The eluate was evaporated to give an oil (1.56 g), which deposited crystals of 7,10-*anti*-di-*tert*-butoxy-6,9-dihydro-5,9-methano-5*H*-benzocycloheptene (**13**) (780 mg), mp 85–7 °C, on addition of cold MeOH (10 mL). The mother liquor was subjected to radial chromatography (5% EtOAc–hexane) to afford a further quantity of **13** (230 mg). The total yield thus was 1.10 g (53%). Recrystallization from MeOH gave plates, mp 88–9 °C: MS *m/z* 300 (M, 0.6), 244 (10), 188 (16), 187 (59), 142 (16), 141 (100), 57 (12); ^{1}H NMR (90 Mz) δ 7.24–7.00 (m, 4 H, aryl), 5.28 (dm, $J_{8,9}$ = 7.0 Hz, 1 H, H8), 4.05 (dd, $J_{10,5} = J_{10,9}$ = 5.0 Hz, 1 H, H10), 3.17 (dd, $J_{9,8}$ = 7.0 Hz, $J_{9,10}$ = 5.0 Hz, 1 H, H9), 3.01 (m, 1 H, H5), 2.63 (ddd, J_{gem} = 16 Hz, $J_{6,5}$ = 5.0 Hz, $J_{6,8}$ = 1.8 Hz, 1 H, H6-exo), 1.84 (ddd, J_{gem} = 16 Hz, $J_{6,5}$ = 1.8 Hz, $J_{6,8}$ = 1.0 Hz, 1 H, H6-endo), 1.24 and 1.23 (2 s, 9 H, 2 *tert*-butyl); ^{13}C NMR 28.6 (q), 29.2 (q), 33.3 (t), 44.3 (d), 44.5 (d), 73.5 (s), 74.5 (d), 77.4 (s), 112.5 (d), 121.0 (d), 124.0 (d), 126.2 (d), 126.5 (d), 143.2 (s), 149.4 (s), 149.6 (s).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found C, 80.16; H, 9.41.

Hydrolysis of the Di-*tert*-butyl Ether 13. A. A solution of the ether **13** (660 mg) in CH_2Cl_2 (20 mL) was added to a slurry of SiO_2 (5 g) and 10% aqueous oxalic acid.[12] The mixture was stirred at room temperature until TLC analysis showed that the starting material had been consumed (2 h). The mixture was treated with solid $NaHCO_3$ (5 g) and filtered, and the filtrate was evaporated. The residue was subjected to radial chromatography (10% EtOAc–hexane) to give *anti*-10-*tert*-butoxy-5,6,8,9-tetrahydro-5,9-methano-7*H*-benzocyclohepten-7-one (**16**) (515 mg, 96%) as colorless crystals, mp 52–3 °C: MS *m/z* 244 (3), 189 (11), 188 (58), 159 (10), 157 (12), 145 (19), 144 (29), 143 (11), 142 (15), 141 (12), 131 (17), 129 (45), 128 (51), 115 (13), 57 (100), 41 (15); ^{1}H NMR (90 Mz) δ 7.16 (narrow m, 4 H, aryl), 4.18 (t, J = 5 Hz, 1 H, H10), 3.17 (m, 2 H, H5, H9), 2.99 and 2.28 (m, AA'BB' part of AA'BB'MM' system, $J_{AB} \sim$ 17 Hz, 4 H, methylenes), 1.29 (s, 9 H, *tert*-butyl); ^{13}C NMR δ 28.5 (q), 43.3 (t), 44.6 (d), 74.0 (s), 74.4 (d), 124.0 (d), 127.7 (d), 143.8 (s), 210.6 (s); IR ν_{max} ($CHCl_3$) 1710 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 79.03; H, 8.52.

B. A solution of the di-*tert*-butyl ether **13** (630 mg) in THF (20 mL) containing concentrated H_2SO_4 (5 mL) and water (5 mL) was refluxed for 3 h. The mixture was diluted with water and thoroughly extracted with ether. The ether extract was washed with aqueous $NaHCO_3$ and water, dried, and evaporated. The residue crystallized from CH_2Cl_2–hexane to give *anti*-10-hydroxy-5,6,8,9-tetrahydro-5,9-methano-7*H*-benzocyclohepten-7-one (**14**) as colorless crystals (318 mg, 81%), mp 146–7 °C: MS *m/z* 189 (M + 1, 14), 188 (M, 100), 159 (14), 158 (14), 157 (12), 145 (43), 144 (37), 143 (31), 142 (36), 141 (28), 131 (42), 130 (15), 129 (88), 128 (97), 127 (26), 118 (10), 117 (43), 116 (37), 115 (74), 103 (19), 91 (24), 77 (17), 43 (12); ^{1}H NMR (90 Mz) δ 7.17 (s, 4 H, aryl), 4.35 (t, J = 4.5 Hz, 1 H, H10), 3.34 (s, 1 H, OH), 3.24 (m, 2 H, H5, H9), 2.97 and 2.31 (m, AA'BB' part of AA'BB'MM' system, $J_{AB} \sim$ 17 Hz, 4 H, methylenes); ^{13}C NMR δ 42.8 (t), 44.3 (d), 73.8 (d), 124.2 (d), 128.0 (d), 143.6 (s), 210.4 (s); IR ν_{max} ($CHCl_3$) 3690, 3610, 3420, 1712 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.42; H, 6.47.

Addition of Dichlorocarbene to 7,7-Dimethoxybenzonorbornadiene (17). A mixture of **17** (1.29 g), $CHCl_3$ (10 mL), 50% NaOH solution (10 mL), and cetyltrimethylammonium bromide (150 mg) was vigorously stirred at 40 °C for 6 h. The mixture was diluted with water and worked up by ether extraction in the usual manner. Distillation (Kugelrohr, 100 °C/0.1 mm) gave unreacted alkene **17** (760 mg). The distillation residue was subjected to radial chromatography using 10% CH_2Cl_2–hexane. The slower moving band afforded additional starting material (120 mg). The faster moving band yielded 6β,7-dichloro-6,9-dihydro-10,10-dimethoxy-5α,9α-methano-5*H*-benzocycloheptene (**19**) (220 mg, 50% based on consumed starting material) as an oil, which crystallized from pentane, mp 86–7 °C: MS *m/z* 251 (M – Cl, 13), 249 (M – Cl, 39), 217 (21), 202 (22), 177 (39), 175 (100), 171 (16), 149 (15), 140 (17), 139 (80), 122 (18), 115 (26), 111 (22), 109 (53), 63 (15), 59 (20); ^{1}H NMR (90 MHz) δ 7.48 (m, 4 H, aryl), 6.30 (dd, $J_{8,9}$ = 7.2 Hz, $J_{8,6}$ = 1.2 Hz, 1 H, H8), 4.93 (dd, $J_{6,5}$ = 5.4 Hz, $J_{6,8}$ = 1.2 Hz, 1 H, H6), 3.76 (dd, $J_{5,6}$ = 5.4 Hz, $J_{5,9}$ = 1.8 Hz, 1 H, H5), 3.50 (dd, $J_{9,8}$ = 7.2 Hz, $J_{9,5}$ = 1.8 Hz, 1 H, H9), 3.26 (s, 3 H, methoxy), 3.15 (s, 3 H, methoxy).

Anal. Calcd for $C_{14}H_{14}Cl_2O_2$: C, 58.97; H, 4.95. Found: C, 58.88; H, 5.27.

Addition of Dichlorocarbene to Benzonorbornadiene (3). A mixture of benzonorbornadiene (14.2 g), $CHCl_3$ (60 mL), 50% NaOH (100 mL), and cetyltrimethylammonium chloride (1.0 g) was stirred at 0 °C for 2 h and then at room temperature overnight. The mixture was diluted with water and extracted with ether, and the ether extract was washed with water, dried, and evaporated (below 30 °C) to give (1aα,2α,7α,7aα)-1,1-dichloro-1a,2,7,7a-tetrahydro-2,7-methanocyclopropa[*b*]naphthalene (**20**) as a pale brown oil (19.6 g, 87%): ^{1}H NMR (60 MHz) δ 7.25–6.85 (AA'BB', 4 H, aryl), 3.54 (broad s, 2 H, H2, H7), 2.60 (A part of AB, further split, J_{AB} = 10 Hz, 1 H, H8), 1.81 (s, 2 H, H1a, H7a), 1.29 (B part of AB, broadened, 1 H, H8); ^{13}C NMR δ 39.5 (t), 41.7 (d), 44.8 (d), 76.8 (s), 121.4 (d), 125.5 (d), 150.1 (s). On vacuum distillation, quantitative isomerization occurred to afford 6α,7-dichloro-6,9-dihydro-5α,9α-methano-5*H*-benzocycloheptene (**21**), bp 117–120 °C/0.8 mm (lit.[2c] bp 92 °C/0.04 mm), having spectral properties identical with those reported.[2] Rearrangement of **20** to **21** also occurred upon attempted flash chromatography on SiO_2.

Registry No. **3**, 4453-90-1; **7**, 15893-89-7; **8**, 125023-43-0; **9**, 125132-87-8; **10**, 125023-44-1; **11**, 125023-45-2; **13**, 125023-46-3; **14**, 55139-53-2; **15**, 125023-47-4; **16**, 125023-48-5; **17**, 42490-91-5; **19**, 125023-49-6; **20**, 125023-50-9; **21**, 54647-00-6; CCl_2, 1605-72-7.

(12) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J.-M. *Synthesis* **1978**, 63.

Total Synthesis of Colneleic Acid

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The lipoxygenase of potato (*Solanum tuberosum*) converts endogenous linoleic acid to a mixture of 9(*S*)- and 13(*S*)-hydroperoxides.[1] The 9(*S*)-hydroperoxide **2** is transformed further by lipoxygenase preparations from potato homogenate under anaerobic conditions to colneleic acid, **1**, an unusual fatty acid which can be isolated from potato tubers.[2] Although the physiological function of colneleic acid in *S. tuberosum* is unknown, the surmise that it might be an important biochemical regulator was rendered more plausible by the finding in this laboratory that **1** is a strong competitive inhibitor of the potato lipoxygenase (K_i at 23 °C and pH 6.3 of 7 μM).[3] For example, it is not unreasonable that hte potato lipoxygenase under regulation by its own product (**1**) could function as an oxygen sensor which links metabolism and oxygen supply.

An earlier research project in our laboratory resulted in the successful development of a biomimetic synthesis of colneleic acid from linoleic acid via the 9(*S*)-hydroperoxide.[3] In this paper we report a totally different chemical route from cheap, non-fatty acid precursors which utilizes novel methodology.

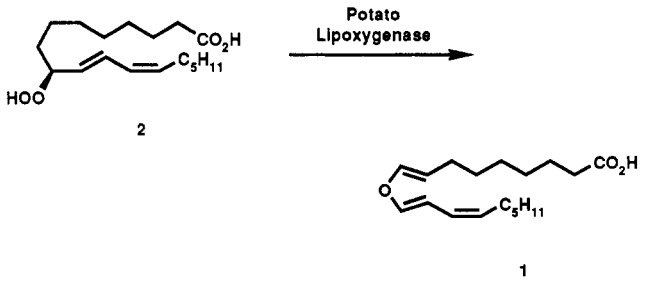
The enol ester **3** was selected as the key intermediate in this synthesis. Stereoselective enolate formation followed by O-phosphorylation was expected to afford the bis enol phosphate **4**. It was anticipated that palladium-

(1) Sekiya, J.; Aoshima, H.; Kajiwara, T.; Togo, T.; Hatanaka, A. *Agric. Biol. Chem.* **1977**, *41*, 827 and references cited therein.

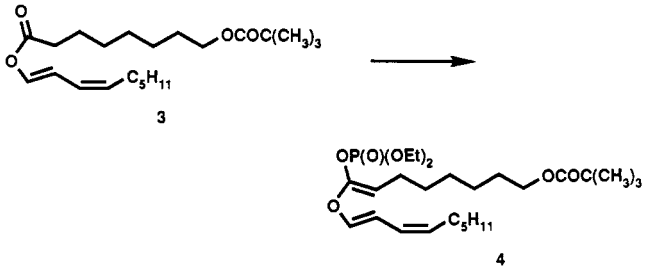
(2) (a) Galliard, T.; Phillips, D. R. *Biochem. J.* **1972**, *129*, 743. (b) Galliard, T.; Phillips, D. R.; Frost, D. J. *Chem. Phys. Lipids* **1973**, *11*, 173. (c) Galliard, T.; Matthew, J. *Biochem. Biophys. Acta* **1975**, *398*, 1.

(3) Corey, E. J.; Nagata, R.; Wright, S. W. *Tetrahedron Lett.* **1987**, *28*, 4917.

0022-3263/90/1955-1670$02.50/0



mediated reductive cleavage of 4 would occur upon exposure to triethylaluminum to generate the bis vinyl ether subunit of 1. The ester 3 was prepared in turn from 3-nonynal (9) and the acid chloride 7.



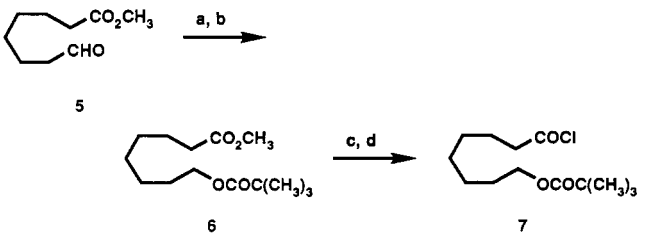
The acid chloride 7 was prepared in five steps from cyclooctene. Ozonolysis of cyclooctene in dichloromethane–methanol at −78 °C followed by treatment with acetic anhydride and triethylamine[4] gave the aldehyde 5. Reduction of 5 to the corresponding alcohol with sodium borohydride in ethanol followed by reaction of the resulting alcohol with pivaloyl chloride in dichloromethane and pyridine afforded the diester 6 (Scheme I). Conversion of 6 to the acid chloride 7 was accomplished by selective saponification of the methyl ester with potassium carbonate in refluxing methanol followed by treatment with oxalyl chloride in benzene.

3-Nonynal was prepared from 1-heptyne in three steps. Sequential treatment of 1-heptyne with ethylmagnesium bromide in ether followed by allyl bromide under copper(I) catalysis gave 1-decen-4-yne,[5] which was oxidized to the diol 8 with *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetraoxide (Scheme II). Oxidative cleavage of 8 to aldehyde 9 was then carried out in a biphasic reaction mixture of dichloromethane and aqueous sodium periodate in the presence of a catalytic amount of tetrabutylammonium periodate.

The preparation of the sensitive and easily polymerized ynenol ester 10 was accomplished by the reaction of the sodium enolate of 9 (prepared by adding 9 to sodium hexamethyldisilazide in THF at −78 °C) with 7 at −78 °C (Scheme III). Hydrogenation of 10 to 3 was effected using Lindlar's catalyst in benzene. Addition of a precooled (−108 °C) solution of 3 to LDA in 3:1 THF–HMPA[6a] at −108 °C[6b] followed by quenching with diethylphosphorobromidate[6c] gave the bis enol phosphate 4 as a 2:1 mixture of isomers about the C(8,9) double bond. Exposure of 4 to 2 equiv of triethylaluminum and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in a mixture of hexane and 1,2-dichloroethane gave the bis vinyl ether 11.[7]

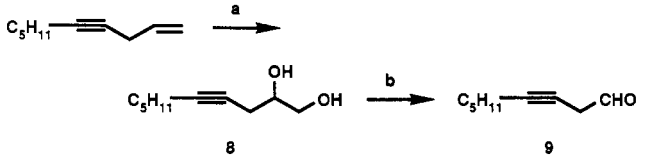
(4) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1985**, *64*, 150.
(5) Danehy, J. P.; Killian, D. B.; Nieuwland, J. A. *J. Am. Chem. Soc.* **1936**, *58*, 611.
(6) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) The enolate suffered rapid elimination to the ketene at higher temperatures, particularly in the presence of HMPA. HMPA began to crystallize from the reaction mixture at −108 °C. (c) Michalski, J.; Pakulski, M.; Skowronska, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 833. See also: Gorecka, A.; Leplawy, M.; Zwierzak, A. *Synthesis* **1978**, 474.

Scheme I[a]



[a] (a) $NaBH_4$, EtOH, 0 °C (98%); (b) $(CH_3)_3CCOCl$, CH_2Cl_2, pyr, 0 °C (88%); (c) K_2CO_3, H_2O, MeOH, 65 °C (96%); (d) $(COCl)_2$, PhH (79%).

Scheme II[a]



[a] (a) OsO_4, NMMO, Me_2CO, H_2O, 25 °C (70%); (b) $NaIO_4$, Bu_4NIO_4, NaOAc, H_2O, CH_2Cl_2, 0 °C (99%).

The transformation of 11 to colneleic acid 1 was completed in four steps as shown in Scheme IV. The pivaloate protecting group was removed by heating 11 under reflux with methanolic potassium hydroxide. Conversion of the resulting alcohol to the mesylate under standard conditions was followed by treatment with excess sodium cyanide in DMSO to give the nitrile 12. Heating this nitrile at reflux with ethanolic potassium hydroxide afforded 1 (61%) as a 2:1 8*E*:8*Z* mixture, separated as methyl esters by preparative HPLC after esterification with gaseous diazomethane. The synthetic colneleic acid methyl ester was indistinguishable from an authentic sample (prepared by incubation of 2 with potato homogenate[2,3] and esterification with gaseous diazomethane) by 500-MHz ^1H NMR, IR, UV, TLC, HPLC, and mass spectral analyses.[8]

Experimental Section

^1H NMR spectra were measured in deuteriochloroform solutions at 270 or 500 MHz. Coupling constants are given in hertz. The usual 6-Hz coupling uniformly observed for vicinal coupling in ethyl groups has been omitted for brevity. Mass spectral data were obtained at an ionization voltage of 70 eV.

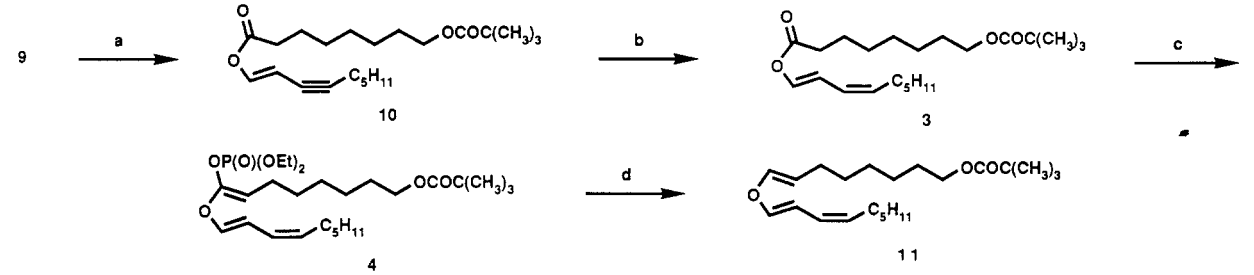
All reactions were carried out with continuous magnetic stirring under an atmosphere of dry nitrogen or argon unless otherwise noted. All extracts were dried over anhydrous magnesium sulfate unless otherwise noted; all evaporations were carried out with a rotary evaporator at ca. 30 Torr.

Tetrahydrofuran (THF) and benzene were distilled from sodium benzophenone ketyl. Hexane, diisopropylamine, and dichloromethane were distilled from calcium hydride. Hexamethylphosphoric triamide (HMPA) was dried over barium oxide, distilled under vacuum from calcium hydride, and stored over 4A molecular sieves. Triethylamine was dried over potassium hydroxide, distilled from calcium hydride, and stored over coarse calcium hydride. Dimethyl sulfoxide was distilled under vacuum from calcium hydride and stored over 4A sieves. 1,2-Dichloroethane was distilled from phosphorus pentoxide and stored over 4A sieves in the dark. Thin layer chromatography was carried out with E. Merck 5715 silica gel plates.

4-Decyne-1,2-diol (8). *N*-Methylmorpholine *N*-oxide (21.82 g, 161 mmol) was dissolved in 30 mL of water, and 50 mg of osmium tetraoxide was added. Acetone (50 mL) was added, and

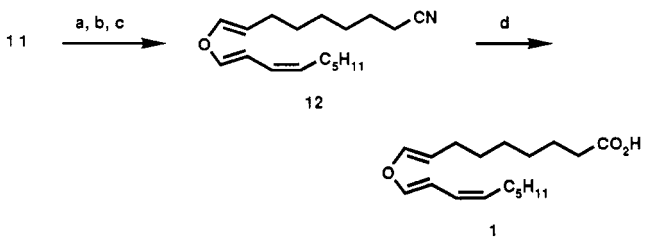
(7) Charbonnier, F.; Moyano, A.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2303.
(8) This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

Scheme III[a]



[a] (a) NaHMDS, THF, −78 °C, 7 (22%, not optimized); (b) H_2, Pd/Pb/$CaCO_3$, PhH (99%); (c) LDA, HMPA, $(EtO)_2POBr$, −108 °C (53%); (d) Et_3Al, $Pd(PPh_3)_4$, hexane, $ClCH_2CH_2Cl$, 25 °C (70%).

Scheme IV[a]



[a] (a) KOH, MeOH, H_2O, 65 °C (96%); (b) MsCl, Et_3N, CH_2Cl_2, −25 °C (100%); (c) NaCN, DMSO, 25 °C (100%); (d) KOH, EtOH, H_2O, 80 °C (61%).

the solution was cooled to 0 °C. Dec-1-en-4-yne (20.00 g, 147 mmol) was added dropwise over 15 min. The very dark reaction mixture was allowed to warm to 20 °C and was maintained at 20 °C for 36 h. A solution of 10 g of sodium bisulfite in 30 mL of water was added. After 1 h, 15 mL of saturated sodium sulfide solution was added, and the mixture was concentrated and extracted with ethyl acetate (3 × 50 mL), and the extracts were washed with water (2 × 30 mL) and brine (1 × 60 mL), dried, and evaporated. Distillation gave 17.24 g (70%) of **8**. NMR ($CDCl_3$): δ 3.81–3.55 (m, 3 H, 1-CH_2 and 2-CH), 2.42 (m, 2 H, 3-CH_2), 2.15 (br t, 2 H, 6-CH_2), 1.55–1.30 (m, 6 H, 7-, 8-, and 9-CH_2), 0.88 (t, 3 H, CH_3). IR (neat): 3700–3100 (OH) cm^{-1}. MS (CI, isobutane): 171 ($M^+ + H^+$). HRMS (EI) for $C_{10}H_{18}O_2$: calcd 171.138 50, found 171.138 74.

3-Nonynal (9). A solution of 2.080 g (12.2 mmol) of **8** in 50 mL of dichloromethane was cooled to 0 °C, and 0.25 g (0.57 mmol) of tetra-*n*-butylammonium periodate was added, followed by a 0 °C solution of 5.228 g (24.4 mmol) of sodium periodate in 50 mL of water. After 1 h, 100 mL of hexane was added, the layers were separated, and the organic layer was washed with water (2 × 50 mL) and brine (1 × 50 mL), dried, and evaporated to yield 1.680 g (99%) of **9**. NMR ($CDCl_3$): δ 9.60 (t, 1 H, CHO), 3.48 (m, 2 H, 2-CH_2), 2.20 (m, 2 H, 5-CH_2), 1.55–1.48 (m, 2 H, 6-CH_2), 1.34–1.25 (m, 4 H, 7- and 8-CH_2), 0.89 (t, 3 H, CH_3). IR (neat): 2720 (CO-H), 1730 (C=O) cm^{-1}.

Methyl 8-Hydroxyoctanoate. Sodium borohydride (0.473 g, 12.5 mmol) was dissolved in 70 mL of cold absolute ethanol. The aldehyde **5**[4] (4.306 g, 25 mmol) in 10 mL of absolute ethanol was added slowly with cooling in ice. After 20 min, the mixture was quenched with 8 mL of acetone and acidified with 7 mL of 2 M citric acid. The ethanol was evaporated, and the residue was treated with 50 mL of saturated aqueous sodium chloride and extracted with 75 mL of ether. The ether was washed with water (1 × 25 mL) and brine (1 × 25 mL), dried, and evaporated to give 4.270 g (98%) of methyl 8-hydroxyoctanoate as a colorless oil. NMR ($CDCl_3$): δ 3.66 (s, 3 H, OCH_3), 3.63 (t, 2 H, 8-CH_2O), 2.30 (t, 2 H, 2-CH_2), 1.69–1.53 (m, 4 H, 3- and 7-CH_2), 1.30–1.40 (m, 6 H, 4-, 5-, and 6-CH_2). IR (neat): 3700–3100 (OH), 1740 (ester C=O) cm^{-1}. MS (CI, isobutane): 175 (M + H^+).

Methyl 8-((2,2-Dimethylpropanoyl)oxy)octanoate (6). Methyl 8-hydroxyoctanoate (2.741 g, 15.7 mmol) was dissolved in 50 mL of anhydrous chloroform and 5.08 mL (62.8 mmol) of pyridine, and the mixture was cooled in ice. Redistilled pivaloyl chloride (2.52 mL, 20.4 mmol) was added over 1 min with vigorous stirring. Stirring was continued for 1 h at 0 °C and then for 14 h at 22 °C. The mixture was quenched with 1 M sodium bicarbonate (25 mL), stirred for 10 min, and diluted with 80 mL of hexane. The organic layer was separated and washed with 3 M sulfuric acid (2 × 25 mL), water (1 × 25 mL), 1 M potassium carbonate (2 × 25 mL), and brine (1 × 25 mL), dried, and concentrated. Chromatography of the residue on basic alumina eluting with 3:1 hexane–ether for elution gave 3.558 g (88%) of **6**. NMR ($CDCl_3$): δ 4.03 (t, 2 H, 8-CH_2O), 3.66 (s, 3 H, OCH_3), 2.30 (t, 2 H, 2-CH_2), 1.65–1.59 (m, 4 H, 3- and 7-CH_2), 1.34–1.21 (m, 6 H, 4-, 5-, and 6-CH_2), 1.19 (s, 9 H, CMe_3). IR (neat): 1735 (ester C=O) cm^{-1}. MS (CI, NH_3): 276 (M + NH_4^+). HRMS (CI, NH_3) for $C_{14}H_{26}O_4$ + NH_4^+: calcd 276.217 47, found 276.217 17.

8-((2,2-Dimethylpropanoyl)oxy)octanoyl Chloride (7). A solution of 3.558 g (13.7 mmol) of **6** and 3.798 g (27.5 mmol) of potassium carbonate in 55 mL of methanol and 27.5 mL of water was heated under reflux for 1 h. After cooling, the methanol was evaporated, and the solution was saturated with sodium chloride and transferred to a separatory funnel. The mixture was carefully acidified with 20 mL of 3 M sulfuric acid and extracted with chloroform (3 × 15 mL) and carbon tetrachloride (1 × 15 mL). The dried extracts were evaporated to give 3.224 g (96%) of the carboxylic acid. NMR ($CDCl_3$): δ 4.04 (t, 2 H, 8-CH_2O), 2.35 (t, 2 H, 2-CH_2), 1.60–1.72 (m, 4 H, 3- and 7-CH_2), 1.30–1.40 (m, 6 H, 4-, 5-, and 6-CH_2), 1.19 (s, 9 H, CMe_3). IR (neat): 3700–2500 (OH), 1730–1700 (ester and acid C=O) cm^{-1}. MS (CI, NH_3): 262 (M + NH_4^+), 244 (M^+).

A solution of the above acid (2.858 g, 11.7 mmol, azeotropically dried with toluene) in 35 mL of dichloromethane was cooled to 0 °C. DMF (30 μL) was added, followed by 1.53 mL (17.6 mmol) of oxalyl chloride, and the mixture was stirred for 45 min. The mixture was evaporated, and the remaining oil was evacuated at 1 Torr for 1 h to afford the acid chloride, which was used without further purification.

(1*E*)-Non-1-en-3-ynyl 8-((2,2-Dimethylpropanoyl)oxy)octanoate (10). A solution of **9** (1.319 g, 9.7 mmol, azeotropically dried with toluene) in 15 mL of THF was added dropwise by cannula over 12 min to a −78 °C solution of 10.5 mmol of sodium bis(trimethylsilyl)amide (1 M in THF) in 30.5 mL of THF. This solution was then added rapidly via a dry ice cooled cannula to a solution of **7** (as prepared above) dissolved in 35 mL of THF at −78 °C. After the addition was complete, the solution was allowed to come to 22 °C and was concentrated to $^1/_3$ volume. Hexane (100 mL) and ether (50 mL) were added, and the solution was washed with water (2 × 40 mL). The aqueous washes were back extracted with ether (2 × 25 mL), and the combined organic solutions were washed with 1 M potassium carbonate (3 × 40 mL), water (1 × 40 mL), 1 M citric acid (2 × 40 mL), water (1 × 40 mL), and brine (1 × 40 mL), dried, and evaporated to give 4.83 g of a red oil. This was flash chromatographed on silica (2:1 benzene–hexane) to give 0.773 g (22%) of **10** as a pale yellow oil. NMR ($CDCl_3$): δ 7.56 (d, J = 12.86 Hz, 1 H, =C′HO), 5.47 (d of t, J = 12.86, 2.31 Hz, 1 H, =C′H), 4.04 (t, 2 H, CH_2O), 2.39 (t, 2 H, 7-CH_2), 2.29 (t of d, J = 6.92, 2.31 Hz, 2 H, 5′-CH_2), 1.72–1.50 (m, 6 H, 2-, 6-, and 6′-CH_2), 1.45–1.30 (m, 10 H, 3-, 4-, 5-, 7′-, and 8′-CH_2), 1.19 (s, 9 H, CMe_3), 0.90 (t, 3 H, 9′-CH_3). IR (neat): 3080 (=CH), 2220 (weak, C≡C), 1760 (enol ester C=O), 1725 (ester C=O), 1635 (C=C) cm^{-1}. UV (EtOH): λ_{max} 235 nm. MS (CI, NH_3): 364 (M + NH_4^+). HRMS (CI, NH_3) for $C_{22}H_{36}O_4$ + NH_4^+: calcd 382.295 71, found 382.295 22.

(1*E*,3*Z*)-1,3-Nonadienyl 8-((2,2-Dimethylpropanoyl)oxy)octanoate (3). A mixture of 0.773 g (2.12 mmol) of **10** and 240 mg of Lindlar's catalyst in 35 mL of benzene was subjected to 20 cycles of evacuation and flushing with hydrogen at 1 atm. The reduction was followed by TLC; after 20 min the reduction was complete. Filtration through Celite and evaporation gave 0.773 g (99%) of **3** as a pale yellow oil. NMR ($CDCl_3$): δ 7.37 (d, J = 12.2 Hz, 1 H, =C'HO), 6.29 (t, 1 H, 2' =CH), 5.91 (t, 1 H, 3' =CH), 5.49 (m, 1 H, 4' =CH), 4.04 (t, 2 H, 8-CH_2O), 2.36 (t, 2 H, 2-CH_2), 2.11 (m, 2 H, 5'-CH_2), 1.72–1.50 (m, 6 H, 3-, 7-, and 6'-CH_2), 1.45–1.30 (m, 10 H, 4-, 5-, 6-, 7'-, and 8'-CH_2), 1.19 (s, 9 H, CMe_3), 0.89 (t, 3 H, 9'-CH_3). IR (neat): 3080 (=CH), 1750 (dienol ester C=O), 1725 (ester C=O), 1650, 1605 (C=C cm^{-1}. UV (EtOH): λ_{max} 240 nM. MS (DCI, NH_3): 384 (M + NH_4^+). HRMS (EI) for $C_{22}H_{38}O_4$: calcd 366.276 99, found 366.275 96.

Enol Phosphate 4. A solution of 0.1270 g (0.35 mmol) of **3** in 1 mL of THF at −108 °C was added dropwise over 4 min via a cold (−108 °C) cannula to a solution of 0.385 mmol of lithium diisopropylamide and 0.7 mL of HMPA in 2 mL of THF at −108 °C. The light yellow solution was stirred for 2 min longer, then 69 μL of diethylphosphorobromidate in 1 mL of THF at −108 °C was added over 1 min. The mixture was kept at this temperature for 1.5 h and then was allowed to warm to 0 °C. The mixture was diluted with 15 mL of ether, washed with water (2 × 4 mL), 1 M potassium carbonate (1 × 4 mL), 1 M lithium chloride (1 × 4 mL), and brine (1 × 4 mL), dried over potassium carbonate, and evaporated. Chromatography on silica (1:1 hexane–ethyl acetate) gave 0.0925 g (53%) of **4**. NMR ($CDCl_3$): δ 6.45 (d, 1 H, 10-CH), 6.14 (t, 1 H, 11-CH), 5.40 (m, 1 H, 12-CH), 4.87 (m, 1 H, 13-CH), 4.26–4.15 (m, 5 H, 7-CH and P-OCH_2), 4.03 (t, 2 H, 1-CH_2), 2.10–1.95 (m, 4 H, 6- and 14-CH_2), 1.63–1.58 (m, 4 H, 5- and 15-CH_2), 1.45–1.20 (m, 27 H, 2-, 3-, 4-, 16-, and 17-CH_2, *t*-Bu and phos-CH_3), 0.89 (t, 3 H, 18-CH_3). IR (neat): 1730 (ester C=O), 1650, 1600 (C=C), 1285 (P=O) cm^{-1}. UV (*c*-C_6H_{12}): λ_{max} 238 nm. MS (DCI NH_3): 503 (M+ NH_4^+).

Vinyl Ether 11. A solution of **4** (92.5 mg, 184 μmol) in 2.6 mL of hexane was cooled to 0 °C, and 0.37 mL of 1 M triethylaluminum in hexane was added by syringe, followed at once by 11 mg of tetrakis(triphenylphosphine)palladium(0) suspended in 0.3 mL of 1,2-dichloroethane. The reaction mixture was brought to 20 °C, and 1,2-dichloroethane was added dropwise until a homogeneous solution was obtained (0.6 mL required). After 10.5 h at 20 °C, the reaction was terminated by the addition of 15 mL of ether, and the solution was washed with 3 M sodium hydroxide (2 × 4 mL), water (2 × 4 mL), and brine (1 × 4 mL), dried, and filtered through Florisil. Chromatography on silica gave 24.3 mg of recovered **4** and 33.3 mg (70% corrected for recovered **4**) of **11**. NMR ($CDCl_3$): δ 6.50 (m, 1 H, 10-CH), 6.26 (m, 1 H, 8-CH), 6.00 (m, 1 H, 11-CH), 5.85 (m, 1 H, 12-CH), 5.31 (m, 1 H, 13-CH), 5.10 (m, 1 H, 7-CH), 4.04 (t, 2 H, 1-CH_2), 2.12 (m, 2 H, 14-CH_2), 1.95 (m, 2 H, 6-CH_2), 1.64 (m, 4 H, 5- and 15-CH_2), 1.45–1.20 (m, 10 H, 2-, 3-, 4-, 16-, and 17-CH_2), 1.19 (s, 9 H, *t*-Bu), 0.89 (t, 3 H, CH_3). IR (neat): 1730 (ester C=O), 1650, 1605 (C=C) cm^{-1}. UV (*c*-C_6H_{12}): λ_{max} 247 nM.

Colneleonitrile (12). Potassium hydroxide (60 mg, 1.07 mmol) was dissolved in 300 μL of water, and the ester **11** (9.3 mg, 26.5 μmol) was added in 2.0 mL of methanol. The mixture was heated at reflux for 4 h, after which it was cooled and the methanol was evaporated. Ether (8 mL) was added, and the mixture was washed with water (1 × 1 mL), 1 M potassium carbonate (1 × 1.5 mL), and brine (1 × 1.5 mL), dried, and evaporated to yield 6.8 mg (96%) of the corresponding alcohol. NMR ($CDCl_3$): δ 6.50 (m, 1 H, 10-CH), 6.21 (m, 1 H, 8-CH), 6.00 (m, 1 H, 11-CH), 5.85 (m, 1 H, 12-CH), 5.31 (m, 1 H, 13-CH), 5.10 (m, 1 H, 7-CH), 3.63 (t, 2 H, 1-CH_2), 2.12 (m, 2 H, 14-CH_2), 1.95 (m, 2 H, 6-CH_2), 1.64 (m, 4 H, 5- and 15-CH_2), 1.45–1.20 (m, 10 H, 2-, 3-, 4-, 16-, and 17-CH_2), 0.89 (t, 3 H, CH_3). IR (neat): 3600–3100 (OH), 1650, 1610 (C=O) cm^{-1}. UV (C_6H_{12}): λ_{max} 246 nM. MS (DCI, NH_3): 267 (M + H^+).

A solution of the above alcohol (6.5 mg, 24.3 μmol) in 800 μL of dichloromethane was cooled to −23 °C, and 5.1 μL (36.4 μmol) of triethylamine was added, followed by 2.1 μL (26.7 μmol) of methanesulfonyl chloride. After 0.5 h at −23 °C, TLC analysis indicated complete conversion to the mesylate had occurred. The mixture was warmed to 20 °C, diluted with 3.5 mL of pentane, washed with 1 M potassium carbonate (2 × 1 mL) and brine (1 × 1 mL), dried, and evaporated. The residue was dissolved in 1.5 mL of DMSO, and 60 mg (1.22 mmol) of finely powdered sodium cyanide was added. After 5 h at 20 °C, the mixture was diluted with 5 mL of ether and washed with water (2 × 1 mL). The water was back-extracted with ether (2 mL). The combined ether extracts were washed with water (2 × 2 mL) and brine (1 × 2 mL), dried, and evaporated to yield 7.0 mg (100%) of **12**. NMR ($CDCl_3$): δ 6.52 (m, 1 H, 10-CH), 6.23 (m, 1 H, 9-CH), 6.00 (m, 1 H, 11-CH), 5.85 (m, 1 H, 12-CH), 5.31 (m, 1 H, 13-CH), 5.10 (m, 1 H, 8-CH), 2.34 (t, 2 H, 2-CH_2), 2.12 (m, 2 H, 14-CH_2), 1.95 (m, 2 H, 7-CH_2), 1.64 (m, 6 H, 3-, 6-, and 15-CH_2), 1.45–1.20 (m, 8 H, 4-, 5-, 16-, and 17-CH_2), 0.89 (t, 3 H, CH_3). IR (neat): 2240 (C≡N), 1650, 1605 (C=C) cm^{-1}. UV (C_6H_{12}): λ_{max} 248 nm. MS (EI): 275 (M^+).

Methyl Colneleate. Six milligrams (21.7 μmol) of **12** was dissolved in 1 mL of ethanol, and 50 mg (0.89 mmol) of potassium hydroxide was added. The mixture was heated at reflux for 5 h. Ether (5 mL) was added to the cooled flask, and the solution was brought to pH 4.0 with 2 M citric acid. The layers were separated, and the aqeous phase was extracted with ether (1 mL) again. The combined ether extracts were washed with water (3 × 1 mL) and brine (1 × 1 mL), dried over sodium sulfate, and transferred to a clean flask. Diazomethane in nitrogen was bubbled through the solution at 0 °C for 10 min. The solution was then evaporated to dryness. The residue was dissolved in 2:1 hexane–ether and filtered through a short plug of silica. Evaporation gave 4.1 mg (61%) of methyl colneleate. The natural 8*E* isomer was separated by preparative HPLC (DuPont Zorbax silica, 4.6 mm × 250 mm, 0.2% THF in hexane, 2 mL min^{-1}, R_t = 21.6 min (8*Z* isomer, R_t = 19.0 min). NMR ($CDCl_3$): δ 6.50 (d, J = 11.8 Hz, 1 H, 11-CH), 6.26 (d, J = 12.2 Hz, 1 H, 9-CH), 5.99 (t, J = 11.8 Hz, 1 H, 12-CH), 5.85 (t, J = 11.1 Hz, 1 H, 13-CH), 5.29 (d of t, J_d = 10.3 Hz, 1 H, 13-CH), 5.14 (d of t, J_d = 12.2 Hz, 1 H, 8-CH), 2.30 (t, 2 H, 2-CH_2), 2.09 (m, 2 H, 15-CH_2), 1.94 (m, 2 H, 7-CH_2), 1.62 (m, 2 H, 3-CH_2), 1.38–1.22 (m, 12 H, 4-, 5-, 6-, 16-, 17-, and 18-CH_2), 0.88 (t, 3 H, CH_3). IR (neat): 3020 (=CH), 1740 (ester C=O), 1645, 1605 (C=C) cm^{-1}. UV (C_6H_{12}): λ_{max} 248 nm. MS (EI): 308 (M^+). HRMS (DCI, NH_3) for $C_{19}H_{32}O_3$: calcd 308.23497, found 308.23498. Synthetic **1** and its methyl ester were identical with reference samples prepared from linoleic acid by incubation with the 15 000 g supernatant from potato homogenate as previously described.[2,3]

Registry No. **1**, 52761-34-9; **3**, 125076-99-5; (8*E*)-**4**, 125077-00-1; (8*Z*)-**4**, 125108-31-8; **5**, 3884-92-2; **6**, 125076-95-1; **7**, 125076-97-3; **8**, 125076-94-0; **9**, 87745-64-0; **10**, 125076-98-4; (8*E*)-**11**, 125077-01-2; (8*Z*)-**11**, 125108-32-9; (8*E*)-**12**, 125077-04-5; (8*Z*)-**12**, 125077-08-9; H_2C=$CHCH_2C$≡$C(CH_2)_4CH_3$, 24948-66-1; $HO(CH_2)_7CO_2Me$, 20257-95-8; $(CH_3)_3CCO_2(CH_2)_7CO_2H$, 125076-96-2; (*E*,*E*,*Z*)-$H_3C(CH_2)_4CH$=$CHCH$=$CHOCH$=$CH(CH_2)_6OH$, 125077-02-3; (*Z*,*E*,*Z*)-$H_3C(CH_2)_4CH$=$CHCH$=$CHOCH$=$CH(CH_2)_6OH$, 125077-06-7; (*E*,*E*,*Z*)-$H_3C(CH_2)_4CH$=$CHCH$=$CHOCH$=$CH(CH_2)_6OSO_2Me$, 125077-03-4; (*Z*,*E*,*Z*)-$H_3C(CH_2)_4CH$=$CHCH$=$CHOCH_2(CH_2)_6OSO_2Me$, 125077-07-8; (*E*,*E*,*Z*)-$H_3C(CH_2)_4CH$=$CHCH$=$CHOCH$=$CH(CH_2)_6CO_2Me$, 52077-21-1; (*E*,*Z*,*Z*)-$H_3C(CH_2)_4CH$=$CHCH$=$CHOCH$=$CH(CH_2)_6CO_2Me$, 125077-05-6.

Tris(2-aminoethyl)amine as a Substitute for 4-(Aminomethyl)piperidine in the FMOC/Polyamine Approach to Rapid Peptide Synthesis

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Recently[1,2] we described the use of FMOC amino acid chlorides as coupling agents in combination with de-

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