percent residual masses were found at the indicated times: 3 h, 96.9%; 27 h, 91.1%; 51 h, 89.6%; 75 h, 88.2%; 99 h, 86.5%; 123 h, 85.1%; 147 h, 83.5%. The IR spectrum ($CH_2Cl_2$) of the residue had some absorption in the region of 3200–3600 $cm^{-1}$. The $^{19}F$ NMR spectrum of a freshly prepared 10% solution of this material in $CD_2Cl_2$ at −80 °C consisted of a singlet for fluoride ion at $\delta$ −112.8 and a double for bifluoride centered at $\delta$ −148.5 ($J_{HF}$ = 123 Hz). The bifluoride ion was present in about 13 mol % originally, but by the time the sample had remained at room temperature for 3 h, the amount of $FHF^-$ had risen to about 61 mol %. Examination of the solution after 12 h at room temperature revealed that all of the fluoride was present as $FHF^-$. No free fluoride was in evidence.

**Attempted Dehydration of Tetraethylammonium Fluoride Dihydrate at 77 °C.** Tetraethylammonium fluoride dihydrate (Eastman) was examined by $^{19}F$ NMR spectroscopy and found to contain no bifluoride ion. A 2.000-g sample of this material was held at 77 °C (2 torr) and weighed as a function of time as was done with TBAF·$3H_2O$. The following percent residual masses were found as a function of time: 0.25 h, 85.6%; 0.5 h, 81.7%; 3 h, 69.9%; 12 h, 52.1%; 24 h, 43.5%. The $^{19}F$ NMR spectrum of a $CD_2Cl_2$ solution of the final product at −70 °C showed only the doublet at $\delta$ 147.7 ($J_{HF}$ = 123.3 Hz) for $FHF^-$. Similar results were obtained when the dihydrate was heated at 56 °C.

**Acknowledgment** is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

**Registry No.** Tetra-*n*-butylammonium fluoride, 429-41-4; tetraethylammonium fluoride, 665-46-3.

## Total Synthesis of Leukotrienes. An Effective Procedure for the Synthesis of Conjugated Dienals by Four-Carbon Homologation

E. J. Corey* and John O. Albright

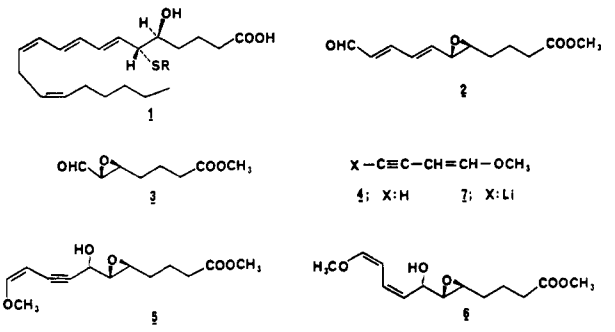
*Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138*

*Received December 13, 1982*

The total synthesis[1] of the spasmogenic leukotrienes (LTs, formally termed slow-reacting substances of anaphylaxis) LTC, LTD, and LTE is of significance not only as a proof of structure but also since it makes available these rare substances for biological study.[2] These leukotrienes, of general formula **1** (Chart I), were made from the epoxy dienal **2** that in turn was obtained by four-carbon chain extension involving the lithio reagent from 1-(tributylstannyl)-4-methoxy-(*E*,*E*)-1,3-butadiene.[3] Although the conversion of **3** to **2** was accomplished in 63% yield under optimum conditions, the process involved several highly critical variables including not only the purity of reactants but also precise reaction and workup details. Because of the importance of the dienal **2** we have searched for a simpler and less critical procedure for its synthesis from **3**. The method that is described herein has been used on many occasions in these laboratories and has proven to be experimentally straightforward and reproducible as well as efficient.

1-Methoxybut-1-en-3-yne (**4**) was isolated from the commercially available methanolic solution and converted

Chart I




to the corresponding lithio acetylide (**7**) in tetrahydrofuran (THF) solution. Reaction of **7** with epoxy aldehyde **3** produced the formyl adduct **5** in 92% crude yield, which without purification was hydrogenated over Lindlar catalyst to form the dienal **6** (97% crude yield). Mesylation of **6** followed by solvolysis with aqueous bicarbonate afforded the dienal **2** in 97% yield and >95% purity by NMR analysis. This sequence does not require chromatography and is easily scaled up.

### Experimental Section

**Purification of 1-Methoxybut-1-en-3-yne (4).**[4] A 100-mL (90 g) portion of commercial **4** (Aldrich) was partitioned between water (35 mL) and 35% (v/v) ether–pentane (3 × 50 mL). The combined organic layers were washed with water (2 × 30 mL) and dried over anhydrous calcium chloride (9 g) and calcium carbonate (1 g) at 4 °C overnight. The dark red solution was filtered, calcium carbonate (1 g) was added, and the solvents were distilled through a 10-cm Vigreux column at atmospheric pressure under argon (distillate 34–36 °C).[5] The remaining oil was distilled at 102 torr (aspirator pressure with an argon bleed), with the fraction boiling at 67–69 °C being collected. The resultant *colorless* liquid (16.5 g) was transferred via cannula to a dry bottle. The bottle was protected from light and stored in a desiccator at −20 °C. Samples were removed as required with a dry glass syringe previously flushed with argon:[6] NMR ($CDCl_3$) $\delta$ 6.32 (dd, 1 H, $J$ = 6.5, 0.8 Hz), 4.50 (dd, 1 H, $J$ = 6.5, 2.4), 3.78 (s, 3 H), 3.04 (dd, 1 H, $J$ = 2.4, 0.8); IR ($CCl_4$): 3310 (vs), 2100 (m), 1630 (vs) $cm^{-1}$.

**4-Lithio-1-methoxybut-1-en-3-yne (7).** A dry reaction vessel was flushed with nitrogen and tared. Purified **4** (0.23 mL) was introduced and the vessel reweighed (+248 mg, 3.0 mmol of **4**). Dry THF (6.7 mL) was added with stirring, and the resultant colorless solution was cooled to −40 °C.[7] To this solution was added slowly[8] 2.32 mmol (0.78 equiv) of *n*-butyllithium dropwise. After being stirred at −40 °C for 30 min, this solution was employed as 0.30 M in **7**.[9,10]

**Methyl 7-Hydroxy-11-methoxy-*trans*-5(*S*),6(*S*)-epoxyundeca-10(*Z*)-en-8-ynoate (5).** Methyl *trans*-5(*S*),6(*R*)-oxido-7-oxoheptanoate (**3**, 155 mg, 0.90 mmol)[1] was azeotropically dried by the repeated evaporation in vacuo of a solution in benzene, dissolved in 20 mL of dry THF and cooled to −78 °C. To this

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(2) See, for example: Weiss, J. W.; Drazen, J. M.; Coles, N.; McFadden, E. R., Jr.; Weller, P. F.; Corey, E. J.; Lewis, R. A.; Austen, K. F. *Science (Washington, D.C.)* **1982**, *216*, 196.
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(5) Enyne **4** is *extremely* sensitive to air. Even brief contact with the atmosphere results in rapid decomposition (discoloration) of the material. Therefore *all* manipulations were performed under an inert atmosphere.
(6) This material could be kept for up to 1 month before requiring redistillation as per above.
(7) Below −40 °C and/or at higher concentrations the acetylide **7** precipitated from solution.
(8) Rapid addition of the *n*-butyllithium resulted in excessive warming and decomposition of the organometallic reagent.
(9) This mixture contained 30% excess **4** to insure the complete consumption of the *n*-butyllithium. Excess **4** was readily removed from the process at a later stage by evaporation.
(10) This reagent must be prepared immediately prior to use and must be maintained below −20 °C to minimize decomposition. It decomposes rapidly upon warming above −10 °C; however, in solution it could be transferred rapidly by using a dry, chilled syringe.

0022-3263/83/1948-2114$01.50/0 

was quickly[10] added 4.20 mL (1.26 mmol, 1.4 equiv) of the acetylide solution 7. The reaction mixture was warmed to −40 °C for 30 min, recooled to −78 °C, and quenched with 1.3 mL of saturated aqueous $KHCO_3$. After slowly warming to room temperature, a pale yellow organic layer separated from the white aqueous paste. Anhydrous sodium sulfate (200 mg) was added, and the mixture was concentrated in vacuo to 40% of its initial volume and was *placed under nitrogen*.[11] This mixture was diluted with 2% (v/v) triethylamine–ether (10 mL),[12] vigorously stirred, and the organic layer removed. The residual paste was similarly washed with fresh 2% triethylamine–ether (6 × 6 mL), the combined organic layers were dried ($Na_2SO_4$, 20 min), evaporated, and azeotropically dried with benzene (2 × 2 mL), affording a pale yellow oil (210 mg, 92%), which by TLC and NMR analyses was enyne **5** contaminated with only traces of **3**:[13] NMR ($CDCl_3$, neutralized[14]) δ 6.28 (d, 1 H, $J$ = 6.2), 4.48 (m, 2 H), 3.76 (s, 3 H), 3.67 (s, 3 H), 3.03 (m, 2 H), 2.39 (t, 2 H, $J$ = 7), 1.68 (m, 5 H); IR ($CH_2Cl_2$) 1735 (vs), 1634 (s); MS, 254 $m/e$ ($M^+$).

**Methyl 7-Hydroxy-11-methoxy-*trans*-5(*S*),6(*S*)-epoxyundeca-8(*Z*),10(*Z*)-dienoate (6).** Crude **5** (160 mg, 0.63 mmol) was added to a 100-mL round-bottom flask and azeotropically dried with benzene (2 × 2 mL). To the flask were added a stirring bar and septum, and an inert atmosphere was established. Toluene (20 mL), pyridine (2 mL), and catalyst (Lindlar,[15] 32 mg) were added, and a hydrogen atmosphere was established. The reaction was monitored by TLC[16] at 15-min intervals and observed to be sluggish; more catalyst was introduced (19 mg), whereupon the reaction proceeded rapidly.[17] Upon completion the hydrogen atmosphere was removed and the reaction mixture was diluted with 20 mL of 2% triethylamine–ether. After filtration through cotton and evaporation in vacuo, the diene **6** was obtained in 97% yield (156 mg):[13] NMR ($CDCl_3$, neutralized[14]) δ 6.39–6.69 (m, 1 H), 5.97–6.06 (m, 1 H), 5.14–5.36 (m, 2 H), 4.33 (dd, 1 H, $J$ = 8.7, 5.0), 3.68 (s, 3 H), 3.67 (s, 3 H), 2.79–2.92 (m, 2 H), 1.65 (m, 5 H); IR ($CH_2Cl_2$) 1735 (vs), 1650 (s) $cm^{-1}$; MS, $m/e$ 238 ($m^+ - H_2O$).

**Methyl *trans*-5(*S*),6(*S*)-Epoxy-11-oxoundeca-7(*E*),9(*E*)-dienoate (2).** A solution of 156 mg (0.61 mmol) of **6** in dry methylene chloride (25 mL) was cooled to −40 °C and treated with triethylamine (0.26 mL, 1.83 mmol, 3 equiv) and mesyl chloride (94 μL, 1.22 mmol, 2 equiv). After 30 min, saturated aqueous $KHCO_3$ (1.0 mL) was introduced and the mixture was slowly warmed to room temperature. Anhydrous sodium sulfate (400 mg) was added and vigorously stirred. The organic layer was removed, and the aqueous paste remaining was washed with methylene chloride (4 × 6 mL). The combined organic layers were dried ($Na_2SO_4$, 15 min), filtered, and evaporated, leaving a yellow-orange paste. Extraction of this paste with 2% triethylamine–ether, evaporation, and azeotropic drying (benzene, 2 × 3 mL) yielded a yellow oil (132 mg, 97%), which by NMR and TLC was >95% pure dienal **2**:[18,19] NMR ($CDCl_3$, neutralized[14]) δ 9.57 (d, 1 H, $J$ = 7.7), 5.81–7.35 (m, 4 H), 3.67 (s, 3 H), 2.87–3.26 (m, 2 H), 2.39 (t, 2 H, $J$ = 7), 1.68 (m, 5 H); IR ($CH_2Cl_2$) 1735 (s), 1682 (s), 1642 (s), 990 (m) $cm^{-1}$.[20]

**Registry No.** **2**, 73958-00-6; **3**, 73427-12-0; **4**, 2798-73-4; **5**, 85749-89-9; **6**, 85749-90-2; **6** mesylate, 85749-91-3; **7**, 76584-33-3.

(11) At this stage excess **4** (prone to oxidation to *non*volatile products) was present in the reaction mixture. Thus the crude mixture containing **5** was kept under a nitrogen atmosphere until the remaining **4** could be removed.

(12) The product was subject to acid decomposition and therefore all the solvents used in its handling were adjusted to 2% triethylamine.

(13) The product was unstable to normal storage but could be kept in a −20 °C matrix of 2% triethylamine–benzene.

(14) The $CDCl_3$ was passed through a short column of basic alumina immediately prior to use to remove any acid present.

(15) Five percent palladium on calcium carbonate, Lindlar poisoned, was obtained from Engelhard Ind. and heated to 80 °C at 0.01 mmHg for 3 h prior to use.

(16) An ~15 μL aliquot of the reaction mixture was added to 100 μL of benzene over 500 μL of saturated aqueous cupric sulfate. After agitation the organic layer was spotted (silica gel plate) vs. **5** and eluted (three elutions) with 35% EtOAc–benzene: $R_f$(**5**) 0.505 (UV), $R_f$(**6**) 0.500(UV).

(17) Different samples of **5** required varying amounts of catalyst, which indicated the presence of variable amounts of catalyst poison. The best hydrogenation procedure was to add initially a 20% (wt/wt of substrate) portion of the catalyst, to monitor the progress of the reaction by TLC, and to add more catalyst until a reasonable reaction rate (3–5 h for completion) was realized.

(18) The product is chromatographically and spectroscopically identical with that prepared as per ref 3.

(19) The product may be further purified by preparative TLC on triethylamine-treated silica gel plates.

(20) This work was assisted financially by a grant from the National Science Foundation.

## 1,3,4,9-Tetramethoxyphenalenyl System

R. C. Haddon,* A. M. Hirani, N. J. Kroloff, and J. H. Marshall

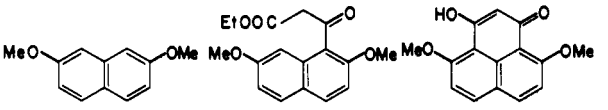
*Bell Laboratories, Murray Hill, New Jersey 07974*

*Received November 9, 1982*

There has been considerable interest in the preparation of 1,3- and 1,9-disubstituted phenalene derivatives,[1,2] but little has been done to further elaborate the system. In the present study we report the synthesis and characterization of the 1,3,4,9-tetramethoxyphenalenyl system (together with associated compounds), in which the disubstitution pattern has been symmetrically extended.

### Results and Discussion

As an entry to these derivatives we sought to prepare 4,9-dimethoxy-3-hydroxyphenalenone (**3**). This compound




was previously synthesized by Morrison and co-workers[3,4] via two different routes, both of which utilized 2,7-dimethoxynaphthalene (**1**) as starting material. These workers[3] obtained **3** from the polyphosphoric acid catalyzed condensation of **1** with malonic acid in a yield of 20%. They also found that **2** could be cyclized with polyphosphoric acid to give **3** in 75% yield.[4] The intermediate **2** was obtained by the reaction of **1** with ethylmalonyl chloride in nitrobenzene in the presence of aluminum chloride.[4] The yield of **2** was 64%, but the reaction was complicated by the formation of 1-acetyl-2,7-dimethoxynaphthalene as a byproduct.

We have found that **2** can be obtained from ethylmalonyl chloride and **1** (without the formation of byproducts) if 1,2-dichloroethane is used as the solvent and the temperature is maintained at or below room temperature. In addition we found concentrated sulfuric acid and especially anhydrous hydrogen fluoride to be more convenient than polyphosphoric acid for the cyclization of **2** to **3**.

The most curious result was obtained when we attempted to sublime **3**, for the sublimate consisted entirely

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