generated dipole **2** reacts with excess thiophenol to give carbanion **9** which then undergoes conjugate addition to the activated acetylene. Further support for this proposal will be presented in our full manuscript.

Acknowledgment. The authors at Emory thank the NIH for its generous support of this research. The authors at Columbia thank the Air Force Office of Scientific Research for its generous support of this research. Both research groups thank NSF for their generous support of this research.

Registry No. 1, 92925-16-1; 2, 98587-57-6; 7, 3168-85-2; 8, 40611-76-5; CH_2N_2, 334-88-3; MeOC(O)C≡CC(O)OMe, 762-42-5; PhCHO, 100-52-7; CH_3CN, 75-05-8; $Me_3SiCH_2OSO_2CF_3$, 64035-64-9; PhSH, 108-98-5; (*E*)-PhSCH=CHC(O)OMe, 49833-37-6; (*Z*)-PhSCH=CHC(O)OMe, 49833-38-7; (*Z*)-MeOC(O)CH=C(SPh)C(O)OMe, 59790-38-4; (*E*)-MeOC(O)CH=C(SPh)C(O)OMe, 59790-39-5; $CH_3C(O)NHCH_2CH(OH)Ph$, 3306-05-6; $NH_2CH_2CH(Ph)OH$, 7568-93-6; $CH_3C(OEt)_3$, 78-39-7; HCHO, 50-00-0; 3*H*-diazirine, 157-22-2; fumaronitrile, 764-42-1; acrylonitrile, 107-13-1; methyl acrylate, 96-33-3; methyl propiolate, 922-67-8; dimethyl fumarate, 624-49-7; *N*-[(trimethylsilyl)methyl]acetonitrilium triflate, 98587-59-8; *N*-benzyl-3-carbomethoxy-2-methyl-1*H*-pyrrole, 87281-49-0; 2-methyl-4-carbethoxy-1*H*-pyrrole, 2199-50-0; 2-methyl-3,4-dicarbomethoxy-1*H*-pyrrole, 90610-59-6; 4,5-dihydro-2-methyl-5-phenyloxazole, 66614-71-9; 2,5-dihydro-4-methyl-5-phenyloxazole, 98587-60-1; 4-methyl-5-phenyloxazolidine, 42794-92-3; (±)-norephedrine, 14838-15-4.

Supplementary Material Available: Experimental details of preparation and reaction of silylthioimidate **1** (8 pages). Ordering information is given on any current masthead page.

Nicholas J. Turro,* Yuan Cha, Ian R. Gould
Department of Chemistry
Columbia University
New York, New York 10027

Albert Padwa,* John R. Gasdaska, Miguel Tomas
Department of Chemistry
Emory University
Atlanta, Georgia 30322

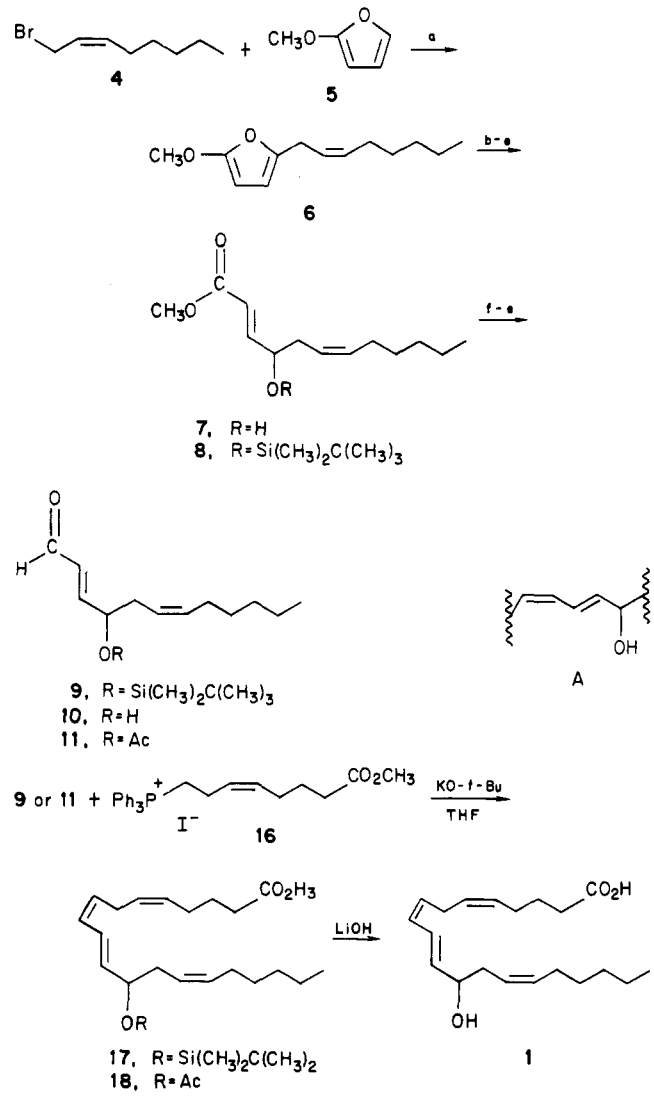
Received July 16, 1985

Total Synthesis of (±)-12-Hydroxy-5(*Z*),8(*Z*),-10(*E*),14(*Z*)-eicosatetraenoic Acid (12-HETE)

Summary: A total synthesis of 12-HETE is reported which incorporates an oxidative cleavage of an appropriately substituted furan to provide a functionalized *trans*-allylhydroxy fragment which is subsequently elaborated in an operationally simple manner affording a practical preparation of 12-HETE.

Sir: The monohydroxyeicosatetraenoic acids (HETEs) have been the focus of intense investigation due to the interesting and varied biological activities they exhibit. In particular, 12-HETE (**1**) is the major lipoxygenase product found in human platelets[1] and has been demonstrated to be present in high levels in epidermal tissue of patients with psoriasis.[2] In connection with an ongoing effort in our laboratories to study the lipoxygenase enzymes, a ready supply to the various HETEs was required. Synthetic studies of the various HETEs have been reported.[3] An efficient practical synthesis of 5-HETE[4] and an enzymatic preparation of 15-HETE[5] provide convenient access to these important natural products. Our interest in securing significant quantities of 12-HETE led us to explore alternative synthetic approaches. The total synthesis of 12-HETE (**1**), reported herein, illustrates a general and

Scheme I[a]



[a] (a) *t*-BuLi (1.1 equiv), THF, **4** (1 equiv), −50 °C, 1 h, 73%; (b) bipyridinium chlorochromate (5 equiv), CH_2Cl_2, room temperature, 2.5 h; (c) I_2 (0.15 equiv), ether, room temperature, 4 h; (d) $NaBH_4$ (1 equiv), MeOH, 0 °C, 15 min; (e) TBDMSCl (1.1 equiv), imidazole (2.2 equiv), DMF, 50 °C, 2.5 h, 42% (over four steps); (f) DIBAL (2 equiv), CH_2Cl_2, −78 °C, 5 min; (g) pyridinium chlorochromate (2 equiv), CH_2Cl_2, room temperature, 2.5 h, 57% (over two steps); (h) 48% HF, CH_3CN, 2 h, room temperature, 83%; (i) Ac_2O (2 equiv), pyridine, room temperature, 4 h, 85%.

(1) Hamberg, M.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 3400.
(2) Hammerstrom, S.; Hamberg, M.; Samuelsson, B.; Duell, E. A.; Stawiski, M.; Voorhees, J. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 5130.
(3) 12-HETE: (a) Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942. (b) Corey, E. J.; Kyler, K.; Raju, N. *Tetrahedron Lett.* **1984**, *25*, 5115. (c) Just, G.; Wang, Z. Y. *Ibid.* **1985**, *26*, 2993. 5-HETE: (d) Zamboni, R.; Rokach, J. *Ibid.* **1983**, *24*, 999. (e) Rokach, J., Adams, J., Perry, R. *Ibid.* **1983**, *24*, 5185.
(4) Corey, E. J.; Albright, J. O.; Barton, A. E.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 1435.
(5) Crawford, C. G.; VanAlphen, G. W. H. M.; Cook, H. W.; Lands, W. E. M. *Life Sci.* **1978**, *23*, 1255.

0022-3263/85/1950-4417$01.50/0

practical synthetic scheme to HETEs and analogues thereof.

Our synthetic strategy is centered on the preparation of the *cis-trans*-dienyl allylhydroxy unit A (Scheme I) which is common to all the HETEs. Disconnection of the C8–C9 olefin in **1** provides two convergent fragments, the C9–C20 aldehyde **11**, and the C1–C8 phosphonium salt **16** which could be assembled via Wittig olefination. A flexible and efficient approach to the sensitive C9–C20 fragment **11** was conceived as arising from oxidative cleavage of an appropriately substituted furan **6**.

Synthesis of the C9–C20 fragment **11** is outlined in Scheme I and described as follows.[6] Alkylation[7] of 2-methoxyfuran (**5**)[8] with *cis*-1-bromo-2-octene (**4**)[9] afforded the requisite substituted furan **6**. Initial attempts to oxidatively cleave the furan[10] with pyridinium chlorochromate[11] gave complex product mixtures and a poor yield of the desired product. However, treatment of furan **6** with bipyridinium chlorochromate[12] effected smooth cleavage to a sensitive cis keto ester which was not isolated but directly isomerized to the trans configuration by treatment with a catalytic amount of iodine in ether solution[13] and then directly reduced with sodium borohydride to give the hydroxy ester **7**. The hydroxy group was protected as a *tert*-butyldimethylsilyl ether and the ester group in **8** was reduced with diisobutylaluminum hydride to the corresponding alcohol which was oxidized by pyridinium chlorochromate[14] to the aldehyde **9**.

Synthesis of the C1–C8 phosphonium salt **16** was accomplished by modification of known procedures.[15] The two convergent fragments **9** and **16** were coupled by using potassium *tert*-butoxide in tetrahydrofuran at −78 °C to give **17**. Attempts to cleave the silyl ether to provide 12-HETE methyl ester resulted in low yields and significant amounts of byproducts. A satisfactory solution to this problem was found by deprotecting at an earlier stage in the synthetic sequence. Treatment of aldehyde **9** with aqueous HF in acetonitrile[17] and subsequent acetylation gave the aldehyde **11**. Wittig olefination, as before, gave the desired cis coupling cleanly, providing **18**. The title compound **1**[18] was obtained quantitatively from **18** by treatment with excess LiOH in aqueous isopropyl alcohol. Treatment of **1** with an ether solution of diazomethane gave the corresponding methyl ester which exhibited identical ^{1}H NMR spectral parameters as that reported by Corey and co-workers for 12-HETE methyl ester.[3a]

This total synthesis of (±)-12-HETE (**1**) illustrates a simple and general synthetic approach to HETE syntheses which is operationally simple and amenable to scale-up. The key step in the synthetic strategy involves the oxidative cleavage of an appropriately substituted furan to prepare the requisite functionalized *trans*-allylhydroxy unit which is subsequently reacted in a cis-selective Wittig olefination reaction to complete the carbon skeleton.

Acknowledgment. We express appreciation to Dr. James Summers for helpful discussions and to M. Cirovic, D. Wittern, and R. Stanaszek for their excellent technical assistance in obtaining NMR spectral data.

Supplementary Material Available: Experimental procedures and spectral data are provided (18 pages). Ordering information is given on any current masthead page.

(6) The experimental procedures and spectral data for pertinent compounds isolated and purified en route to 12-HETE and a copy of the 300-MHz ^{1}H NMR of 12-HETE is provided as supplementary material.

(7) For a related alkylation, see: Krause, G. A.; Sugimoto, H. *J. Chem. Soc., Chem. Commun.* **1978**, 30.

(8) Alkylation of furan with **4** proceeded smoothly; however, oxidative cleavage provided the corresponding cis keto aldehyde which was very unstable and difficult to manipulate further.

(9) Synthesis of *cis*-1-bromo-2-octene (**4**) was readily accomplished from 2-octyn-1-ol ((a) Pd/$BaSO_4$, H_2, quinoline poisoning, 90%; (b) PPh_3, Br_2, room temperature, 3 h, 95%).

(10) Oxidative cleavage of substituted furans to provide enediones has been demonstrated, for example, by Williams, P. D.; LeGoff, E. *Tetrahedron Lett.* **1985**, *26*, 1367.

(11) Antonioletti, R.; D'Auria, M.; DeMico, A.; Piancatelli, G.; Sceltri, A. *Synthesis* **1984**, 280.

(12) Guziec, F. S.; Luzzio, F. A. *Synthesis* **1980**, 691.

(13) Hirsch, J. A.; Szur, A. J. *J. Heterocycl. Chem.* **1972**, *9*, 523.

(14) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(15) Alkylation of 5-chloro-1-pentyne with ethylene oxide (*n*-BuLi, BF_3·Et_2O, −78 °C, 1 h, 45%) gave 7-chloro-3-heptyn-1-ol. The following sequence of reactions then provided **16**: (a) NaCN, Me_2SO, 70 °C, 1 h, 93%; (b) EtOH/H_2O 1:1, NaOH, reflux, 18 h, 70%; (c) CH_2N_2, ether, 0 °C, 5 min, 100%; (d) Pd/$BaSO_4$, quinoline poisoning, H_2, 86%; (e) PPh_3, Br_2, CH_2Cl_2, room temperature, 2.5 h; (f) NaI, acetone, reflux, 1 h; (g) PPh_3, CH_3CN, 2.5 days, 80 °C, 80% (over three steps). A similar reaction sequence has been reported by Perchonock, C. D.; Finkelstein, J. A.; Uzinskas, I.; Gleason, J. G.; Sarau, H. M.; Cieslinski, L. B. *Tetrahedron Lett.* **1983**, *24*, 2457.

(16) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(17) Newton, R. F.; Reynolds, D. P.; Finch, M.; Kelly, D.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(18) Spectral data for (±)-12-HETE (**1**): 300-MHz ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.2 Hz, 3 H), 1.15–1.35 (m, 6 H), 1.63 (m, 2 H), 1.95–2.15 (m, 6 H), 2.28 (t, J = 7.2 Hz and m, 4 H), 2.80 (m, 1 H), 2.92 (m, 1 H), 4.23 (q, J = 5.4 Hz, 1 H), 5.20–5.45 (m, 4 H), 5.50 (m, 1 H), 5.65 (dd, J = 7.2, 16.2 Hz, 1 H), 5.91 (t, J = 10.8 Hz, 1 H), 6.53 (dd, J = 10.8, 16.2 Hz, 1 H); 75.5-MHz ^{13}C NMR ($CDCl_3$) 14.01; 22.53, 24.50, 26.18, 26.42, 27.40, 29.24, 31.49, 33.12, 35.24, 72.07, 124.12, 125.50, 127.59, 128.25, 129.26, 130.22, 133.66, 135.19, 177.99.

Bruce P. Gunn,* Dee W. Brooks
Abbott Laboratories
Abbott Park, Illinois 60064
Received May 21, 1985

Total Synthesis of Quadrone and Terrecyclic Acid A[1]

Summary: Syntheses of quadrone (**1**) and terrecyclic acid A (**2a**) are described which feature a Diels–Alder cycloaddition, ring expansion sequence for construction of their complex skeletal core and a nickel-mediated coupling reaction which serves as a preparatively useful enone γ-alkylation method.

Sir: The antitumor activity of the fungal metabolite quadrone (**1**)[2] coupled with its novel structural features and the more recent characterization of its biologically active congeners, terrecyclic acid A (**2a**)[3a] and terrecyclol (**2b**),[3b] have elicited considerable interest in synthetic approaches[4] to this new family of natural products. We describe in this communication syntheses of quadrone (**1**) and terrecyclic acid A (**2a**) which additionally provide general access to other analogues of biological interest in this series.

Our synthetic design for quadrone evolved from a long-standing interest[5] in the development of generic

(1) Presented in part at the 185th National Meeting of the American Chemical Society, March 1983, Seattle, WA. This work was taken, in part, from the Ph.D. dissertation of D. J. Wolanin, Harvard University, Cambridge, MA, 1983.

(2) (a) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, *19*, 499. (b) Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978**, *31*, 38.

(3) (a) Terrecyclic acid A: Hirota, A.; Nakagawa, M.; Sakai, H.; Isogai, A. *J. Antibiot.* **1982**, *35*, 783. (b) Terrecyclol: Nakagawa, M.; Sakai, H.; Isogai, A.; Hirota, A. *Agric. Biol. Chem.* **1984**, *48*, 117.

0022-3263/85/1950-4418$01.50/0