (s), 1584 (w), 1425 (m), 1358 (m), 1338 (m), 1244 (m), 1192 (m), 1166 (m), 1100 (s), 1082 (s), 815 (m), 724 (m), 695 (s).

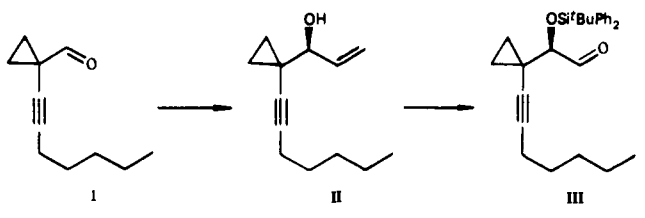
(8*E*,10*E*)-Methyl 5(*S*),12(*R*)-Bis(*tert*-butyldiphenylsiloxy)eicosa-8,10-diene-14,16-diynoate (17). To a magnetically stirred solution of phosphonate **2** (1.08 g, 2.0 mmol) in THF (15 mL) under argon was dropwise added a solution of lithium diisopropylamide (LDA, 2.16 mL, 1.0 M in THF, 2.16 mmol) at −78 °C. The reaction mixture was stirred for 1 min, and aldehyde **3** (0.74 g, 1.8 mmol) in THF (4.0 mL) was added in one portion. The reaction mixture was stirred at −78 °C for 8 h, −20 °C for 1 h, and ambient temperature for 1 h. Ether (250 mL) was added followed by aqueous saturated NH_4Cl solution (10 mL), and the organic layer was washed with water (30 mL) and brine (30 mL) and dried ($MgSO_4$). Removal of the solvent afforded **17** as a 90:10 *E*:*Z* mixture at the newly formed double bond. Separation of the two isomers was performed by repeated flash column chromatography (silica gel; 1% ethyl acetate in petroleum ether; trans, R_f = 0.029, cis, R_f = 0.036). Pure **17**: ^1H NMR (250 MHz, $CDCl_3$, Me_4Si)H δ 7.79–7.61 (m, 8 H, aromatic), 7.45–7.29 (m, 12 H, aromatic), 6.19 (dd, 1 H, H-9, $J_{9,8}$ = 15.4 Hz, $J_{9,10}$ = 10.5 Hz), 5.94 (dd, 1 H, H−10, $J_{10,11}$ = 15.1 Hz, $J_{10,9}$ = 10.5 Hz), 5.77 (dd, 1 H, H-11, $J_{11,12}$ = 6.1 Hz, $J_{11,10}$ = 15.1 Hz), 5.30 (dd, 1 H, H-8, $J_{8,5}$ = 1.1 Hz, $J_{8,9}$ = 15.5 Hz), 4.52–4.45 (m, 1 H, H-5), 4.32–4.20 (m, 1 H, H-12), 3.65 (s, 3 H, $COOCH_3$), 2.37–2.25 (m, 4 H, H-2, H-13), 2.13–2.03 (m, 2 H, H-16), 1.85–1.64 (m, 4 H, H-3, H-4), 1.47–1.20 (m, 6 H, H-17, H-18, H-19), 1.10 (s, 18 H, *t*-Bu), 0.88 (t, 3 H, H-20, J = 6.2 Hz); IR (thin film) ν_{max} (cm^{-1}) 3065 (m), 3046 (m), 2926 (s), 2858 (s), 1740 (s), 1590 (w), 1461 (m), 1426 (s), 1360 (m), 1100 (s), 1070 (s), 984 (m), 821 (m), 738 (m), 700 (s).

(8*E*,10*E*,6*Z*,14*Z*)-Methyl 5(*S*),12(*R*)-Bis(*tert*-butyldiphenylsiloxy)-6,8,10,14-eicosatetraenoate (18). To a solution of **17** (130 mg, 0.15 mmol) in CH_2Cl_2 (25 mL) at room temperature was added 60 mg of Lindlar catalyst, and the mixture was magnetically stirred over H_2 (balloon, TLC monitoring). After 4 h, an additional 30 mg of catalyst was added, and hydrogenation was continued for an additional 18 h. Filtering and removal of the solvent followed by flash column chromatography (silica gel, 2% ethyl acetate in petroleum ether) provided **18** (78 mg, 60%, R_f = 0.11), **19** (19 mg, 15%, R_f = 0.08), and starting material (**17**, 8%). Pure **18**: ^1H NMR (250 MHz, $CDCl_3$, Me_4Si) δ 7.74–7.58 (m, 8 H, aromatic), 7.44–7.25 (m, 12 H, aromatic), 5.93 (dd, 1 H, H-10,

(16) The ^1H NMR data (C_6D_6, 250 MHz) of the methyl ester diacetate of this material was in accord with the data reported by Corey.[17] Our synthetic LTB_4 was also identical with both synthetic and biosynthetic material supplied by Smith Kline and French laboratories. We are indebted to Drs. C. Perchonock, K. Erhard, P. Bender, and K. Razgaitis for making these comparisons.

(17) Corey, E. J.; Hopkins, P. B.; Barton, A. E.; Borgeat, P. *Tetrahedron* **1982**, *38*, 2653.

(18) Since III was mixed with its enantiomer the resulting compounds **22–24** were formed as mixtures with their 12-epimers. The synthesis of racemic III proceeded from I[19] via II as follows: (a) vinylmagnesium bromide, THF, −78 °C; (b) *t*-$BuPh_2SiCl$–imidazole, DMF, 25 °C; (c) controlled ozonolysis, Me_2S (80% overall yield). Compound II has now been resolved by Sharpless kinetic resolution[20] and, therefore, the option to optically active **22–24** is available.



I II III

(19) Nicolaou, K. C.; Petasis, N. A.; Li, W. S.; Ladduwahetty, T.; Randall, J. L.; Webber, S. E.; Hernandez, P. E. *J. Org. Chem.* **1983**, *48*, 5400.

(20) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(21) This work was first described in part at the 1st Cyprus Conference on New Methods in Drug Research, Limassol, Cyprus, April 1983.

(22) Financial support for this work by the A. P. Sloan Foundation, the Camille and Henry Dreyfus Foundation, Merck Sharp & Dohme, Smith Kline & French, and the National Institutes of Health is gratefully acknowledged. We also thank the National Science Foundation for a minority fellowship to B. D. Harris.

$J_{10,11}$ = 15.1 Hz, Hz, $J_{10,9}$ = 10.5 Hz), 5.87-5.56 (m, 4 H), 5.46-5.17 (m, 3 H), 4.54-4.42 (m, 1 H, H-5), 4.23-4.12 (m, 1 H, H-12), 3.61 (s, 3 H, $COOCH_3$), 2.30-2.08 (m, 4 H), 1.87-1.77 (m, 2 H), 1.62-1.37 (m, 4 H), 1.32-1.12 (m, 6 H), 1.10 (s, 9 H, *t*-Bu), 1.05 (s, 9 H, *t*-Bu), 0.85 (t, 3 H, H-20, J = 6.2 Hz); IR (thin film), ν_{max} (cm^{-1}) 3070 (m), 3045 (m), 3015 (m), 2930 (s), 2855 (s), 1739 (s), 1589 (w), 1460 (m), 1425 (s), 1360 (m), 1103 (s), 1070 (s), 992 (m), 815 (m), 732 (m), 695 (m).

Leukotriene B_4 (1). To a magnetically stirred solution of **18** (52 mg, 0.06 mmol) in THF (2.0 mL) at room temperature was added *n*-Bu_4NF (1 M; THF, 0.60 mmol) under an argon atmosphere. The reaction mixture was stirred for 5 h (TLC monitoring) and then diluted with ether (50 mL) and brine (2 mL). The aqueous layer was reextracted with ether (5 × 25 mL) and dried ($MgSO_4$). Concentration of the combined ether solution and purification by either flash column chromatography (silica gel, 5→50% CH_3OH in ether) or preparative-layer chromatography (silica gel, 2% methanol in ether, R_f = 0.22) provided LTB_4 (**1**) (16 mg, 73%). RP-HPLC (Altex ultrasphere, ODS, 5-μm 4.6-mm × 25-cm column; CH_3OH:H_2O:AcOH:concentrated NH_4OH, 67:33:0.08:0.07) showed ≥95% purity for synthetic LTB_4: ^1H NMR (250 MHz, $CDCl_3$, Me_4Si[4]) δ 6.47 (dd, J = 14.0 and 12.0 Hz, 1 H, H-8), 1.28 (m, 2 H, H-9, H-10), 6.09 (t, J = 11.0 Hz, 1 H, H-7), 5.78 (dd, J = 15.0 and 6.5 Hz, 1 H, H-11), 5.65-5.25 (m, 4 H, H-6, H-14, H-15, O*H*), 4.62 (m, 1 H, H-5), 4.23 (m, 1 H,, H-12), 2.35 (m, 4 H, CH_2), 2.04 (m, 2 H, CH_2), 1.80-1.15 (m, 12 H, CH_2, O*H*), 0.90 (t, J = 6.5 Hz, 3 H, H-20); IR (thin film) ν_{max} (cm^{-1}) 3360 (s, OH), 3020 (w), 2970 (m), 2935 (s), 2860 (m), 1715 (s, CO). The methyl ester diacetate of LTB_4 exhibited identical ^1H NMR data with those reported previously,[17] and its retention time on the above mentioned reverse-phase HPLC conditions was identical with that of natural LTB_4.[16]

Supplementary Material Available: Listing of selected spectroscopic data (^1H NMR, IR) of compounds **2**, **3**, **19**, and **22-24** (3 pages). Ordering information is given on any current masthead page.

Chloroacetylenes as Michael Acceptors. 3. Mechanism and Synthetic Utility of Enolate Reactions with Halogenated Olefins and Chloroacetylenes

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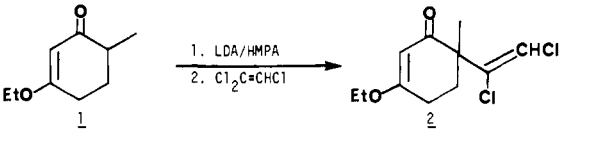
Abstract: Condensations of tertiary conjugated enolates with a variety of polyhalogenated olefins were explored. Trichloroethylene led to (*E*)-1,2-dichlorovinyl adducts which could be further converted to acetylenes in good yield. 1,2-Dichloro-1-fluoroethylene (1/1 cis/trans) led to a single regio- and stereoisomeric adduct ((*E*)-2-chloro-1-fluorovinyl) in 30% yield, whereas tetrachloroethylene led to a chloroethynyl adduct in 25% yield. Attempts to broaden the scope of these condensations to include other types of enolates were unsuccessful. Condensations of enolates with hexachlorobutadiene were also examined. The kinetic lithium enolates of ethyl isobutyrate and of 2,6-dimethyl-2-cyclohexen-1-one led to trichloroenyne adducts in 63% and 56% yields, respectively, whereas the sodium enolate of diethyl methylmalonate gave a pentachlorodienyl adduct in 61% yield. The trichloroenyne adducts were shown to arise from a perchlorobutenyne intermediate. Several unusual transformations of the hexachlorobutadiene adducts are also described. A mechanistic investigation demonstrated that the trichloroethylene condensation proceeds by a carbanion chain mechanism involving dichloroacetylene as an obligatory intermediate. This prompted the general examination of enolate condensations with 1-chloroalkynes. Preformed dichloroacetylene and phenylchloroacetylene reacted with a variety of tertiary enolates in 64-90% yields to give α-chloroethynyl and α-phenylethynyl ketones and esters. The chloroethynyl group was smoothly converted to the ethynyl group (74-77% yields) or vinyl group (94-98% yields). 1-Chloro-1-hexyne did not react with enolates, whereas (phenylthio)chloroacetylene reacted to yield α-phenylthioethynyl adducts in 43-75% yields, pointing to a probable addition-elimination mechanism for these additions to 1-chloroalkynes.

The development of new methods for carbon-carbon bond formation is one of the fundamental challenges confronting the synthetic chemist. In this context, condensation chemistry of ketone and ester enolates has been a cornerstone of synthetic methodology.[1] Polyhalogenated ethylenes have enjoyed a much more modest role in carbon-carbon bond formation.[2-4] To date, there are only scattered references to the reaction between simple polyhalogenated ethylenes and carbon nucleophiles. Indeed, this type of reaction is limited to the addition of aryl- and alkyllithiums to polyhalogenated ethylenes to give addition or substitution products.[4] This paper describes our efforts to harness the powerful chemistry of the enolate to the repertoire of halogenated ethylene chemistry.

Results and Discussion

Condensation of Enolates with Trichloroethylene.[5] When the kinetic lithium enolate derived from 3-ethoxy-6-methyl-2-cyclohexenone (**1**) was reacted with 1.0 equiv of trichloroethylene, the major product was the dichlorovinyl ketone **2** (eq 1). The yield



1 2 (1)

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(1) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Reading, MA 1972; Chapters 9 and 10.
(2) For such condensations involving metalated derivatives with electrophiles see the following examples: (a) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: New York, 1974. (b) Tarrant, P.; Johncock, P.; Savory, J. *J. Org. Chem.* **1963**, *28*, 839. (c) Drakesmith, F. G.; Richardson, R. D.; Stewart, O. J.; Tarrant, P. *Ibid.* **1968**, *33*, 286. (d) Köbrich, G.; Flory, K. *Chem. Ber.* **1966**, *99*, 1773. (e) Negishi, E. "Organometallics in Organic Synthesis"; Wiley: New York, 1980; Vol. 1. (f) Sauvetre, R.; Masure, D.; Chuit, C.; Normant, J. F. *C. R. Acad. Sci.* **1979**, *288*, 335. (g) Sauvetre, R.; Masure, D.; Chuit, C.; Normant, J. F. *Synthesis* **1978**, 128. (h) Masure, D.; Chuit, C.; Sauvetre, R.; Normant, J. F. *Ibid.* **1978**, 458.

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