sodium metal (0.17 g, 7.5 mmol), and the solution was stirred at room temperature for 1 h. After benzaldehyde (0.80 g, 7.5 mmol) dissolved in 10 mL of ethanol was added to the solution, the reaction mixture was refluxed for 10 h. After the usual workup, distillation of the residue produced 0.74 g (3.94 mmol, 52%) of a 7:2 mixture of **(*E*)- and (*Z*)-1-benzylidene-2-ethoxycyclobutane [5a,b**; bp 109 °C (1.5 mm)] whose ratio was determined by gas chromatographic analysis and by ^{1}H NMR: IR (neat) 1680, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.17 and 1.24 (t, J = 7.14 Hz, 3 H, Me), 1.80–3.0 (m, 4 H, cyclobutyl CH_2), 3.25–3.75 (2 q, 2 H, OCH_2), 4.35–4.95 (m, 1 H, O–CH), 6.21 (q, J = 2.38 Hz, $^2/_9$ H, vinyl H), 6.41 (q, J = 2.20 Hz, $^7/_9$ H, vinyl H), 7.05–7.60 (m, 5 H, phenyl H); MS, m/e 188 (M^+). Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found (for a mixture of **5a** and **5b**): C, 83.33; H, 8.40.

1-Benzylidene-2-butylcyclobutane (6). To a solution of the 2-butylcyclobutylphosphonium ylide, generated from **2** (2.07 g, 5 mmol) and *n*-butyllithium (5 mmol), in 40 mL of dry THF at room temperature was added a solution of benzaldehyde (0.53 g, 5 mmol) in 10 mL of dry THF. Then the solution was stirred for 1 h at this temperature and for 8 h at reflux. After the usual workup, distillation of the residue afforded 0.56 g (2.80 mmol, 56%) of a 1:1 mixture of **(*E*)- and (*Z*)-1-benzylidene-2-butylcyclobutane [6a,b**; bp 130 °C (2 mm)]. Pure samples of each were obtained by preparative GLC. The product **6a** had the following properties: IR (neat) 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.75–3.45 (m, 14 H, *n*-C_4H_9, cyclobutyl CH_2 and CH), 5.90–6.10 (m, 1 H, olefinic H), 7.05–7.35 (m, 5 H, phenyl H); MS, m/e 200 (M^+). The product **6b** had the following properties: IR (neat) 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.75–3.20 (m, 14 H, *n*-C_4H_9, cyclobutyl CH_2 and CH), 6.0–6.20 (m, 1 H, olefinic H), 7.05–7.40 (m, 5 H, phenyl H); MS, m/e 200 (M^+). Anal. Calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found (for a mixture of **6a** and **6b**): C, 89.70; H, 9.70.

Reaction of 2 with Sodium Salicylaldehyde. The salt **2** (3.11 g, 7.5 mmol) and sodium salicylaldehyde (1.15 g, 8 mmol) were mixed in 35 mL of dry DMF, and this solution was stirred at 120 °C for 15 h. After evaporation of DMF in vacuo, the residue was extracted with ether, followed by washing with 5 % aqueous NaOH and with water. After removal of the ether, the remaining oil was distilled to give a 0.56 g (3.54 mmol, 47%) yield of **7**: bp 68 °C (1 mm); IR (neat) 1670, 1605, 1580, 1480, 1455, 1235, 1210, 1190, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.0–2.90 (m, 4 H, CH_2), 4.75–5.17 (m, 1 H, O–CH), 5.99 (d, J = 1.65 Hz, 1 H, CH=C), 6.60–7.20 (m, 4 H, aromatic H); MS, m/e 158 (M^+). The residue was chromatographed on preparative TLC with hexane–ether (4:1) as the eluent to give **8a** (0.23 g, 0.73 mmol, 19.4%) and **8b** (0.14 g, 0.44 mmol, 11.6 %). The product **8a** had the following properties: mp 142–143 °C; MS, calcd for $C_{22}H_{20}O_2$ m/e 316.1462 (M^+), found 316.1462. The product **8b** had the following properties: mp 96–101 °C; MS, calcd for $C_{22}H_{20}O_2$ m/e 316.1462 (M^+), found 316.1474.

Cyclobuta[*b*]chroman (9). The hydrogenation of **7** (0.38 g, 2.4 mmol) was accomplished in 5 h in ethanol over Pt to give **9** (0.36 g, 2.3 mmol, 94%) as a colorless oil: bp 75 °C (3 mm); IR (neat) 1600, 1575, 1480, 1450, 1220, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20–3.0 (m, 7 H, CH_2 and CH), 4.40–4.85 (m, 1 H, O–CH), 6.60–7.25 (m, 4 H, aromatic H); MS, m/e 160 (M^+). Anal. Calcd for $C_{11}H_{12}O$: C, 82.46% H, 7.55. Found: C, 82.50; H, 7.27.

(*cis*-4,5-Bis(ethoxycarbonyl)-1-cyclohexenyl)diphenylphosphine Oxide (11a). A mixture of **4** (0.69 g, 2.7 mmol) and diethyl maleate (7 mL) was heated at 150 °C for 10 h. Removal of excess diethyl maleate under reduced pressure left 0.82 g (1.92 mmol, 71 %) of a white solid (mp 124–125 °C) whose structure was assigned as **11a** on the basis of its spectral properties: IR (KBr) 1720, 1640, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 and 1.22 (2 t, J = 7.14 Hz, 6 H, CH_3), 2.30–3.30 (br m, 6 H, CH_2 and CH), 3.80–4.35 (m, 4 H, OCH_2), 6.38 (br d, J = 19.0 Hz, 1 H, olefinic H), 7.20–7.95 (m, 10 H, phenyl H); MS, m/e 426 (M^+). Anal. Calcd for $C_{24}H_{27}O_5P$: C, 67.60; H, 6.38. Found: C, 67.21; H, 6.46.

(*trans*-4,5-Bis(ethoxycarbonyl)-1-cyclohexenyl)diphenylphosphine Oxide (11b). The adduct **11b** was similarly obtained from **4** (0.25 g, 1.0 mmol) and diethyl fumarate (4 mL) as a sticky oil: yield 0.25 g (0.59 mmol, 59%); IR (neat) 1725, 1635, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 and 1.24 (2 t, J = 7.08 Hz, 6 H, CH_3), 2.40–3.10 (m, 6 H, CH_2 and CH), 4.09 and 4.15 (2 q, 4 H, OCH_2), 6.32 (br d, J = 18 Hz, 1 H, olefinic H), 7.40–7.90 (m, 10 H, phenyl H); MS, calcd for $C_{24}H_{27}O_5P$ m/e 426.1595 (M^+), found 426.1591.

***N*-Phenyl-1,2,3,6-tetrahydro-4-(diphenylphosphinyl)phthalimide (11c).** Equimolar amounts of **4** (0.25 g, 1 mmol) and *N*-phenylmaleimide (**10c**) (0.17 g, 1 mmol) in benzene (5 mL) were reacted in a sealed tube at 150 °C for 6 h. After removal of the solvent in vacuo, the residue was crystallized from ether to give pure **11c**: 325 mg (0.76 mmol, 76%); mp 174.5–176 °C; IR (KBr) 1710, 1615, 1190 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40–3.40 (br m, 6 H, CH_2 and CH), 6.80–7.80 (br m, 16 H, phenyl H and olefinic H); MS, calcd for $C_{26}H_{22}NO_3P$ m/e 427.1336, found 427.1325.

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Registry No. $1^+ClO_4^-$, 86046-71-1; 1^+Br^-, 86046-87-9; **2**, 86046-73-3; **3a**, 86046-74-4; **3b**, 86046-75-5; **4**, 86046-76-6; **5a**, 86046-77-7; **5b**, 86046-78-8; **6a**, 86046-79-9; **6b**, 86046-80-2; **7**, 86046-81-3; **8**, 86046-82-4; **9**, 86046-83-5; **10c**, 941-69-5; **11a**, 86046-84-6; **11b**, 86046-85-7; **11c**, 86046-86-8; PhSeBr, 34837-55-3; PhCHO, 100-52-7; diethyl maleate, 141-05-9; diethyl fumarate, 623-91-6; cyclobutyltriphenylphosphonium ylide, 53213-06-2; sodium salicylaldehyde, 3116-83-4.

Supplementary Material Available: The ^{13}C NMR data (Table II) for compounds **2**, **4**, **13**, **14**, and **15** (1 page). Ordering information is given on any current masthead page.

Synthesis of 4,5,8-Eicosatrienoic Acids[1]

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The synthesis of (7-(*tert*-butyldimethylsiloxy)hepta-3,4-dien-1-yl)triphenylphosphonium iodide (**1**) is described. The ylide derived from **1** undergoes highly stereoselective Wittig reactions with aliphatic aldehydes to give a series of (7*Z*)-nonadeca-3,4,7-trien-1-ols (**4**) which were transformed into arachidonic acid analogues including (8*Z*,11*Z*,14*Z*)-eicosa-4,5,8,11,14-pentaenoic acid (**9**).

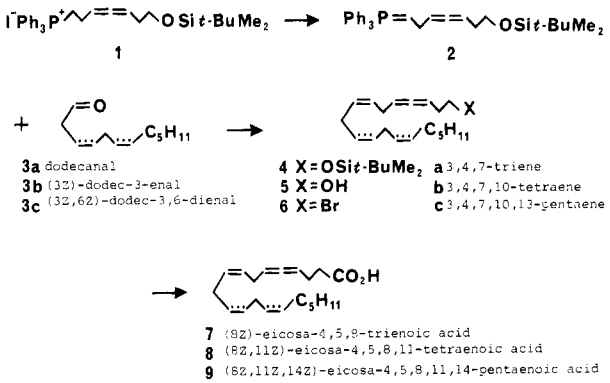
The recent determination of the structure of SRS-A and the discovery of leukotriene B_4 have opened a broad field to chemical investigation with the potential of unraveling the biochemical events in a variety of inflammatory and allergic diseases.[2] An early step in the biogenesis of these compounds was the oxygenation of arachidonic acid to 5-HPETE, catalyzed by a 5-lipoxygenase enzyme.[3] Nearly

(1) Contribution No. 641 from the Institute of Organic Chemistry, Syntex Research.

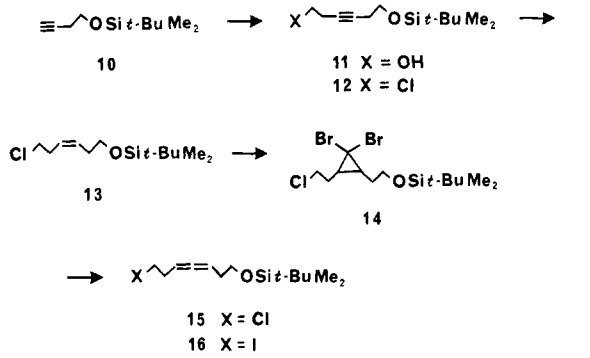
(2) For a recent survey see J. L. Marx, *Science (Washington, D.C.)*, **25**, 1380 (1982).

0022-3263/83/1948-2572$01.50/0

Scheme I



Scheme II

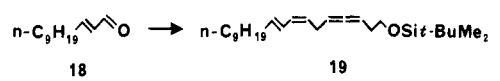


20 years ago Blain and Schearer[4] reported that 5,8,11,14-eicosatetraynoic acid, the acetylenic analogue of arachidonic acid, inhibited soybean 15-lipoxygenase. In recent years much work has centered on the synthesis of similar acetylenic fatty acids, and many of these compounds have been shown to selectively inhibit various lipoxygenases.[5] Several mechanisms, involving the intermediacy of allenes[6,7] or allene hydroperoxides,[8] have been proposed for the inactivation of lipoxygenases by acetylenes. The synthesis of 4,5,8-eicosatrienoic acids described here is an attempt to prepare substrate analogues of arachidonic acid that specifically inhibit 5-lipoxygenase. In this study we have devised a synthesis of the β-allenyl ylide **2** and examined in detail the stereochemistry of the Wittig reactions of **2** with several aldehydes.

The synthesis of these 4,5-allenyl eicosanoic acids, depicted in Scheme I, employs a stereoselective Wittig coupling of the allenyl ylide **2** with the appropriate aldehyde (**3a–c**) resulting in the nonadecanyl silyl ethers **4a–c**. Following conversion of the silyl ethers to the bromides **6a–c**, the carboxyl group was introduced by reaction of the corresponding Grignard reagents with carbon dioxide, yielding the 4,5-allenyleicosanoic acids **7–9**.

The common intermediate in the synthesis of these eicosanoic acids, namely (7-(*tert*-butyldimethylsiloxy)-hepta-3,4-dien-1-yl)triphenylphosphonium iodide (**1**), was prepared by the sequence of reactions shown in Scheme II. Thus, the lithium salt of 3-butyn-1-yl *tert*-butyldimethylsilyl ether (**10**) was alkylated with ethylene oxide to produce 6-hydroxy-3-hexyn-1-yl *tert*-butyldimethylsilyl ether (**11**).[10] This monoprotected diol was converted to the chloride **12** by esterification with methanesulfonyl chloride[11] followed by displacement with lithium chloride. Catalytic reduction of **12** with Lindlar's catalyst[12] gave (3*Z*)-1-chloro-3-hexen-6-yl *tert*-butyldimethylsilyl ether (**13**). This olefin was transformed into the corresponding dibromocyclopropane **14** by reaction with bromoform and potassium hydroxide under phase transfer conditions.[13] Conversion of cyclopropane **14** into 1-chlorohepta-3,4-dien-6-yl *tert*-butyldimethylsilyl ether (**15**) was effected by reaction with *n*-butyllithium.[14] The required phosphonium salt **1** was then prepared from chloride **15** by sequential displacement of the chloride function with iodide and quaternization with triphenylphosphine.

Scheme III



The Wittig reaction of ylide **2** with dodecanal was then investigated to determine if phosphonium salt **1** would form a ylide[15] and to measure the stereoselectivity of the condensation of this ylide with a simple aldehyde. The treatment of the phosphonium iodide **1** with *n*-butyllithium gave a yellow solution of yide **2**, which was diluted with HMPA[16] (hexamethylphosphoramide) and reacted with dodecanal to give (7*Z*)-nonadeca-3,4,7-trien-1-yl *tert*-butyldimethylsilyl ether (**4a**). In agreement with literature precedent[16] the NMR spectrum of **4a** showed the sterochemistry of the newly formed double bond to be cis, and the carbon NMR spectrum had no extraneous peaks.

In order to establish that the Wittig coupling could be accomplished on a β,γ-unsaturated aldehyde, the condensation of ylide **2** with (3*Z*)-dodec-3-enal (**3b**)[9] was examined next. In this instance the Wittig reaction under the conditions described for dodecanal gave three products in the ratio of 4:87:9 by vapor-phase chromatography (VPC). The proton and carbon NMR spectra of this mixture were compatible with the desired structure, (7*Z*,10*Z*)-nonadeca-3,4,7,10-tetraen-1-yl *tert*-butyldimethylsilyl ether (**4b**); however the carbon NMR spectra contained several extraneous absorptions due to an impurity. This impurity, 9% in the product mixture, was thought to be (7*Z*,9*E*)-nonadeca-3,4,7,9-tetraen-1-yl *tert*-butyldimethylsilyl ether (**19**), which arose from condensation of the ylide **2** with a small amount of (2*E*)-dodec-2-enal present in the crude aldehyde obtained from the

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(9) T. Kajiwara, J. Sekiya, Y. Okade, and A. Hatanaka, *Agric. Biol. Chem.*, **41**, 1481 (1977).
(10) Similar to the method used to prepare the mono-THP ether: (a) R. F. Borch, A. J. Evans, and J. J. Wade, *J. Am. Chem. Soc.*, **99**, 1612 (1977). (b) E. J. Corey, H. Niwa, and J. Knolle, *ibid.*, **100**, 1942 (1978).
(11) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).
(12) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).
(13) L. Skattebol, G. A. Abskharoun, and T. Greibrokk, *Tetrahedron Lett.*, 1367 (1973).
(14) (a) W. E. Doering and P. M. La Flame, *Tetrahedron*, **2**, 75 (1958). (b) W. R. Moore and H. R. Ward, *J. Org. Chem.*, **25**, 2073 (1960). (c) L. Skattebol, *Acta Chem. Scand.*, **17**, 1683 (1963).
(15) In view of the ability of 1-butyllithium to deprotonate allenes at −78 °C in preparatively useful yields, it was not obvious that ylide **2** could be generated from the phosphonium salt **1**; see G. Linstrumelle and D. Michelot, *J. Chem. Soc., Chem. Commun.*, 561 (1975), and subsequent papers.
(16) The use of HMPA in the Wittig reaction solvent mixture in this case increases the stereoselectivity from about 85:15 (cis:trans) to essentially pure cis. The use of HMPA for this purpose has been reviewed [R. J. Anderson and C. A. Henrick, *J. Am. Chem. Soc.*, **97**, 4327 (1975)] and has found wide use in leukotriene synthesis, e.g., S. R. Baker, W. B. Jamieson, S. W. McKay, S. E. Morgan, D. M. Rackman, W. J. Ross, and P. R. Schrubsall, *Tetrahedron Lett.*, **21**, 4123 (1980), and E. J. Corey, Y. Arai, and C. Mioskowski, *J. Am. Chem. Soc.*, **101**, 6748 (1979).

Collins oxidation of (3Z)-dodec-3-enol. This was confirmed by the unambituous synthesis of **19** shown in Scheme III.

Propargyl alcohol was converted to its dianion with lithum amide in ammonia–tetrahydrofuran (THF), which was alkylated with 1-bromononane and then reduced in situ with lithium metal to give (2Z)-dodec-2-enol (**17**).[17] Pyridinium chlorochromate (PCC) oxidation of this allylic alcohol gave (2E)-dodec-2-enal (**18**), which was condensed with ylide **2** to give the 3,4,7Z,9E-tetraene **19**. This material was identical with the 9% impurity in the Wittig reaction of (3Z)-dodec-3-enal by VPC and its carbon NMR spectrum coincided with the impurity absorptions in that product mixture. Having established that ylide **2** could be successfully condensed with β,γ-unsaturated aldehydes, the Wittig reaction with (3Z,6Z)-dodeca-3,6-dienal (**3c**) was examined.

Ylide **2** was condensed with (3Z,6Z)-dodeca-3,6-dienal (**3c**)[9] under the same conditions described for dodecanal to give a product with spectral properties in agreement with the desired (7Z,10Z,13Z)-nonadeca-3,4,7,10,13-pentaen-1-yl *tert*-butyldimethylsilyl ether (**4c**), although the carbon NMR spectrum again showed extraneous peaks with intensities of 10–20% of those due to the major product.

To complete the synthesis of the required eicosanoic acids, the silyl ether protecting groups were removed from compounds **4a–c** with tetrabutylammonium fluoride[18] to give alcohols **5a–c**. The alcohols were esterified with methanesulfonyl chloride, and the resulting mesylates reacted with lithium bromide to produce bromides **6a–c**. Conversion of these bromides by reaction with magnesium in THF to the corresponding Grignard reagents and quenching with carbon dioxide gave the desired eicosanoic acids **7**, **8**, and **9**.

Preliminary screening of two of these eicosanoic acids (**7** and **9**) in an assay[19] using intact human polymorpho nuclear leukocytes measuring inhibition of the formation of 5-HETE and LTB_4 has been conducted. Compound **7** had approximately the same inhibitory activity as ETYA toward the formation of LTB_4 and was twice as potent as ETYA toward the formation of 5-HETE. The pentaene **9** was found to be only about half as potent as an inhibitor of LTB_4 formation as ETYA and had little effect on the amount of 5-HETE formed.

Experimental Section

All reactions were run under a dry nitrogen atmosphere with magnetic stirring except where mechanical stirring is specified. THF was purified by distillation from sodium/benzophenone immediately prior to use. Infrared spectra were recored on a Pye Unicam 3-200 spectrometer as neat films unless KBr is specified. The ^1H NMr spectra were recorded in $DCCl_3$ with Me_4Si as an internal standard on a Varian EM 390 spectrometer (90 MHz) or a Bruker WM 300 spectrometer (300 MHz), and ^{13}C NMR spectra were recorded on a Bruker WH-90 spectrometer.

3-Butyn-1-yl *tert*-Butyldimethylsilyl Ether (10). This ether was prepared by the standard procedure[20] from 3-butyn-1-ol in 86% yield: bp 80–83 °C (25 mm); IR 3310 (≡CH) and 2120 cm^{-1} (C≡C); ^1H NMR (90 MHz) δ 3.74 (t, 2, J = 6 Hz, CH_2O), 2.40 (dt, 2, J = 6 and 2 Hz, ≡CCH_2), 1.94 (t, 1, J = 2 Hz, ≡CH), 0.90 (s, 9, *t*-Bu), and 0.07 ppm (s, 6, $SiMe_2$).

Anal. Calcd for $C_{10}H_{20}OSi$: C, 65.15; H, 10.94. Found: C, 65.20; H, 11.03.

6-Hydroxy-3-hexyn-1-yl *tert*-Butyldimethylsilyl Ether (11). A suspension of lithium amide in NH_3 (liquid) was prepared by slow addition of 2.36 g (340 mmol) of lithium wire to 1 L of NH_3 (liquid) and 0.05 g of ferric nitrate in a 3-L three-necked flask equipped with a mechanical stirrer, a dry ice condenser, and a KOH drying tube. A solution of 46.1 g (350 mmol) of acetylene **10** in 500 mL of THF was added over 45 min, and the reaction mixture was refluxed for another 60 min. Liquified ethylene oxide (75 mL, 1500 mmol) was added, and the reaction vessel was wrapped in Styrofoam while the ammonia evaporated over a 14 h period. The resulting residue was poured onto 1 L of ice and extracted with ether (2 × 500 mL). The ethereal extracts were washed with brine, dried over K_2CO_3, evaporated, and distilled through a short-path apparatus to yield 30.13 g (53%) of **11**: bp 100–150 °C (0.8 mm); IR 3450 (OH) and 2180 cm^{-1} (C≡C); ^1H NMR (90 MHz) δ 3.8–3.5 (m, 4, CH_2O), 2.5–2.25 (m, 4, CH_2C≡), 1.95 (s, 1, OH), 0.90 (s, 9, *t*-Bu), and 0.07 ppm (s, 6, $SiMe_2$).

Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 63.10; H, 10.59. Found: C, 63.07; H, 10.62.

6-Chloro-3-hexyn-1-yl *tert*-Butyldimethylsilyl Ether (12). A solution of 20.7 (91 mmol) g of alcohol **11** in 200 mL of CH_2Cl_2 and 21 mL (150 mmol) of triethylamine was cooled to −20 °C and treated with 8 mL (104 mmol) of methanesulfonyl chloride over 30 min. After being stirred another 15 min at −20 °C, the reaction mixture was washed with water and brine, dried over K_2CO_3, and concentrated. This crude mesylated was added to a solution of 15.2 g of LiCl in 120 mL of dimethylformamide (DMF) and stirred at ambient temperature for 48 h. The reaction mixture was then extracted with hexane (3 × 100 mL), and the extracts were washed with water, dried over K_2CO_3, concentrated, and chromatographed on 300 g of silica gel. Elution with 2% ether/hexane and distillation of the principal product gave 11.2 g (50%) of **12**: bp 75 °C (0.4 mm); IR 2180 cm^{-1} (C≡C); ^1H NMR (90 MHz) δ 3.77 (t, 2, J = 6 Hz, OCH_2), 3.61 (t, 2, J = 7 Hz, $ClCH_2$), 2.75–2.25 (m, 4, ≡CCH_2), 0.90 (s, 9, *t*-Bu), and 0.07 ppm (s, 6, $SiMe_2$).

Anal. Calcd for $C_{12}H_{33}ClOSi$: C, 58.39; H, 9.39. Found: C, 58.48; H, 9.40.

(3Z)-6-Chloro-3-hexen-1-yl *tert*-Butyldimethylsilyl Ether (13). The chloroacetylene **12** (11.2 g, 45 mmol) in 120 mL of ethanol was treated with 0.3 g of Lindlar catalyst and 3 drops of quinoline and hydrogenated at 1 atm until 935 mL (43.5 mmol) of hydrogen was absorbed. The catalyst was removed by filtration through Celite, and the filtrate was concentrated and distilled to give 10.2 g (91%) of olefin **13**: bp 75 °C (0.4 mm); IR 3020 cm^{-1} (vinyl CH); ^1H NMR (90 MHz) δ 5.50 (m, 2, =CH), 3.62 (t, 2, J = 7 Hz, OCH_2), 3.50 (t, 2, J = 7 Hz, $ClCH_2$), 2.52 (m, 2, =CCH_2), 2.28 (m, 2, =CCH_2), 0.90 (s, 9, *t*-Bu), and 0.07 ppm (s, 6, $SiMe_2$).

Anal. Calcd for $C_{12}H_{25}ClOSi$: C, 57.91; H, 10.13. Found: C, 58.21; H, 10.44.

***cis*-2-(2-Chloroethyl)-1,1-dibromo-3-(2-(*tert*-butyldimethylsiloxy)ethyl)cyclopropane (14).** A mixture of 6 mL (69 mmol) of bromoform and 2 mL of 50% KOH was placed in a 250-mL three-necked flask equipped with a mechanical stirrer. Olefin **13** (16.5 g, 66 mmol) was added in one portion and followed by dropwise addition of 100 mL (890 mmol) of 50% KOH over 4 h and addition of 0.1-g portions of n-Bu_4NBr every hour. At the end of this period 18 mL (206 mmol) of $HCBr_3$ was added over 30 min and the reaction mixture was stirred another 3 h. The reaction mixture was treated with 200 mL of ether, 800 mL of hexane, and 500 mL of water and filtered through glass wool. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over K_2CO_3, and evaporated. A small amount (3 g) of unreacted **13** was removed by distillation through a short-path apparatus. The residue was then distilled in a Kugelrohr to give 21.14 g (76%) of dibromide **14**: bp 100–105 °C (0.01 mm); ^1H NMR (90 MHz) δ 3.78 (t, 2, J = 6 Hz, OCH_2), 3.67 (t, 2, J = 6 Hz, $ClCH_2$), 1.5–2.0 (m, 6, CH_2 and CH), 0.90 (s, 9, *t*-Bu), and 0.10 ppm (s, 6, $SiMe_2$).

Anal. Calcd for $C_{13}H_{25}Br_2ClOSi$: C, 37.12; H, 5.99. Found: C, 37.32; H, 5.72.

7-Chlorohepta-3,4-dien-1-yl *tert*-Butyldimethylsilyl Ether (15). A solution of dibromocyclopropane **14** (21.14 g, 50 mmol)

(17) This one pot alkylation–reduction of acetylenic alcohols is a convenient alternative to the usual two-step procedure (alkylation followed by $LiAlH_4$ reduction of the isolated propargylic alcohol) for the synthesis of a variety of hydroxy trans olefins and will be the subject of another note.

(18) E. J. Corey and B. B. Snider, *J. Am. Chem. Soc.*, **94**, 2549 (1972).

(19) For a detailed description of this assay method, see Jurg R. Pfister and D. V. Krishna Murthy, *J. Med. Chem.*, submitted for publication.

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in 80 mL of ether was cooled to −70 °C in a three-necked flask equipped with a mechanical stirrer and treated with 33.4 mL (50 mmol) of 1.5 N *n*-butyllithium over 25 min. The reaction mixture was stirred at −70 °C for another 60 min and then poured into ice water and extracted with ether. The ethereal solution was washed with brine, dried over K_2CO_3, and concentrated and the residue distilled to give 11.02 g (84%) of allene **15**: bp 80 °C (0.5 mm); IR 1960 cm^{-1} (C=C=C); ^1H NMR (300 MHz) δ 5.23–5.07 (m, 2, =CH), 3.67 (t, 2, *J* = 7 Hz, OCH_2), 3.56 (t, 2, *J* = 7 Hz, $ClCH_2$), 2.45 (ddt, 2, *J* = 7, 7, and 3Hz, $=CCH_2$), 2.23 (ddt, 2, *J* = 7, 7, and 3 Hz, $=CCH_2$), 0.89 (s, 9, *t*-Bu), and 0.06 ppm (s, 6, $SiMe_2$).

Anal. Calcd for $C_{13}H_{25}ClOSi$: C, 59.85; H, 9.66. Found: C, 59.91; H, 9.67.

7-Iodohepta-3,4-dien-1-yl *tert*-Butyldimethylsilyl Ether (16). A solution of chloride **15** (6.8 g, 26 mmol) in 30 mL of acetone was treated with 9.3 g (62 mmol) of NaI and refluxed 24 h. The reaction mixture was poured into ice water and extracted with ether. The ethereal solution was washed with brine, dried over K_2CO_3, concentrated, and chromatographed on 400 g of silica gel eluting with 1–5% ether/hexane to give 9.1 g (98%) of iodide **16**: IR 1960 cm^{-1} (C=C=C); ^1H NMR (300 MHz) δ 5.11 (m, 1, =CH), 5.03 (m, 1, =CH), 3.61 (t, 2, *J* = 6 Hz, OCH_2), 3.13 (t, 2, *J* = 7 Hz, ICH_2), 2.47 (ddt, 2, *J* = 7, 7, and 3 Hz, $=CCH_2$), 2.17 (ddt, 2, *J* = 7, 7, and 3 Hz, $=CCH_2$), 0.90 (s, 9, *t*-Bu), and 0.07 ppm (s, 6, $SiMe_2$).

Anal. Calcd for $C_{13}H_{25}IOSi$: C, 44.32; H, 7.15. Found: C, 44.36; H, 7.18.

(7-(*tert*-Butyldimethylsiloxy)hepta-3,4-dien-1-yl)triphenylphosphonium Iodide (1). A mixture of iodide **16** (8.9 g, 24 mmol), 8 g (30 mmol) of Ph_3P, and 50 mL of acetonitrile was refluxed for 3 h. The solvent was evaporated and the residue crystallized from ethyl acetate/ether to give 10.4 g (70%) of **1**: mp 65–72 °C; IR (KBr) 1960 cm^{-1} (C=C=C); ^1H NMR (300 MHz) δ 7.7–7.9 (m, 15, Ar H), 5.37 (m, 1, =CH), 5.16 (m, 1, =CH), 3.7 (m, 2, PCH_2), 3.59 (t, 2, *J* = 7 Hz, OCH_2),2.50 (m, 2, $=CCH_2$), 2.17 (m, 2, $=CCH_2$), 0.90 (s, 9, *t*-Bu), and 0.06 ppm (s, 6, $SiMe_2$).

Anal. Calcd for $C_{31}H_{40}IOPSi$: C, 60.58; H, 6.56. Found: C, 60.26; H, 6.63.

(7*Z*)-Nonadeca-3,4,7-trien-1-yl *tert*-Butyldimethylsilyl Ether (4a). A solution of phosphonium salt **1** (1.86 g, 3 mmol) in 40 mL of THF was cooled to −70 °C and treated with 2.2 mL (3.3 mmol) of 1.5 N *n*-butyllithium. After stirring at −70 °C for 1 h, 3 mL of HMPA in 6 mL of THF was added to the reaction mixture followed after 3 min by 0.64 g (3.5 mmol) of dodecanal in 6 mL of THF. The reaction mixture was stirred at −70 °C for 15 min and then allowed to warm to −20 °C at which time it was poured into aqueous $NaHCO_3$ and extracted with ether. The ethereal solution was washed with brine, dried over K_2CO_3, concentrated, and chromatographed on 40 g of silica gel eluting with 10% ether/hexane to give 1.10 g (93%) of triene **4a**: bp 110 °C (0.02 mm); IR 3020 (=CH) and 1960 cm^{-1} (C=C=C); ^1H NMR (300 MHz) δ 5.42 (m, 2, H-7,8), 5.10 (m, 2, H-3,5), 3.66 (t, 2, *J* = 7 Hz, H-1), 2.74 (m, 2, H-6), 2.10 (ddt, 2, *J* = 7, 7, and 3 Hz, H-2), 2.03 (dt, 2, *J* = 6 and 6 Hz, H-9), 1.27 (m, 18, CH_2), 0.90 (m, 12, *t*-Bu and H-19), and 0.06 ppm (s, 6, $SiMe_2$). Decoupling H-6 at δ 2.74 reduced the high-field side of the H-7,8 multiplet to a doublet at 5.38 ppm with *J* = 10 Hz, and decoupling H-9 at 2.03 ppm reduced the low-field side to a doublet at 5.44 with *J* = 10 Hjz. ^{13}C NMR δ 204.87, 131.04, 127.21, 89.92, 88.23, 63.13, 32.74, 31.99, 29.71, 29.39, 27.31, 26.92, 25.97 22.76, 18.37, 14.14, and −5.23 ppm.

Anal. Calcd for $C_{25}H_{48}OSi$: C, 76.46; H, 12.32. Found: C, 76.32; H, 12.09.

(7*Z*,10*Z*)-Nonadeca-3,4,7,10-tetraen-1-yl *tert*-Butyldimethylsilyl Ether (4b). This compound was synthesized from (3*Z*)-dodec-3-enal in a reaction analogous to the preparation of triene **4a** in 41% yield: bp 120 °C (0.015 mm); ^1H NMR (300 MHz) δ 5.38 (m, 4, =CH), 5.10 (m, 2, H-3,5), 3.66 (t, 2, *J* = 7 Hz, H-1), 2.77 (m, 4, H-6,9), 2.21 (ddt, 2, *J* = 7, 7, and 3 Hz, H-2), 2.05 (dt, 2, *J* = 6 and 6 Hz, H-12), 1.28 (m, 12, CH_2), 0.90 (m, 12, *t*-Bu and H-19) and 0.06 ppm (s, 6, $SiMe_2$); ^{13}C NMR δ 204.73, 130.47, 129.04, 127.58, 127.39, 89.60, 88.28, 63.03, 32.68, 31.91, 29.67, 29.53, 29.32, 27.27, 26.90, 25.95, 25.68, 22.69, 18.36, 14,09, and −5.24 ppm. Smaller absorptions at δ 135.58, 129.44, 126.76, and 125.38 ppm indicated the presence of **19**.

Anal. Calcd for $C_{25}H_{46}OSi$: C, 76.85; H, 11.87. Found: C, 77.14; H, 11.73.

(7*Z*,10*Z*,13*Z*)-Nonadeca-3,4,7,10,13-pentaen-1-yl *tert*-Butyldimethylsilyl Ether (4c). This pentaene was prepared from (3*Z*,6*Z*)-dodec-3,6-dienal by the procedure used in the preparation of triene **4a** in 48% yield: bp 120 °C (0.01 mm); IR 3020 (=CH) and 1960 cm^{-1} (C=C=C); ^1H NMR (300 MHz) δ 5.4 (m, 6, =CH), 5.11 (m, 2, H-3,5), 3.66 (t, 2, *J* = 7 Hz, H-1), 2.8 (m, 6, H-6,9,12), 2.21 (ddt, 2, *J* = 7, 7, and 3 Hz, H-2), 2.04 (m, 2, H-14), 1.30 (m, 6, CH_2), 0.90 (m, 12, *t*-Bu and H-19), and 0.06 ppm (s, 6, $SiMe_2$).

Anal. Calcd for $C_{25}H_{44}OSi$: C, 77.25; H, 11.41. Found: C, 77.37; H, 11.76.

(7*Z*)-Nonadeca-3,4,7-trien-1-ol (5a). A solution of silyl ether **4a** (1.05 g, 2.6 mmol) in 9 mL of THF was treated with 8 mL of 1 N n-Bu_4NF/THF for 1 h at 23 °C. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with brine, dried over K_2CO_3, and concentrated, and the resulting residue was distilled to give 0.67 g (87%) of alcohol **5a**: bp 125–30 °C (0.02 mm); IR 3320 (OH) and 1960 cm^{-1} (C=C=C); ^1H NMR (300 MHz) δ 5.45 (m, 2, H-7,8), 5.16 (m, 2, H-3,5), 3.70 (br t, 2, *J* = 6 Hz, H-1), 2.75 (ddd, 2, *J* = 6, 6, and 3.5 Hz, H-6), 2.26 (ddt, 2, *J* = 7, 7, and 3 Hz, H-2), 2.04 (dt, 2, *J* = 6 and 6 Hz, H-9), 1.3 (m, 18, CH_2), and 0.88 ppm (t, 3, *J* = 7 Hz, H-19).

Anal. Calcd for $C_{19}H_{34}O$: C, 81.95; H, 12.31. Found: C, 81.86; H, 12.13.

Alcohols **5b** and **5c** were similarly prepared from **4b** and **4c**:

(7*Z*,10*Z*)-Nonadeca-3,4,7,10-tetraen-1-ol (5b): 95% yield; IR 3340 and 1960 cm^{-1}; ^1H NMR (300 MHz) δ 5.4 (m, 4, =CH), 5.17 (m, 2, H-3,5), 3.68 (t, 2, *J* = 7 Hz, H-1), 2.8 (m, 4, H-6,9), 2.25 (ddt, 2, *J* = 7, 7, and 3 Hz, H-2), 2.04 (dt, 2, *J* = 6 and 6 Hz, H-12), 1.27 (m, 12, CH_2), and 0.88 ppm (t, 3, *J* = 7 Hz, H-19).

Anal. Calcd for $C_{19}H_{32}O$: C, 82.55; H, 11.67. Found: C, 82.56; H, 11.88.

(7*Z*,10*Z*,13*Z*)-Nonadeca-3,4,7,10,13-pentaen-1-ol (5c): 90% yield; IR 3440 and 1960 cm^{-1}; ^1H NMR (300 MHz) δ 5.4 (m, 6, H-7,8,10,11,13,14), 5.18 (m, 2, H-3,5), 3.69 (t, 2, *J* = 7 Hz, H-1), 2.8 (m, 6, H-6,9,12), 2.26 (ddt, 2, *J* = 7, 7, and 3 Hz, H-2), 2.06 (dt, 2, *J* = 6 and 6 Hz, H-15), 1.3 (m, 6H, CH_2), and 0.89 ppm (t, 2, *J* = 6 Hz, H-19).

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.17; H, 11.07.

(7*Z*)-1-Bromononadeca-3,4,7-triene (6a). A solution of 0.55 g (2 mmol) of trienol **5a** in 30 mL of CH_2Cl_2 and 1 mL (7 mmol) of Et_3N was cooled to −20 °C and treated with 0.6 mL (7 mmol) of methanesulfonyl chloride. After stirring 20 min at −20 °C, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic solution was washed with brine, dried over K_2CO_3, and concentrated. The resulting mesylate was added to a solution of 4.7 g (54 mmol) of LiBr in 20 mL of acetone. This reaction mixture was refluxed for 15 min, cooled, diluted with ice water, and extracted with ether. The ethereal solution was washed with brine, dried over K_2CO_3, and concentrated to give a residue which on distillation gave 0.502 g (74%) of bromide **6a**: bp 120 °C (0.01 mm); IR 3020 (=CH) and 1960 cm^{-1} (C=C=C); ^1H NMR (300 MHz) δ 5.4 (m, 2, H-7,8), 5.16 (m, 2, H-3,5), 3.41 (t, 2, *J* = 7 Hz, H-1), 2.75 (m, 2, H-6), 2.55 (m, 2, H-2), 2.03 (dt, 2, *J* = 6 and 6 Hz, H-9), 1.3 (m, 18, CH_2), and 0.88 ppm (t, 3, *J* = 7 Hz, H-19).

Anal. Calcd for $C_{19}H_{33}Br$: C, 66.85; H, 9.74. Found: C, 66.69; H, 9.79.

Bromides **6b** and **6c** were similarly prepared from **5b** and **5c**.

(7*Z*,10*Z*)-1-Bromononadeca-3,4,7,10-tetraene (6b): 70% yield; bp 120 °C (0.01 mm); IR 3020 and 1960 cm^{-1}; ^1H NMR (300 MHz) δ 5.4 (7, 4, H-7,8,10,11), 5.17 (m, 2, H-3,5), 3.41 (t, 2, *J* = 7 Hz, H-1), 2.8 (m, 4, H-6,9), 2.55 (m, 2, H-2), 2.05 (dt, 2, *J* = 6 and 6 Hz, H-12), 1.3 (m, 12, CH_2), and 0.88 ppm (t, 2, *J* = 7 Hz, H-19).

Anal. Calcd for $C_{19}H_{31}Br$: C, 67.24, H, 9.21. Found: C, 67.43; H, 8.89.

(7*Z*,10*Z*,13*Z*)-1-Bromononadeca-3,4,7,10,13-pentaene (6c): 54 yield; bp 120 °C (0.01 mm); ^1H NMR (300 MHz) δ 5.4 (m, 6, H-7,8,10,11,13,14), 5.18 (m, 2, H-3,5), 3.41 (6, 2, *J* = 7 Hz, H-1), 2.8 (m, 6, H-6,9,12), 2.54 (m, 2, H-2), 2.07 (dt, 2, *J* = 6 and 6 Hz, H-15), 1.3 (m, 6, CH_2), and 0.90 ppm (t, 3, *J* = 6 Hz, H-19).

Anal. Calcd for $C_{19}H_{29}Br$: C, 67.65; H, 8.65. Found: C, 67.78; H, 8.97.

(8Z)-Eicosa-4,5,8-trienoic Acid (7). A mixture of 0.60 g (25 mmol) of magnesium turnings in 15 mL of THF was treated with 1.0 mL (13 mmol) of ethyl bromide and briefly refluxed to initiate the Grignard reaction. The mixture was cooled to room temperature and 0.487 g (1.4 mmol) of bromide **6a** in 3 mL of THF was added. The mixture was refluxed for 15 min, cooled, and poured into a slurry of 100 g of CO_2 (s) and 100 mL of ether. When the CO_2 had evaporated, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ether. The organic solution was washed with brine, dried over Na_2SO_4, concentrated, and chromatographed on 40 g of silica gel, eluting with 10% ether/hexane to give 0.083 g (19%) of acid **7**: IR 1960 (C=C=C) and 1710 cm^{-1} (C=O); ^1H NMR (300 MHz) δ 5.4 (m, 2, H-8,9), 5.16 (m, 2, H-4,6), 2.73 (m, 2, H-7), 2.47 (t, 2, J = 7 Hz, H-2), 2.32 (m, 2, H-3), 2.02 (dt, 2, J = 6 and 6 Hz, H-10), 1.3 (m, 18, CH_2), and 0.88 ppm (t, 3, J = 6 Hz, H-20).

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.44;, H, 11.01.

Carboxylic acids **8** and **9** were prepared in the same manner from bromides **6b** and **6c**.

(8Z,11Z)-Eicosa-4,5,8,11-tetraenoic acid (8): 10% yield; IR 1960 and 1710 cm^{-1}; ^1H NMR (300 MHz) δ 5.4 (m, 4, H-8,9,11,12), 5.19 (m, 2, H-4,6), 2.78 (m, 4, H-7,10), 2.47 (t, 2, J = 7 Hz, H-2), 2.32 (m, 2, H-3), 2.05 (dt, 2, J = 6 and 6 Hz, H-13), 1.3 (m, 12, CH_2), and 0.89 ppm (t, 3, J = 6 Hz, H-20).

Anal. Calcd for $C_{20}H_{32}O$: C, 78.90; H, 10.59. Found: C, 78.61; H, 10.38.

(8Z,11Z,14Z)-Eicosa-4,5,8,11,14-pentaenoic acid (9): 35% yield; IR 1960 and 1710 cm^{-1}; ^1H NMR (300 MHz) δ 5.4 (m, 6, H-8,9,11,12,14,15), 5.20 (m, 2, H-4,6), 2.8 (m, 6, H-7,10,13), 2.47 (t, 2, J = 7 Hz, H-2), 2.32 (m, 2, H-3), 2.05 (dt, 2, J = 6 and 6 Hz, H-16), 1.3 (m, 6, CH_2), and 0.90 ppm (t, 3, J = 7 Hz, H-20).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.58; H, 10.32.

(2E)-Dodec-2-en-1-ol (17). To a mixture of 1 L of NH_3 (liquid) and 0.3 g of ferric nitrate in a 3 L three-necked flask equipped with a dry ice condenser, KOH drying tube, and mechanical stirrer was added 3.1 g of lithium wire in small portions, allowing the blue color to discharge between additions. A solution of 10 mL of propargyl alcohol in 250 mL of THF was added over 30 min, and the reaction mixture was allowed to reflux 1 h. Then 20 mL of 1-bromononane in 200 mL of THF was added over 30 min, and the reaction mixture was allowed to reflux 1 h. At the end of this period 2.1 g of lithium wire was added in portions that resulted in a persistent dark blue color. After 10 min NH_4Cl was added to discharge the blue color and the NH_3 was evaporated with a stream of N_2. The residue was poured onto 1 L of ice, and the resulting mixture was saturated with NaCl and extracted with ether (3 × 400 mL). The extracts were dried over K_2CO_3, concentrated, and distilled to give 15.33 g (89%) of alcohol **17**: bp 95-97 °C (0.8 mm); IR 3400 cm^{-1}; ^1H NMR (90 MHz) δ 5.66 (m, 2, =CH), 4.1 (d, 2, J = 5 Hz, OCH_2), 2.05 (m, 2, =CCH_2), 2.30 (m, 14, CH_2), and 0.9 ppm (t, 3, J = 6 Hz, CH_3).

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.34; H, 12.90.

(2E)-Dodec-2-enal (18). This aldehyde was prepared from alcohol **18** by PCC oxidation[21] (74%): bp 85 °C (0.4 mm); IR 1685 cm^{-1} (C=O); ^1H NMr (300 MHz) δ 9.50 (d, 1, J = 8 Hz, CHO), 6.84 (dt, 1, J = 17 and 6 Hz, =$CHCH_2$), 6.08 (ddt, 1, J = 17, 8, and 1.5 Hz, =C*H*CHO), 2.33 (m, 2, =CCH_2), 1.25 (m, 14, CH_2), and 0.85 ppm (t, 3, J = 6 Hz, CH_3).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.09; H, 11.97.

(7Z,9E)-Nonadeca-3,4,7,9-tetraen-1-yl *tert*-Butyldimethylsilyl Ether (19). The Wittig reaction between aldehyde **18** and the ylide derived from phosphonium salt **1** under the conditions for the preparation of **4a** gave the tetraene **19** in 62% yield: bp 120 °C (0.02 mm); IR 3020 (=CH) and 1960 cm^{-1} (C=C=C); UV 236 nm (E 25,000); ^1H NMR (300 MHz) δ 6.28 (dd, 1, J = 16 and 10 Hz, H-9), 5.99 (dd, 1, J = 10 and 10 Hz, H-8), 5.68 (dt, 1, J = 16 and 7 Hz, H-10), 5.30 (dt, 1, J = 11 and 8 Hz, H-7), 5.11 (m, 2, H-3,5), 3.66 (t, 2, J = 7 Hz, H-1), 2.86 (m, 2, H-6), 2.20 (ddt, 2, J = 7, 7, and 3.5 Hz, H-3), 2.10 (dt, 2, J = 7 and 7 Hz, H-11), 1.4-1.2 (m, 14, CH_2), 0.90 (m, 12, *t*-Bu and H-19), and 0.06 ppm (s, 6, $SiMe_2$); ^{13}C NMR δ 204.75, 135.59, 129.42, 126.73, 125.35, 89.56, 88.37, 63.00, 32.92, 32.65, 31.91, 29.58, 29.53, 29.38, 29.34, 29.28, 27.30, 25.95, 22.69, 18.36, 14.12, and -5.24 ppm.

Anal. Calcd for $C_{25}H_{46}OSi$: C, 76.85; H, 11.87. Found: C, 77.02; H, 11.75.

Registry No. 1, 86118-22-1; **2**, 86118-23-2; **3a**, 112-54-9; **3b**, 68141-15-1; **3c**, 13553-09-8; **4a**, 86118-24-3; **4b**, 86118-25-4; **4c**, 86118-26-5; **5a**, 86118-27-6; **5b**, 86118-28-7; **5c**, 86118-29-8; **6a**, 86118-30-1; **6b**, 86118-31-2; **6c**, 86118-32-3; **7**, 86118-33-4; **8**, 86118-34-5; **9**, 85654-39-3; **10**, 78592-82-2; **11**, 86118-35-6; **12**, 86118-36-7; **13**, 86118-37-8; **14**, 86118-38-9; **15**, 86118-39-0; **16**, 86118-40-3; **17**, 69064-36-4; **18**, 20407-84-5; **19**, 86118-41-4; methanesulfonyl chloride, 124-63-0; arachidonate lipoxygenase, 63551-74-6.

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New Trichoverroids from *Myrothecium verrucaria*: Verrol and 12,13-Deoxytrichodermadiene

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Two new naturally occurring trichothecenes have been isolated as minor metabolites from a culture of *Myrothecium verrucaria*. The metabolites verrol, previously obtained only as a hydrolysis product, and 12,13-deoxytrichodermadiene were characterized by NMR and mass spectral data. The latter compound is only the second trichothecene reported to be lacking the 12,13-epoxy functional group.

The trichothecene group of antibiotics has attracted a good deal of attention in recent years due principally to the high degree of biological activity associated with these potent mycotoxins.[1] During the course of the workup of