during the esterification step. Both **4e** and **4t** proved to be optically pure.

The synthesis presented here is very convenient, owing to the simplicity of the different steps, avoiding in particular use of protection and deprotection operations, which are often a real problem with fluoro amino acids.[20,21] The enzymatic conversion leads directly to the desired optically pure products in very high yield.

Experimental Section

General Methods. Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. ^1H NMR and ^{19}F NMR spectra were recorded at 90 MHz on a JEOL FX90Q spectrometer. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter with 10 cm path length cells.

Chemicals. Ethyl fluoroacetate was purchased from Fluka, boron tribromide was purchased from Merck, and ethyl bromoacetate and diethyl oxalate were purchased from Prolabo. Glutamate dehydrogenase (from beef liver) and NAD^+ (100%) were obtained from Boehringer; yeast alcohol dehydrogenase was from Sigma. Dowex resins were purchased from Fluka.

Diethyl Fluorooxaloacetate Sodium Salt (1). Compound 1 was obtained in 82% yield from ethyl fluoroacetate and diethyl oxalate according to Bergmann et al.,[8] mp 175–177 °C dec. The protonated form of 1 was recovered by acidification to pH 1 with sulfuric acid and extraction with diethyl ether: ^1H NMR ($CDCl_3$, TMS) δ 1.37 (6 H, m, 2 OCH_2CH_3), 4.37 (4 H, m, 2 OCH_2CH_3), 5.20 (0.75 H, d, J_{HF} = 46.8 Hz, CHF), 5.95 (0.25 H, d, J_{HF} = 47.5 Hz, CHF).

Diethyl 2-Oxo-3-carbethoxy-3-fluoroglutarate (2). Ethyl bromoacetate (25.5 mL, 0.23 mol) was added dropwise within 1 h to a solution of 1 (35 g, 0.153 mol) in dry dimethylformamide (125 mL) cooled at 0 °C. After the mixture was stirred at room temperature overnight, the sodium bromide was filtered, and the solvent was eliminated under vacuum, the product was taken up in ethyl acetate, washed with water, dried, and evaporated to dryness (47 g). Chromatography on silica gel with ethyl acetate–hexane (1:1) as solvent of 15 g of this crude product yielded **2** (7.5 g, 52%): ^1H NMR ($CDCl_3$, TMS) δ 1.30 (9 H, m, 3 OCH_2CH_3), 2.35–3.88 (2 H, m, CH_2), 4.25 (6 H, m, 3 OCH_2CH_3); ^{19}F NMR ($CDCl_3$, $CF_3C_6H_5$) δ −103.0 (X part of an ABX spectrum, $J_{AX} + J_{BX}$ = 49.6 Hz), −108.9 (X part of an ABX spectrum, $J_{AX} + J_{BX}$ = 47.3 Hz); mass spectrum (positive chemical ionization), m/z 310 ($(M + NH_4)^+$), 290 ($(M + NH_4 - HF)^+$ and **2'** (5.5 g, 48%); ^1H NMR ($CDCl_3$, TMS) δ 1.35 (9 H, m, 3 OCH_2CH_3), 4.35 (6 H, m, 3 OCH_2CH_3), 4.63 + 4.67 (2 H, CH_2); ^{19}F NMR ($CDCl_3$, $CF_3C_6H_5$) δ −88.0; mass spectrum (positive chemical ionization), m/z 310 ($(M + NH_4)^+$).

Disodium 2-Oxo-3-fluoroglutarate (3). Compound **2** (8 g; 25.8 mmol) was hydrolyzed at room temperature by a 2:1 solution of acetic acid–hydrochloric acid (60 mL) for 3 days and decarboxylated by heating at 50 °C for 5 h. After elimination of the solvent under reduced pressure, the crude product was stored in a dessicator on potassium hydroxide: ^1H NMR (D_2O with CF_3COOH, TMS) δ 2.7–3.3 (2 H, m, CH_2), 5.15 (1 H, dm, J_{HF} = 46.7 Hz, CHF); ^{19}F NMR (D_2O, CF_3COOH) δ −117.7 (eight lines). Anal. of the 2,4-dinitrophenylhydrazone of the dimethyl ester. Found: C, 41.97; H, 3.52; N, 14.86. Calcd for $C_{13}H_{13}FN_4O_8$: C, 41.93; H, 3.49; N, 15.05.

Neutralization with sodium bicarbonate and recrystallization from water–ethanol afforded **3** (3.55 g; 66%). Anal. Found: C, 26.59; H, 2.41. Calcd for $C_5H_3FO_5Na_2 \cdot 1H_2O$: C, 26.54; H, 2.21.

(2*R*,3*R*)- and (2*R*,3*S*)-3-Fluoroglutamic Acids (4t and 4e). A solution of **3** (1.04 g; 5 mmol) in 0.5 M ammonium phosphate buffer at pH 7 (100 mL) containing ethanol (2 mL), EDTA (5 mg), NAD^+ (400 mg), bovine serum albumin (100 mg), glutamate dehydrogenase (20 mg; 420 units) and yeast alcohol dehydrogenase (350 μL; 3000 units) was incubated at 30 °C. The same amounts of ethanol, NAD^+, GDH, and YADH were added after 24, 48, and 72 h. After precipitation of the proteins by addition of trichloroacetic acid (6 g) and centrifugation at 10 000 rpm for 10 min, the supernatant was applied to a Dowex 50W×2 column (100–200 mesh; 50 × 3.6 cm; H^+ form). After the mixture was washed with water, elution with 0.5 N acetic acid yielded a mixture of **4e** and **4t** (800 mg; 96%). The two diastereoisomers (500 mg) were separated on Dowex 1×4 (200–400 mesh; 92 × 3 cm; acetate form, 10 mL/fraction). After the mixture was washed successively with water and 0.1 and 0.2 N acetic acid, elution with 0.5 N acetic acid yielded **4e** [(0.72–1.03 L, 220 mg); recrystallized in water–acetone; mp 194–195 °C; $[\alpha]^{20}_D$ = +20° (*c* = 1, H_2O); $[\alpha]^{20}_D$ = +38° (*c* = 1, HCl, 1 N): ^1H NMR of the sodium salt (D_2O, TMS) δ 2.30–2.88 (2 H, m, CH_2), 4.06 (1 H, dd, J_{HH} = 2.6 Hz, J_{HF} = 20.5 Hz, CHN), 5.31 (1 H, dm, J_{HF} = 47.1 Hz, CHF); ^{19}F NMR of the sodium salt (D_2O, CF_3COOH) δ −156.0 (17 lines). Anal. Calcd for $C_5H_8FNO_4$: C, 36.36; H, 4.84; N, 8.48. Found: C, 36.24; H, 4.91; N, 8.32] and **4t** (1.13–1.49 L, 220 mg): recrystallized in water; mp 190–191 °C; $[\alpha]^{20}_D$ = +3° (*c* = 1, H_2O); $[\alpha]^{20}_D$ = +13.6° (*c* = 1, HCl, 1 N); ^1H NMR of the sodium salt (D_2O, TMS) δ 2.53–3.10 (2 H, m, CH_2), 3.91 (1 H, dd, J_{HH} = 3.9 Hz, J_{HF} = 26.3 Hz, CHN), 5.38 (1 H, dm, J_{HF} = 45.1 Hz, CHF); ^{19}F NMR of the sodium salt (D_2O, CF_3COOH) δ −154.0 (12 lines). Anal. Calcd for $C_5H_8FNO_4$: C, 36.36; H, 4.84; N, 8.48. Found: C, 36.23; H, 4.69; N, 8.38.

Optical Purity Determination. Compounds **4e** and **4t** were separately submitted to the following reactions:

(a) Acetylation. 3-Fluoroglutamic acid (7 mg) was treated with dry acetic anhydride (15 μL) in dry methanol (300 μL) at room temperature until complete dissolution (~2.1 h). After evaporation of the solvents, the crude product was applied to a Dowex 50W×2 column and eluted with water.

(b) Esterification. The *N*-acetyl-3-fluoroglutamic acid was treated for 15 min at 60 °C with dry 2-propanol–hydrogen chloride (1.5 mol/L, 300 μL). After elimination of the solvent under vacuum, the crude product was analyzed by gas chromatography on a Chrompack-fused silica capillary column (50 m × 0.25 mm) coated with XE-60-S-valine-(*S*)-phenylethylamide (175 °C, helium (1.5 bar)).

Registry No. 1, 7582-61-8; 1 (protonated), 55475-75-7; **2**, 1608-58-8; **2'**, 117860-26-1; **3**, 117860-25-0; **3** (dimethyl ester, 2,4-dinitrophenylhydrazone), 117860-27-2; **4e**, 97315-76-9; **4t**, 97315-77-0; FCH_2COOEt, 459-72-3; $(COOEt)_2$, 95-92-1; $BrCH_2COOEt$, 105-36-2; glutamate dehydrogenase, 9001-46-1.

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Synthesis of *all-cis*-1-Bromo-4,7,10,13-nonadecatetraene: A Precursor to C-1 Labeled Arachidonic Acid

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Received September 12, 1988

Arachidonic acid is a biosynthetic precursor to several biologically important compounds (e.g., prostaglandins, thromboxanes, prostacyclins, leukotrienes).[1] Progress in studying the enzymology of the arachidonic cascade is critically dependent on the availability of specifically labeled fatty acid precursors. The standard approach for the chemical synthesis of arachidonic acid is the preparation of the corresponding homoconjugated tetrayne followed by selective hydrogenation of the acetylenic bonds to cis olefins.[2] Because of the great instability[3] of these

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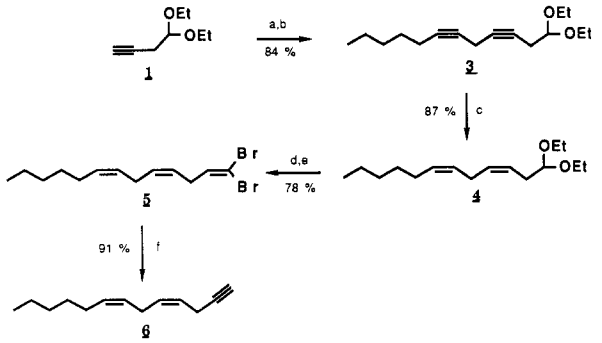
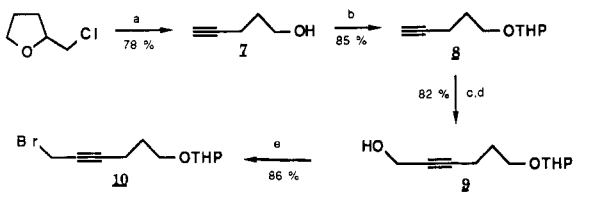
0022-3263/89/1954-0500$01.50/0

Scheme I[a]



[a] (a) EtMgBr, THF, 1-h reflux; (b) $CH_3(CH_2)_4C{\equiv}CCH_2Br$ (2), CuBr, THF, 12-h reflux; (c) P-2 Ni, H_2, 1 atm, EtOH; (d) 50% aqueous TFA, CH_2Cl_2, 0 °C; (e) PPh_3, CBr_4, CH_2Cl_2, 0 °C; (f) *n*-BuLi, THF, −78 °C.

Scheme II[a]



[a] (a) *n*-BuLi, THF, reflux; (b) DHP, Amberlyst-15, CH_2Cl_2, reflux; (c) EtMgBr, THF, reflux; (d) $(CH_2O)_n$, reflux; (e) $P(OPh)_3$, Br_2, CH_2Cl_2, 0 °C.

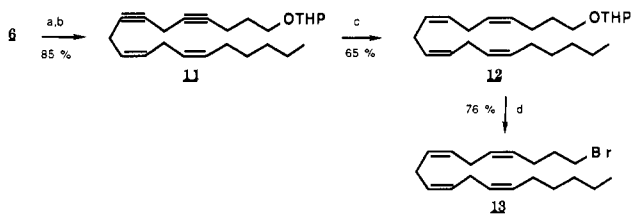
polyacetylenic intermediates, none of these syntheses are suitable for the production of notable amounts of arachidonic acid. We now describe a practical new synthetic route to the title compound, a convenient precursor to C-1 labeled arachidonic acid, via Grignard coupling of two readily prepared and stable C_{13} and C_7 fragments.

Synthesis of the C_{13} Fragment. Acetylene **6** was synthesized in 52% overall yield as summarized in Scheme I.

Coupling of the Grignard reagent prepared from acetal[4] **1** with bromide **2**, made by bromination of the corresponding alcohol with PBr_3,[5] yielded the homoconjugated diacetylene **3**, which was then stereospecifically hydrogenated to *all-cis*-diene **4** by using P-2 nickel catalysis.[6] Acetylene **6** was obtained from **4** by sequential acidic acetal hydrolysis, homologation with CBr_4/PPh_3,[7] and conversion[8] of the resultant 1,1-dibromide **5** to the terminal acetylene.

Synthesis of the C_7 Fragment. The bromide **10** was synthesized as outlined in Scheme II. Commercially available tetrahydrofurfuryl chloride on treatment with lithium amide in liquid ammonia or *n*-BuLi gave rise to acetylenic alcohol **7**,[9] which was protected as its tetrahydropyranyl ether **8**. The Grignard reagent of **8** was condensed with paraformaldehyde to give alcohol **9**, which was transformed to the corresponding bromide **10** by using 1 equiv of triphenyl phosphite dibromide.[10]

Scheme III[a]



[a] (a) EtMgBr, THF, reflux; (b) **10**, CuBr, THF, 12-h reflux; (c) P-2 Ni, H_2, 1 atm, EtOH; (d) PPh_3, CBr_4, CH_2Cl_2, 0 °C to room temperature.

Coupling and Conversion to 13. Coupling of the Grignard from acetylene **6** and bromide **10** in the presence of a stoichiometric amount of cuprous bromide led to intermediate **11**,[11] which was reduced over P-2 nickel to *all-cis*-tetraene **12** with a purity >95% (GC determination). The conditions of the hydrogenation must be carefully controlled to minimize the formation of byproducts. Direct bromination of the THP ether with triphenylphosphine/carbon tetrabromide[12] gave the bromine precursor of arachidonic acid **13** as outlined in Scheme III.

Conclusion

We report herein the first practical multigram synthesis of *all-cis*-1-bromo-4,7,10,13-nonadecatetraene, a convenient precursor to C-1 labeled arachidonic acid. Additionally, it is possible to introduce regiospecifically labeled hydrogen at the four olefins by catalytic hydrogenation with $^3H_2$ or $^2H_2$ gas[13] using the intermediates described above.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 257 or Beckman Acculab 4 instrument. A Brucker WP-200 SY spectrometer was used for the 200-MHz ^1H NMR spectra and the 60-MHz ^{13}C NMR spectra. NMR spectra were measured in $CDCl_3$, and chemical shifts are given in parts per million relative to $CDCl_3$ (7.27 ppm, ^1H; 77.00 ppm, ^{13}C). Elemental analyses were performed by the service de microanalyse du CNRS, Strasbourg, France. Mass spectra were determined with a VG ZAB 3F (70 eV) instrument. GC analyses were performed on a Vega 2000 Carlo Erba chromatograph using a SE-54 capillary column. Analytical thin-layer chromatography was performed on precoated silica gel 60 plates (0.25 mm; F-254, E. Merck), and silica gel (0.063–0.020 mm, E. Merck) was used for column chromatography. Tetrahydrofuran (THF) and diethyl ether were dried by distillation from sodium benzophenone ketyl under dry nitrogen. CH_2Cl_2 was distilled over P_2O_5.

1,1-Diethoxy-3,6-dodecadiyne (3). To a Grignard solution, prepared from ethyl bromide (4.25 g, 39.0 mmol) and magnesium powder (0.85 g, 39.0 mmol) in dry THF (40 mL), was added at room temperature 1,1-diethoxy-3-butyne[4] (5.0 g, 35.0 mmol) in dry THF (5 mL). After heating at reflux for 1 h, the reaction mixture was cooled to room temperature. A catalytic amount of copper bromide (50 mg) was added, followed by dropwise addition of 1-bromo-2-octyne (6.60 g, 35.0 mmol) in dry THF (5 mL). The resulting reaction mixture was heated at reflux for 12 h, then cooled to room temperature, and quenched with a saturated ammonium chloride solution (60 mL) basified with NH_4OH (12 N, 2 mL). The reaction mixture was extracted with ether (3 ×

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(3) We have observed that, in contrast to homoconjugated diynes, higher homologues display markedly greater instability and cannot be routinely purified by chromatography or distillation.
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(10) Black, D. K.; Landor, S. R.; Patel, A. N.; Whiter, P. R. *Tetrahedron Lett.* **1963**, 483.
(11) The related one carbon homologous diacetylenic acid, i.e., (*Z,Z*)-11,14-eicosadiene-5,8-diynoic acid, is a potent inhibitor of 5- and 9-lipoxygenase. Chan, K. K.; Holland, G. W.; Rosen, P. U.S. Patent 4345084, 1982; *Chem. Abstr.* **1983**, *98*, 34250v.
(12) This new procedure for the direct bromination of a THP ether with PPh_3/CBr_4 is submitted for publication in *Tetrahedron Lett.*
(13) (a) Lellouche, J. P.; Aubert, F.; Beaucourt, J. P. *Tetrahedron Lett.* **1988**, *29*, 3069. (b) Lellouche, J. P.; Deschamps, J.; Boullais, C.; Beaucourt, J. P. *Tetrahedron Lett.* **1988**, *29*, 3073.

100 mL), and the combined organic extracts were washed with brine (2 × 100 mL), dried (Na_2SO_4), and concentrated. Purification of the residue on silica gel (hexane/5% ether) gave 7.29 g (84%) of acetal **3** as a colorless liquid: ^{1}H NMR δ 0.85 (t, J = 7.5 Hz, 3 H, CH_3), 1.05–1.53 (m, 18 H, alkyls + 2CH_3), 2.08 (tt, J = 7.0, 2.5 Hz, 2 H, $CH_2CH_2C{\equiv}C$), 2.46 (td, J = 6.5, 2.5 Hz, 2 H, $C{\equiv}CCH_2CH(OEt)_2$), 3.10 (quint, J = 2.5 Hz, 2 H, $C{\equiv}CCH_2C{\equiv}C$), 3.43–3.85 (m, 4 H, OCH_2), 4.59 (t, J = 6.5 Hz, 1 H, $CH(OEt)_2$); ^{13}C NMR δ 100.9, 76.1, 75.3, 73.9, 61.7, 30.9, 28.3, 24.9, 22.0, 18.5, 15.0, 13.8, 9.6; IR ($CHCl_3$) ν 2900, 2220, 1445, 1370, 1340, 1310, 1115, 1050 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.74; H, 10.49. Found: C, 76.87; H, 10.58.

(*Z*,*Z*)-1,1-Diethoxy-3,6-dodecadiene (4). P-2 nickel was prepared[6] via sodium borohydride reduction of $Ni(OAc)_2{\cdot}4H_2O$ (1.0 g, 4.0 mmol) in absolute ethanol (110 mL). The reactor was purged with hydrogen, and ethylenediamine (1 mL, 15 mmol) was added followed by diyne **3** (10.0 g, 39.9 mmol) in absolute ethanol (10 mL). Hydrogen uptake was quantitative in 4 h. The reaction mixture was filtered through Celite 545, diluted with water (100 mL), and extracted with ether (3 × 100 mL). The combined ether extracts were washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated. Purification of the residue on silica gel (hexane/5% ether) gave 8.84 g (87%) of diene **4** as a colorless liquid: ^{1}H NMR δ 0.90 (t, J = 7.0 Hz, 3 H, CH_3), 1.10–1.46 (m, 18 H, alkyls + 2CH_3), 2.05 (q, J = 6.0, 2 H, $C{=}CCH_2CH_2$), 2.43 (t, J = 6.0 Hz, 2 H, $CH_2CH(OEt)_2$), 2.80 (t, J = 6.0 Hz, 2 H, $C{=}CCH_2C{=}C$), 3.44–3.77 (m, 4 H, OCH_2), 4.51 (t, J = 6.0 Hz, 1 H, $CH(OEt)_2$), 5.27–5.57 (m, 4 H, vinyl); ^{13}C NMR δ 130.4, 130.3, 127.4, 124.0, 102.5, 61.1, 32.0, 31.5, 29.3, 27.2, 25.8, 22.6, 15.2, 14.0; IR ($CHCl_3$) ν 2950, 2920, 2850, 1640 cm^{-1}. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.52; H, 11.91. Found: C, 75.75; H, 12.01.

(*Z*,*Z*)-1,1-Dibromo-1,4,7-tridecatriene (5). To a solution of acetal **4** (4.2 g, 16.5 mmol) in CH_2Cl_2 (60 mL) at 0 °C under argon was added a 50% aqueous trifluoroacetic acid solution (15 mL, 97 mmol). After stirring for 3 h at 0 °C, the reaction mixture was quenched by the dropwise addition of sodium hydroxide (32 mL of a 3 M aqueous solution, 96 mmol) followed by a saturated solution of sodium carbonate (10 mL). Extraction with CH_2Cl_2 (2 × 50 mL), drying (Na_2SO_4), and concentration gave the crude aldehyde (2.89 g, 97%) as a slightly yellow oil, which was immediately used in the next reaction without further purification: ^{1}H NMR δ 0.89 (t, J = 7.0 Hz, 3 H, CH_3), 1.11–1.46 (m, 6 H, alkyls), 1.93–2.14 (m, 2 H, $C{=}CCH_2$), 2.79 (t, J = 6.5 Hz, 2 H, $C{=}CCH_2C{=}C$), 3.24 (dt, J = 6.5, 2.0 Hz, 2 H, CH_2CHO), 5.23–5.79 (m, 4 H, vinyl), 9.68 (t, J = 2.0 Hz, 1 H, CHO); IR (film) ν 2950, 2920, 2850, 1710, 1640, 1445, 1375, 1115, 1055 cm^{-1}.

To a mixture of dodecadienal (2.89 g, 16.0 mmol) and triphenylphosphine (10.0 g, 38.0 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C was added a solution of CBr_4 (6.0 g, 18.0 mmol) in dry CH_2Cl_2 (20 mL). After 1 h at 0 °C, the reaction mixture was quenched by the addition of a saturated sodium bicarbonate solution (20 mL). The reaction mixture was extracted with ether (3 × 100 mL), and the combined organic extracts were washed with brine (2 × 100 mL), dried (Na_2SO_4), and concentrated. Purification of the residue on silica gel (hexane) gave 4.30 g (80%) of 1,1-dibromide **5** as a colorless oil: ^{1}H NMR δ 0.90 (t, J = 7.5 Hz, 3 H, CH_3), 1.48–1.18 (m, 6 H, alkyls), 1.94–2.18 (m, 2 H, $C{=}CCH_2CH_2$), 2.72–2.85 (m, 4 H, $CH_2C{=}CBr_2$ + $C{=}CCH_2C{=}C$), 5.23–5.58 (m, 4 H, vinyl), 6.47 (t, J = 7.5 Hz, 1 H, $CH{=}CBr_2$); ^{13}C NMR δ 136.6, 130.8, 130.7, 126.9, 123.8, 89.3, 31.5, 31.4, 29.3, 27.3, 25.8, 22.6, 14.1; IR (film) ν 2900, 2840, 1640, 1615, 1450, 1385, 1370, 1070, 960, 820 cm^{-1}. Anal. Calcd for $C_{13}H_{20}Br_2$: C, 46.45; H, 6.01. Found: C, 46.54; H, 6.20.

(*Z*,*Z*)-4,7-Tridecadien-1-yne (6). *n*-Butyllithium (16 mL of a 1.6 M solution in hexane, 25.6 mmol) was added dropwise at −78 °C to a solution of 1,1-dibromide **5** (4.30 g, 12.8 mmol) in dry THF (45 mL). The resulting solution was stirred at −78 °C for 1 h, warmed to 0 °C over 30 min, and quenched by addition of water (10 mL). After extraction with ether (3 × 50 mL), the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (silica gel, hexane) gave 2.06 g (91%) of a slightly yellow oil: ^{1}H NMR δ 0.90 (t, J = 7.0 Hz, 3 H, CH_3), 1.20–1.47 (m, 6 H, alkyls), 1.94–2.14 (m, 3 H, $HC{\equiv}C$ + $C{=}CCH_2$), 2.81 (t, J = 6.0 Hz, 2 H, $C{=}CCH_2C{=}C$), 2.98 (dd, J = 6.0, 2.5 Hz, 2 H, $C{\equiv}CCH_2C{=}C$), 5.26–5.55 (m, 4 H, vinyl); ^{13}C NMR δ 130.8, 130.3, 126.7, 123.6, 82.5, 67.9, 31.4, 29.2, 27.0, 25.4, 22.6, 22.5, 16.7, 14.0; IR (film) ν 3270, 2810, 2100, 1635 cm^{-1}; MS (CI), m/e 177 (MH^+).

1-(Tetrahydropyranyloxy)-4-pentyne (8). To a mixture of 4-pentyn-1-ol (16.5 g, 196 mmol) and Amberlyst 15 (1.0 g) in dry CH_2Cl_2 (250 mL) at reflux was added dropwise dihydropyran (18.8 mL, 206 mmol). After 10 min, the reaction mixture was cooled to room temperature, the catalyst filtered, and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, 9:1 hexane/ether), giving 28 g (85%) of THP ether **8**: ^{1}H NMR δ 1.45–1.87 (m, 8 H, alkyls), 1.95 (t, J = 2.6 Hz, 1 H, $C{\equiv}CH$), 2.33 (td, J = 7.2, 2.6 Hz, 2 H, $CH_2C{\equiv}C$), 3.42–3.88 (m, 4 H, OCH_2 + $CHOCH_2$), 4.61 (t, J = 3.1 Hz, 1 H, OCHO); ^{13}C NMR δ 98.5, 83.7, 67.8, 65.5, 62.1, 30.5, 28.5, 25.3, 19.3, 15.5; IR ($CHCl_3$) ν 3290, 2925, 2850, 2110, 1445, 1435, 1360, 1315, 1065, 990 cm^{-1}.

6-(Tetrahydropyranyloxy)-2-hexyn-1-ol (9). To a Grignard solution, prepared from ethyl bromide (7.85 g, 72.0 mmol) and magnesium (1.43 g, 58.8 mmol) in dry THF (40 mL), at room temperature was added 1-(tetrahydropyranyloxy)-4-pentyne (**8**; 6.60 g, 39.3 mmol) in dry THF (5 mL). After heating at reflux for 2 h, the reaction mixture was cooled to 0 °C, then dried paraformaldehyde (1.74 g, 58.0 mmol) was added, and the resulting reaction mixture was heated at reflux. After 2 h, the reaction was quenched with a saturated sodium bicarbonate solution and filtered through Celite 545. The reaction mixture was extracted with ether (3 × 50 mL), and the combined ether extracts were washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated. Purification of the residue on silica gel (8:2 hexane/ether) gave 6.38 g (82%) of alcohol **9**: ^{1}H NMR δ 1.42–1.83 (m, 9 H, alkyls + OH), 2.35 (tt, J = 6.8, 2.2 Hz, 2 H, $CH_2C{\equiv}C$), 3.42–3.92 (m, 4 H, OCH_2), 4.24 (t, J = 2.2 Hz, 2 H, $C{\equiv}CCH_2OH$), 4.60 (t, J = 3.1 Hz, 1 H, OCHO); ^{13}C NMR δ 98.5, 84.8, 78.8, 65.7, 61.9, 50.6, 30.3, 28.5, 25.2, 19.2, 15.4; IR ($CHCl_3$) ν 3590, 3420, 2930, 2860, 1720, 1460, 1450, 1435, 1375, 1130, 1115, 1030, 905 cm^{-1}.

1-Bromo-6-(tetrahydropyranyloxy)-2-hexyne (10). To a solution of Br_2 (4.40 g, 27.0 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was added dropwise a solution of triphenyl phosphite (8.62 g, 27.0 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was warmed to room temperature, and after 30 min, a solution of alcohol **9** (5.0 g, 25.0 mmol) and pyridine (2.3 mL, 27.0 mmol) in dry CH_2Cl_2 (5 mL) was added rapidly. The reaction was immediately quenched with a saturated sodium bicarbonate solution (10 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined CH_2Cl_2 extracts were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and evaporated. Purification of the residue on silica gel (0.5:9.5 ether/hexane) gave 5.20 g (86%) of bromide **10** as a colorless liquid: ^{1}H NMR δ 1.45–1.68 (m, 6 H, alkyls), 1.80 (quint, J = 7.1 Hz, 2 H, $C{\equiv}CCH_2CH_2$), 2.38 (tt, J = 7.1, 2.3 Hz, 2 H, $C{\equiv}CCH_2$), 3.41–3.88 (m, 4 H, OCH_2), 3.93 (t, J = 2.3 Hz, 2 H, CH_2Br), 4.60 (t, J = 3.1 Hz, 1 H, OCHO); ^{13}C NMR δ 98.5, 87.2, 75.4, 65.5, 61.9, 30.4, 28.4, 25.3, 19.3, 15.7, 15.4; IR ($CHCl_3$) ν 2935, 2860, 2215, 1435, 1350, 1135, 1115, 1070, 1030, 990, 905 cm^{-1}.

(*Z*,*Z*)-1-(Tetrahydropyranyloxy)-10,13-nonadecadiene-4,7-diyne (11). To an EtMgBr solution (5 mL of a 2 M solution in THF, 10.0 mmol) at 0 °C was added dropwise a solution of **6** (1.90 g, 10.0 mmol) in dry THF (3 mL). The reaction mixture was warmed to room temperature over 10 min and then heated at reflux for 10 min. After cooling at 0 °C, copper bromide (1.44 g, 10.0 mmol) was added, followed by dropwise addition of bromide **10** (2.61 g, 10.0 mmol) in dry THF (3 mL). The resulting reaction mixture was heated at reflux for 12 h, then cooled to room temperature, quenched by addition of water (10 mL), and filtered through Celite 545. The reaction mixture was extracted with ether (2 × 60 mL), and the combined organic extracts were washed with brine (2 × 50 mL), dried (Na_2SO_4), and concentrated. Purification of the crude product on silica gel (hexane/5% ether) gave 3.03 g (85%) of **11** as a colorless oil: ^{1}H NMR δ 0.89 (t, J = 6.3 Hz, 3 H, CH_3), 1.22–1.43 (m, 6 H, alkyls), 1.45–1.64 (m, 6 H, alkyls), 1.87–1.92 (m, 2 H, CH_2CH_2OTHP), 2.05 (q, J = 6.8 Hz, 2 H, $CH_2C{=}C$), 2.29 (tt, J = 7.1, 2.4 Hz, 2 H, $C{\equiv}CCH_2CH_2$), 2.79 (t, J = 6.0 Hz, 2 H, $C{=}CCH_2C{=}C$), 2.92–3.01 (m, 2 H, $C{\equiv}CCH_2C{=}C$), 3.13 (q, J = 2.4 Hz, 2 H, $C{\equiv}CCH_2C{\equiv}C$), 3.94–3.44 (m, 4 H, OCH_2), 4.60 (t, J = 3.4 Hz, 1 H, OCHO), 5.26–5.51 (m, 4 H, vinyl); ^{13}C NMR δ 130.8, 129.8, 126.9, 124.5, 98.7, 79.8, 78.4, 79.5, 74.4, 65.9, 62.1, 31.5, 30.6, 29.3, 28.8, 27.2, 25.5, 22.6, 19.5,

17.1, 15.6, 140.0, 9.7; IR ($CHCl_3$) ν 2900, 2830, 2210, 1690, 1430, 1305, 1130, 1055, 1020, 980, 895 cm^{-1}; MS (CI), m/e 357 (MH^+); MS (EI), m/e (relative intensity) 355 (11), 297 (21), 283 (100), 271 (91), 253 (15), 245 (25), 213 (44), 201 (58), 157 (15), 85 (100).

(Z,Z,Z,Z)-1-(Tetrahydropyranyloxy)-4,7,10,13-nonadecatetraene (12). By use of a procedure identical with that described for the preparation of **4**, compound **11** (1.0 g, 2.8 mmol) in absolute EtOH (5 mL) was hydrogenated over P-2 Ni, prepared via sodium borohydride reduction of $Ni(OAc)_2 \cdot 4H_2O$ (0.7 g, 2.8 mmol) in absolute EtOH (15 mL). Hydrogen uptake was quantitative in 5 h. Workup followed by flash chromatography (hexane/2% ether) gave 680 mg (65%) of tetraene **12** as a colorless oil (purity >95% by GC): ^1H NMR δ 0.89 (t, J = 6.9 Hz, 3 H, CH_3), 1.19–1.44 (m, 6 H, alkyls), 1.95–2.24 (m, 4 H, C=CCH_2), 2.70–2.92 (m, 6 H, C=CCH_2C=C), 3.33–3.89 (m, 4 H, OCH_2), 4.58 (t, J = 3.4 Hz, 1 H, OCHO), 5.27–5.48 (m, 8 H, vinyl); ^{13}C NMR δ 130.2, 129.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.4, 98.6, 66.7, 62.0, 31.4, 30.6, 29.5, 29.2, 27.1, 25.5, 25.4, 23.8, 22.5, 19.4, 14.0; IR ($CHCl_3$) ν 2830, 2720, 2650, 1650, 1445, 1370, 1345, 1320, 1255, 1115, 1070, 1020, 990, 970, 900, 865 cm^{-1}; MS (CI); m/e 361 (MH^+); MS (EI), m/e (relative intensity) 360 (5), 276 (8), 150 (44), 95 (100).

(Z,Z,Z,Z)-1-Bromo-4,7,10,13-nonadecatetraene (13). To a solution of triphenylphosphine (0.94 g, 3.6 mmol) in dry CH_2Cl_2 (0.6 mL) at 0 °C was added dropwise a solution of CBr_4 (0.59 g, 1.8 mmol) in dry CH_2Cl_2. After 10 min at 0 °C, the reaction mixture was warmed to room temperature over 45 min and then cooled to 0 °C, and **12** (0.25 g, 0.7 mmol) in CH_2Cl_2 (1 mL) was added. The resulting mixture was warmed to room temperature and stirred for 10 min. The triphenyl phosphite was precipitated by addition of hexane (20 mL). After filtration, the organic extracts were washed with sodium bicarbonate (20 mL) and brine (20 mL), then dried (Na_2SO_4), and concentrated. Purification of the residue on silica gel (pentane) gave 0.17 g (76%) of bromide **13** as a colorless liquid (purity >95% by GC): ^1H NMR δ 0.90 (t, J = 6.7 Hz, 3 H, CH_3), 1.10–1.44 (m, 6 H, alkyls), 1.80–2.17 (m, 4 H, CH_2CH_2Br + C=CCH_2), 2.35 (apparent q, J = 7.0 Hz, 2 H, C=CCH_2), 2.89–2.71 (m, 6 H, C=CCH_2C=C), 3.42 (t, J = 6.6 Hz, 2 H, CH_2Br), 5.20–5.48 (m, 8 H, vinyl); ^{13}C NMR δ 130.5, 129.5, 128.7, 128.4, 128.0, 127.9, 127.8, 127.5, 34.1, 33.4, 32.5, 31.5, 29.3, 27.2, 25.7, 25.5, 22.3; IR ($CHCl_3$) ν 2995, 2950, 2920, 2840, 1650, 910, 680 cm^{-1}; MS (CI), m/e 340 (MH^+), MS (EI), m/e (relative intensity) 339 (9), 242 (30), 227 (25), 149 (26), 119 (24), 105 (28), 91 (44), 79 (100), 57 (50).

Acknowledgment. We are grateful to Jean Desmurs, Rhône-Poulenc, Centre de Recherches des Carrières, Saint-Fons for providing the MS spectra.

Relative Reactivities and Stereochemistry for Free-Radical Eliminations of 2-(Aryloxy)-1-phenylpropyl Radicals[1]

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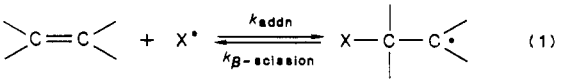
Received June 8, 1988

The formation of C–C bonds by addition of free radicals to double bonds is gaining wide recognition in the synthesis of organic compounds. The utility of this approach is clearly elucidated by the importance of radical-induced polymerization in chemical industry and, more recently, by the successful application of stereospecific radical addition reactions in the synthesis of natural products.[2,3] The steric and electronic influence of substituents on the rate of addition of free radicals to multiple bonds has been extensively investigated and reviewed.[4]

The unimolecular fragmentation of radical species that occur by scission of the C–heteroatom or C–C bond β to the radical center represents the reverse of radical additions to olefins.



Numerous examples of C–C bond cleavage of alkoxyl radicals exist in the literature, and in general, the reactions are well understood in terms of steric and polar considerations.[5] Analogous β-scission reactions of carbon-centered radicals have extensive precedent in the high-temperature cracking of paraffins.[6] A representative example is the thermolysis of 1,3-diphenylpropane, which yields an Arrhenius expression of $10^{14.8}$ exp(−28 300/RT) s^{-1} for the β-scission of benzyl radical from 1,3-diphenyl-1-propyl radical.[7]

Studies of the elimination reactions of β-phenylthiyl, β-phenylsulfinyl, and β-phenylsulfonyl radicals have also been conducted.[8-10] These investigations found no stereoselectivity for the loss of either phenylthiyl or phenylsulfonyl radicals. In contrast, reactions of diastereomeric 2-bromo-3-(phenylsulfinyl)butanes were found to eliminate phenylsulfinyl radicals in a stereoselective manner. This result indicated the rapid loss of phenylsulfinyl radical from the initial nonequilibrium conformations of the radical and was thought to be consistent with the order of leaving-group stability: phenylsulfinyl > phenylsulfonyl ~ phenylthiyl.

Other investigations have addressed the question of substituent effects on the reversible addition of substituted phenylthiyl radicals to olefins.[11,12] These studies concluded that the reaction is goverened by both the thermodynamic stability of $XC_6H_4S^\bullet$ and the electronic nature of the olefin, which influences the polar resonance structures in the transition state.

Early studies of the substituent effects on abstraction of hydrogen from phenols by oxygen- and carbon-centered radicals[13-15] revealed excellent correlation with σ^+ parameters and negative ρ value, implying the development of positive charge in the transition state. However, the relative contributions of bond-dissociation energies, resonance effects, and polar transition structures to the observed substituent effects remains controversial.[16,17]

From hydrogen-abstraction studies, we expected the β-scission reactions to exhibit substantial substituent effects. To examine this possibility, and to gain an estimate of the energetics of β-scission, the present study was ini-

(1) This work was supported by the Office of Basic Energy Sciences, U.S. Department of Energy, under contract DE-AC06-76RLO 1830.

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