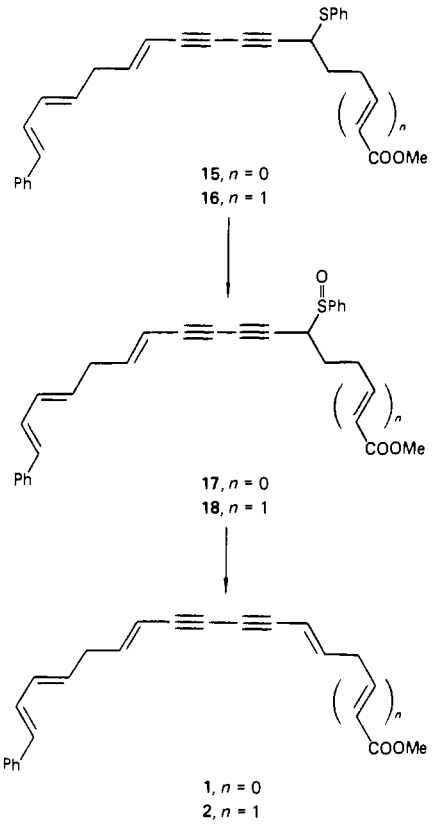
Scheme IV. Synthesis of Acetylenic Precursors 1 and 2



phenylthio-1-propyne (**3**)[6] (1.1 equiv of LDA, THF, −78 °C) with 3-iodo-1-(*tert*-butyldimethylsiloxy)propane ($ICH_2CH_2CH_2OSi$-*t*-$BuMe_2$,[7] 1.0 equiv, mixed with HMPA, 2.0 equiv) to afford the acetylenic compound **4** (90% yield), which was selectively desilylated at the hydroxy function by exposure to AcOH–THF–H_2O (3:2:2) at 40 °C, leading to alcohol **5** (75% yield). Carefully controlled Jones oxidation of **5** (acetone, −10 °C) followed by diazomethane treatment (ether, 0 °C) furnished the methyl ester **6** (75% yield), which upon removal of the trimethylsilyl group (1.1 equiv of KF, 0.05 equiv of 18-crown-6, DMF, 25 °C) led to the requisite terminal acetylene **7** in 90% yield. On a different course the alcohol **5** was mildly oxidized (1.3 equiv of CrO_3·pyr·HCl, CH_2Cl_2, 25 °C, 76% yield or 7.0 equiv of SO_3·pyr, 15.0 equiv of Et_3N, Me_2SO, 25 °C, 80%) to the aldehyde **8**, which served as a common intermediate for the production of both building blocks **10** and **14**. Thus, condensation of **8** with $(MeO)_2P(O)CH_2COOMe$–NaH (1.2 equiv of each, THF, 25 °C) afforded the *E* α,β-unsaturated methyl ester **9** (76% yield), from which the terminal acetylene **10** was smoothly generated (92% yield) as in **6** → **7** (vide supra). On the other hand, condensation of **8** with *trans*-$(EtO)_2P(O)CH_2CH{=}CHPh$–LDA (1.1 equiv of each, THF, −78 → 25 °C) furnished stereoselectively[8] compound **11** in 78% yield, which was cleanly oxidized to the sulfoxide **12** (1.1 equiv of *m*-CPBA, CH_2Cl_2, −78 °C, 98% yield mixture of diastereoisomers ca. 1:1 by ^1H NMR). Thermolysis of **12** (toluene, 50 °C) caused smooth syn elimination, leading to a mixture of *E* and *Z* olefins (**13** and isomer, ca. 1:1 by ^1H NMR) in 95% total yield, which were separated either by flash column or preparative layer chromatography (silica, ether–petroleum ether, 1:99, $R_f(E)$ 0.31, $R_f(Z)$ 0.36). Finally, the initially desired *E* isomer **13** was desilylated (1.3 equiv of $AgNO_3$, 6.0 equiv of KCN, EtOH–H_2O, 25 °C), leading to key intermediate **14** in 98% yield. With these key intermediates at hand, we then proceeded to assemble the complete skeletons of **1** and **2** as follows.

Coupling of **14** (1 equiv) with the more plentiful **7** (5 equiv) in pyridine–methanol (1:1) containing $Cu(OAc)_2$ (2.0 equiv) at 25 °C[10] led to the diacetylene **15** (70% yield based on **14**), which was then oxidized at the sulfur as in **11** → **12** (vide supra), affording the sulfoxide **17** (Scheme IV) (90% yield, ca. 1:1 by ^1H NMR). Thermolysis of this sulfoxide proceeded smoothly as in **12** → **13** (vide supra), leading to the desired acetylenic precursor **1** together with its geometrical isomer at the newly generated unsaturated site in 78% total yield (ca. 1:1 by ^1H NMR). Pure **1**[11] was obtained by either flash column or preparative layer chromatography (silica, ether–petroleum ether, 1:9, $R_f(E)$ 0.16, $R_f(Z)$ 0.19). In a parallel fashion and in similar yields **10** and **14** were coupled and elaborated via **16** (72% yield) and **18** (85% yield) to **2**[11] and its geometrical isomer (75% total yield, ca. 1:1 by ^1H NMR, silica, ether–petroleum ether 1:9, $R_f(E)$ 0.11, $R_f(Z)$ 0.13).

With these highly unsaturated substrates (**1** and **2**) secured, the stage was now set for triggering the endiandric acid cascade and thus testing experimentally Black's hypothesis. The results are described in the following communication.[12]

Registry No. 1, isomer 1, 82706-76-1; **1**, isomer 2, 82768-67-0; **2**, isomer 1, 82706-77-2; **2**, isomer 2, 82768-68-1; **3**, 82707-19-5; **4**, 82707-20-8; **5**, 82707-21-9; **6**, 82707-22-0; **7**, 82707-23-1; **8**, 82707-24-2; **9**, 82731-54-2; **10**, 82707-25-3; **11**, 82707-26-4; **12**, isomer 1, 82707-27-5; **12**, isomer 2, 82707-34-4; **13**, isomer 1, 82707-28-6; **13**, isomer 2, 82707-35-5; **14**, 82707-29-7; **15**, 82707-30-0; **16**, 82707-31-1; **17**, isomer 1, 82707-32-2; **17**, isomer 2, 82707-36-6; **18**, isomer 1, 82707-33-3; **18**, isomer 2, 82768-71-6; *trans*-$(EtO)_2P(O)CH_2CH{=}CHPh$, 52378-69-5; $(MeO)_2P(O)CH_2COOMe$, 5927-18-4; 3-iodo-1-(*tert*-butyldimethylsiloxy)propane, 78878-05-4.

Supplementary Material Available: Listing of selected physical properties of key compounds (5 pages). Ordering information is given on any current masthead page.

(6) This compound (**3**) was prepared in 90–95% overall yield from propargyl bromide by sequential treatment with (a) PhSH–DBU, THF, −10 °C; (b) EtMgBr, THF, −78 °C; (c) Me_3SiCl, THF, −78 °C.

(7) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Dolle, R. E., III *J. Am. Chem. Soc.* **1981**, *103*, 6967.

(8) The *E*:*Z* ratio of the newly formed double bond in this reaction is determined to be ≥20 by ^1H NMR spectroscopy.

(9) The *Z* isomer was destined to produce the *Z*,*Z*,*Z*,*Z* conjugated tetraenes II and IV (Scheme I) although this has not been completed as yet.

(10) Eglinton, G.; McCrae, W. *Adv. Org. Chem.* **1963**, *4*, 225.

(11) ^1H NMR, IR, and mass spectroscopic data are recorded in the supplementary material.

(12) This work was financially supported by Merck Sharp and Dohme, the A. P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation.

The Endiandric Acid Cascade. Electrocyclizations in Organic Synthesis. 4. "Biomimetic" Approach to Endiandric Acids A–G. Total Synthesis and Thermal Studies

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In the preceding paper[1] we described the synthesis of suitably designed precursors for the generation of the postulated polyunsaturated pregenetors of endiandric acids. In this communication, we detail the chemical events observed upon triggering the endiandric acid cascade (Scheme I, paper 3 in this series)[1] from these precursors and also describe thermal stability studies on various members of this cascade.

When the acetylenic precursor **1** (Scheme I) was mildly hydrogenated (H_2, Lindlar catalyst,[2] quinoline, CH_2Cl, 25 °C)

† Fellow of the A. P. Sloan Foundation, 1979–1983; recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980–1984.

(1) Paper 3: Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) This Lindlar catalyst, supplied to us as a gift from Hoffmann-LaRoche, Nutley, NJ, courtsey of Dr. John Partridge, proved superior to commercially available catalysts.

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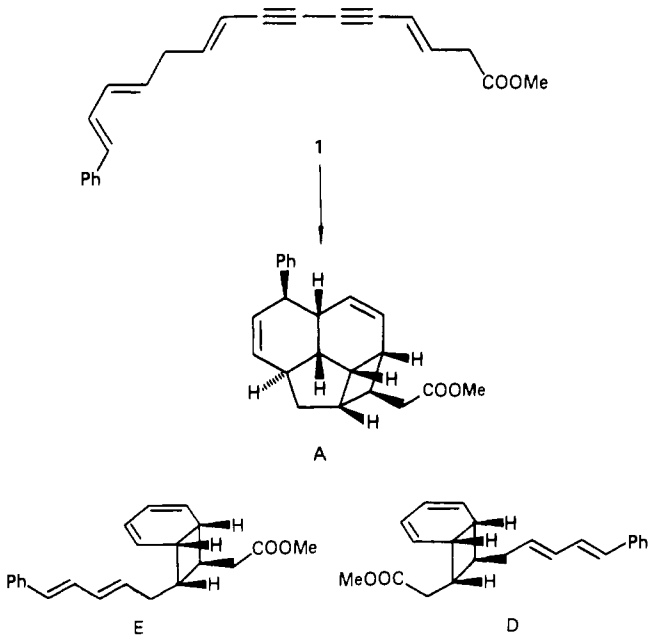
Scheme I. One-Step Generation of Endiandric Acids A, E, and D Methyl Esters from Acetylenic Precursor 1



followed by brief heating of the resulting mixture at 100 °C (toluene), there was produced and chromatographically isolated endiandric acid A methyl ester (A)[3] (ca. 30% yield). *Thus, in this reaction, the endiandric acid A complex polycyclic framework was formed essentially in a single operation by creating stereospecifically four new rings and eight asymmetric centers from an achiral open-chain precursor.* Interestingly, no endiandric acid D methyl ester (D) was isolated under these conditions. However, careful examination of the hydrogenation mixture prior to thermolysis in the above operation revealed the presence of endiandric acids D and E methyl esters[3] (D and E, Scheme I), which were chromatographically isolated in 12% and 10% yields, respectively. We were unable to observe under these conditions the cyclooctatrienes or the conjugated tetraenes postulated in the cascade (Scheme I, paper 3 in this series[1]) presumably due to rapid electrocyclizations leading to the bicyclo[4.2.0] systems.

Similarly mild hydrogenation of the diacetylene **2** (Scheme II) as described for **1** (vide supra) led, after brief thermolysis at 100 °C, to the isolation of endiandric acid B methyl ester (B)[3] and endiandric acid C methyl ester (C)[3] in ca. 28% yield (B:C ca. 4.5:1 by ^{1}H NMR and isolation). *In this reaction the two seemingly unrelated complex polycyclic structures of endiandric acids B and C were formed in essentially one operation by creating four new rings and eight asymmetric centers from achiral, open-*chain *precursors in a stereospecific manner.* By operating exclusively at 25 °C, however, we were again able to detect and isolate from the hydrogenation mixture endiandric acids F and G methyl esters[3] (F and G, Scheme II) in ca. 15% and 12% yields, respectively. The presumed intermediates, open-chain conjugated tetraene and cyclooctatriene (Scheme I, paper 3 in this series[1]) were not detected, apparently due to their fast conversion to the bicyclo[4.2.0] systems F and G by rapid electrocyclizations. At this stage it became quite apparent that indeed the genesis of endiandric acids in nature from polyunsaturated achiral precursors is feasible without enzyme participation and according to Black's hypothesis. To elucidate further the final steps of this cascade leading to the structures of endiandric acids A–C from the bicyclo[4.2.0] series

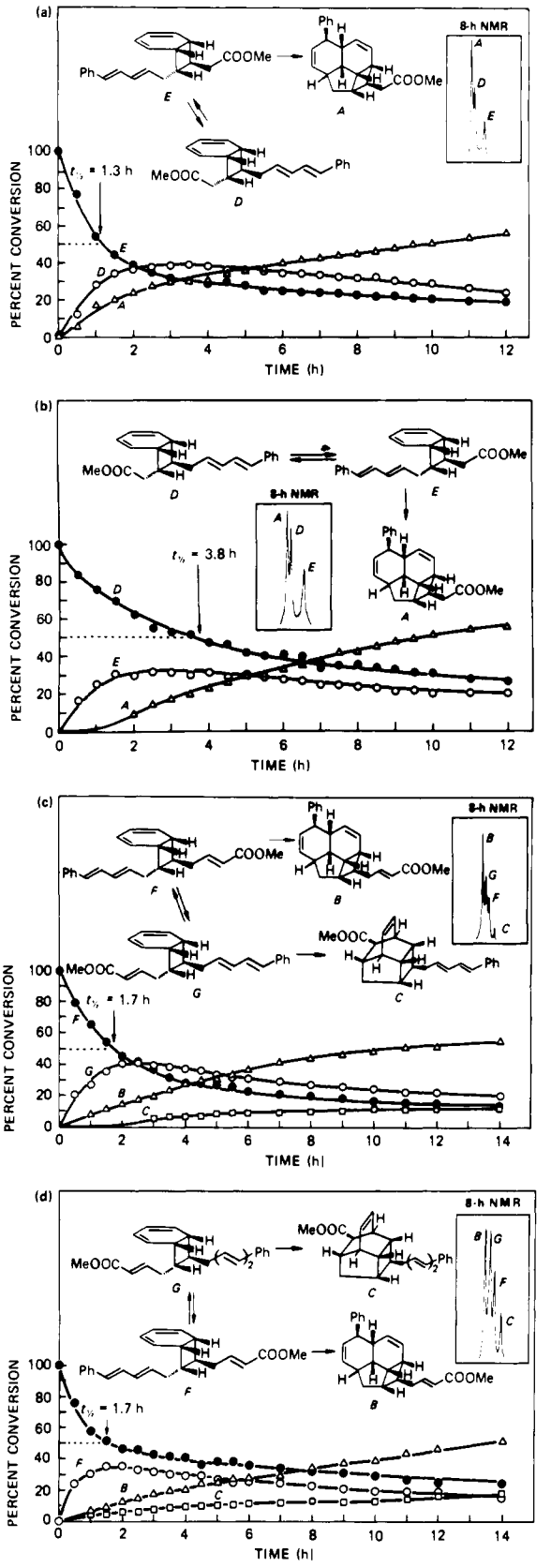


Figure 1. Thermolysis of endiandric acids E (a), D (b), F (c), and G (d) methyl esters at 70 °C in toluene-d_8 followed by ^{1}H NMR spectroscopy ($COOCH_3$) at 250 MHz.

of compounds (see Scheme I), paper 3 in this series[1]), we undertook a careful investigation of their thermal behavior. The thermally induced transformations of these compounds (endiandric acids D–G methyl esters) were conveniently observed in toluene-d_8 at 70 °C by following the methyl ester signal in the ^{1}H NMR

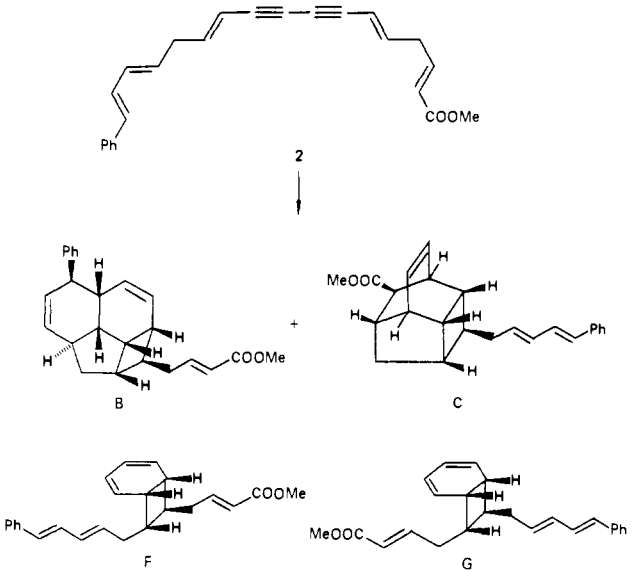
(3) The spectral and chromatographic data of this compound were identical with those of a synthetic and/or natural authentic sample.[4-6]

(4) Paper 1: Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E.; Uenishi, J. *J. Am. Chem. Soc.*, preceding paper in this issue.

(5) Paper 2: Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc.*, preceding paper in this issue.

(6) Natural endiandric acids A–D were kindly supplied to us by Professor D. St. C. Black, Monash University, Australia.

Scheme II. One-Step Generation of Endiandric Acids B, C, F, and G Methyl Esters from Acetylenic Precursor 2



spectrum at 250 MHz. The results were quite interesting and revealing and are graphically depicted in Figure 1. Thus, when endiandric acid E methyl ester (E) was maintained at 70 °C (toluene-d_8, NMR tube), it was observed to undergo (a) reversible isomerization to endiandric acid D methyl ester (D)[7] and (b) intramolecular $\pi 4s + \pi 2s$ cycloaddition (intramolecular Diels–Alder reaction) to endiandric acid A methyl ester (A)[7] with a half-life of disappearance $t_{1/2}$(70 °C) ca. 1.3 h (Figure 1a). Eventually, all the material was totally consumed, and endiandric acid A methyl ester (A) was formed in high yield. Endiandric acid D methyl ester (D) was observed (Figure 1b) under the same conditions and found to undergo a reversible isomerization to endiandric acid E methyl ester (E)[7] followed by an irreversible entry into the endiandric acid A skeleton (A)[7] by an intramolecular $\pi 4s + \pi 2s$ cycloaddition. Thus, endiandric acid D methyl ester (D) is converted to endiandric acid A methyl ester (A) in high yield with a half-life of disappearance $t_{1/2}$(70 °C) ca. 3.8 h. This observation explains the absence of endiandric acid D methyl ester in the hydrogenation–thermolysis experiment initiated with **1** (vide supra, Scheme I). The thermally induced chemical fates of endiandric acid F and G methyl esters (F) and (G) were monitored in a similar fashion (Figure 1c,d) and found to involve reversible equilibration of F[7] and G[7] and final conversion to both endiandric acids B[7] and C[7] methyl esters. Compound D disappeared with a half-life $t_{1/2}$(70 °C) ca. 1.7 h and produced endiandric acids B and C methyl esters (B and C) in a ratio of ca. 4.5:1, whereas compound F was consumed with a half-life $t_{1/2}$(70 °C) ca. 3.6 h and produced endiandric acid B and C methyl esters (B and C) in a ratio of ca. 3.7:1 in high yield (in both cases). The observed isomerizations E $\rightleftharpoons$ D and F $\rightleftharpoons$ G obviously proceed by a thermally allowed opening of the bicyclo[4.2.0] system to a cyclooctatriene systems, which after undergoing rapid conformational scrambling, reclose to a mixture of the bicyclo[4.2.0] compounds (see Scheme I, paper 3 in this series[1]). Extrapolation of these results to ambient temperatures makes it clear that these phenomena could take place in a natural environment, although at slower rates, and indeed such observations have been made on samples left standing at 25 °C for prolonged periods of time in these laboratories.

In conclusion, we have demonstrated in this series of papers the powerful nature of thermally allowed by the Woodward–Hoffmann rules $8\pi e$ and $6\pi e$ electrocyclizations in the stereospecific construction of polycyclic and complex systems. Our studies culminated in total syntheses of all endiandric acids A–G by both a stepwise stereocontrolled fashion and by a one-operation "biomimetic" approach from open-chain achiral precursors. Furthermore, these investigations provided an experimental test and final verification of Black's hypothesis postulating a possible nonenzymatic genesis of endiandric acids in nature from polyunsaturated achiral substrates.[8] It can also be deduced that endiandric acids E–G, which have not as yet been found in nature, should be stable enough for isolation from *Endiandra introrsa* (*Lauraceae*), particularly with the availability of synthetic samples. Questions still under investigation in this area concern whether these series of compounds originate from precursors with the E,Z,Z,E conjugated tetraene systems I and III or the Z,Z,Z,Z systems II and IV (Scheme I, paper 3 in this series[1]) or both, and the possible physiological role of endiandric acids in nature. Finally, the methodology described here should find numerous and novel applications in the construction of other polycyclic frameworks including both natural and unnatural products.

Acknowledgment. We express our many thanks to Professor D. St. C. Black, Monash University, Australia, for samples of the natural endiandric acids, spectral data, and many other helpful communications and exchanges. We also thank John Partridge of Hoffmann-LaRoche, Nutley, NJ, for the generous gifts of superior Lindlar catalyst. Our thanks are also due to Drs. George T. Furst, Mike Mitchell, and Tom Terwilliger of this department for their superb spectroscopic assistance and helpful discussions. Finally, we acknowledge generous financial support of our programs by Merck Sharp & Dohme, the A. P. Solan Foundation, and the Camille and Henry Dreyfus Foundation.

Registry No. 1, isomer 1, 82706-76-1; **2**, isomer 1, 82706-77-2; A, 74635-24-8; B, 82730-19-6; C, 81757-51-9; D, 82706-78-3; E, 82768-65-8; F, 82706-79-4; G, 82768-66-9; **1**, isomer 2, 82768-67-0; **2**, isomer 2, 82768-68-1.

(7) All compounds detected in these experiments were isolated chromatographically and characterized spectroscopically by comparisons with authentic samples.[4-6]

(8) These results taken together with the racemic nature of the natural endiandric acids strongly point to a nonenzymatic pathway to these compounds from the postulated achiral precursors although the participation of enzymes cannot be rigorously excluded at this point. Similar thermal changes were observed within the endiandric acid cascade utilizing free carboxylic acids in this series of compounds. It is possible that some of these changes may be somewhat solvent dependent, although such studies have not been done yet.

Extremely Facile Reaction between the Ultimate Carcinogen Benzo[*a*]pyrene-7,8-diol 9,10-Epoxide and Ellagic Acid

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Intensive efforts by several laboratories have led to tumor studies that have identified (+)-7β,8α-dihydroxy-9α-10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene as an ultimate carcinogenic metabolite of benzo[*a*]pyrene.[1] In accord with predictions of the bay region theory,[2] related diol epoxides either have been shown

† National Institutes of Health.
§ Hoffmann-La Roche Inc.

(1) Review: Levin, W.; Wood, A. W.; Wislocki, P. G.; Chang, R. L.; Kapitulnik, J.; Mah, H. D.; Yagi, H.; Jerina, D. M.; Conney, A. H. In "Polycyclic Hydrocarbons and Cancer: Environment, Chemistry, and Metabolism"; Gelboin, H. V., Ts'o, P. O. P., Eds.; Academic Press: New York, 1978; Vol. 1, pp 189–202.

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