(1.5 equiv of $n$-$Bu_4NF$–THF, 0–25 °C, 90%); (b) **10** → **11** (2.0 equiv of $CBr_4$, 2.0 equiv of $PPh_3$, $CH_2Cl_2$, −10 °C, 90%); (c) **11** → **12** (1.5 equiv of NaCN, HMPA, 25 °C, 92%); (d) **12** → **13** (2.0 equiv of LiOH, 2:1 THF–$H_2O$, 25 °C, 86%); (e) **13** → **14** (2.2 equiv of Dibal, $CH_2Cl_2$, −78 °C, then acidic workup, 95% crude). The rather labile aldehyde **14** was reacted (−78 → 25 °C, 24 h) with the lithio derivative (LDA) of diethyl cinnamylphosphonate [*trans*-PhCH=$CHCH_2P(O)(OEt)_2$] (3 equiv of each, THF, −78 °C, 15 min) to afford endiandric acid C (**1**)[4] in 75% overall yield from **13**. Synthetic endiandric acid C (**1**) and natural endiandric acid C (**1**)[5] exhibited identical properties ($^1H$ NMR, IR, mass spectroscopy, TLC, mp) and so did their methyl esters (**15**)[6] ($CH_2N_2$, 0 °C, 100%).

Endiandric acid D (**2**, Scheme I), predicted by Black's "biogenetic" hypothesis (ref 1 in paper 1 in this series[1]) to be a member of the endiandric acid cascade (see Scheme I, paper 3 in this series[2]), has recently been isolated from *Endiandra introrsa* (*Lauraceae*).[7] The following total synthesis of this compound was completed in our laboratories before its presence in nature was proven. The key intermediate **6**[1] (Scheme I) was desilylated as above (**9** → **10**) to afford the hydroxy cyanide **16** (95% yield), which was smoothly hydrolyzed (excess KOH, $H_2O_2$, $H_2O$, 4 days) to the hydroxy acid **17** (92%) and then methylated ($CH_2N_2$), leading to the methyl ester **18** (100%). The sequence **18** → **19** → **20** → **21** → **22** (ca. 50% overall yield) proceeded unevenfully and in similar manner and yields as in **10** → **11** → **12** → **13** → **14** described above. Finally condensation of **22** with [*trans*-PhCH=$CHCHP(O)(OEt)_2]^-Li^+$ according to the procedure outlined for **14** → **1** led to endiandric acid D (**2**)[4] (80% yield) and thence to its methyl ester (**23**) ($CH_2N_2$, 100%). Both synthetic endiandric acid D (**2**) and its methyl ester (**23**)[6] exhibited identical properties ($^1H$ NMR, IR, mass spectroscopy, TLC, mp) to naturally derived materials.[7]

The total syntheses of the as yet undetected endiandric acids E (**3**), F (**4**) (see Scheme I, paper 3 in this series[2]), and their methyl esters were completed as outlined in Scheme II. Thus, the intermediate **24**[1] was converted to the aldehyde **29** via compounds **25**–**27** and by the standard chemistry already discussed, in 90% overall yield. This substance (**29**) conveniently served as common precursor to endiandric acid E (**3**) (5 equiv of freshly prepared $Ag_2O$, NaOH, THF–$H_2O$, 25 °C, 90%) endiandric acid E methyl ester (**28**)[6] ($CH_2N_2$, 100%) endiandric acid F methyl ester (**30**)[6] (1.2 equiv of each $(MeO)_2P(O)CH_2COOMe$–NaH, THF, 85%)[3] and endiandric acid F (**4**) (1.5 equiv of 1 N LiOH, aq THF, 25 °C, 90%). The synthesis of the remaining, and as yet undiscovered compound of the bicyclo[4.2.0] series, endiandric acid G (**5**, Scheme III; see also Scheme I, paper 3 in this series[2]) and its methyl ester (**33**), was finally carried out as illustrated in Scheme III. The starting material for this synthesis was endiandric acid D methyl ester (**23**, Scheme I), which was reduced to the aldehyde **32** (1.2 equiv of Dibal, $CH_2Cl_2$, −78 °C, 70% yield separated chromatographically from ca. 20–25% of alcohol **31**, which was converted to **32** by Swern oxidation) and then condensed with $(MeO)_2P(O)CH_2COOMe$–NaH (1.5 equiv of each, THF, 25 °C), leading to endiandric acid G methyl ester (**33**)[3] (84%). Alkaline hydrolysis of **33** as in **30** → **4** (Scheme II) furnished endiandric acid G (**5**) in essentially quantitative yield.

With the completion of the stepwise and stereocontrolled total synthesis of all endiandric acids A–G and with authentic samples of all these compounds at hand, we then turn our attention to a "one-step biomimetic" approach to these molecules. These results are described in the following communications.[8]

(4) The stereoselectivity of this olefination was estimated by $^1H$ NMR spectroscopy to be $E$:$Z$ ≥ 20:1. The $Z$ isomer was lost after chromatographic purification followed by crystallization (ether–petroleum ether).

(5) Authentic endiandric acid C (**1**) was generously supplied to us by Professor D. St. C. Black, Monash University, Australia.

(6) $^1H$ NMR, IR, and mass spectroscopic data are recorded in the supplementary material.

(7) Professor D. St. C. Black recently informed us of the discovery of endiandric acid D (**2**) in *Endiandra introrsa* (*Laureceae*) and kindly provided us with a natural sample.

**Registry No. 1**, 76060-34-9; **2**, 82679-68-3; **3**, 82863-34-1; **4**, 82808-36-4; **5**, 82863-35-2; **6**, 82863-36-3; **7**, 82863-37-4; **8**, 82808-37-5; **9**, 82808-38-6; **10**, 82808-39-7; **11**, 82808-40-0; **12**, 82808-41-1; **13**, 82808-42-2; **14**, 82808-43-3; **15**, 81757-51-9; **16**, 82808-44-4; **17**, 82808-45-5; **18**, 82808-46-6; **19**, 82808-47-7; **20**, 82808-48-8; **21**, 82808-49-9; **22**, 82808-50-2; **23**, 82706-78-3; **24**, 82863-38-5; **25**, 82808-51-3; **26**, 82808-52-4; **27**, 82808-53-5; **28**, 82768-65-8; **29**, 82808-54-6; **30**, 82706-79-4; **31**, 82808-55-7; **32**, 82863-39-6; **33**, 82768-66-9; $(MeO)_2P(O)CH_2COOMe$-NaH, 5927-18-4; *trans*-PhCH:$CHCH_2P(O)(OEt)_2$, 52378-69-5.

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

(8) 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. 3. "Biomimetic" Approach to Endiandric Acids A–G. Synthesis of Precursors

K. C. Nicolaou,*† R. E. Zipkin, and N. A. Petasis

*Department of Chemistry, University of Pennsylvania*
*Philadelphia, Pennsylvania 19104*

*Received May 3, 1982*

A brilliant and rather daring hypothesis was recently advanced by Black et al.[1b] as to the possible "biosynthesis" of endiandric acids A–D,[1] which accommodates the observation of both structural types represented by endiandric acids A–C in the same plant species and also their racemic nature. This hypothesis postulates the formation of endiandric acids A–D from acyclic, nonchiral polyunsaturated precursors by nonenzymatic reactions as indicated in Scheme I, which represents the complete endiandric acid cascade. It was specifically proposed that these polycyclic natural products are formed from carboxylic acids I, II (R = H), and/or III, IV (R = H) by a series of cyclizations thermally allowed by the Woodward–Hoffman rules,[2] namely an $8\pi e$ conrotatory electrocyclization, followed by a $6\pi e$ disrotatory electrocyclization, followed by an intramolecular $\pi 4s + \pi 2s$ cycloaddition (intramolecular Diels–Alder). Although our stepwise, stereocontrolled total syntheses of these substances described in the preceding papers[3,4] provide support for the feasibility of such sequences, we felt that this hypothesis could be directly tested by generating the postulated polyunsaturated substrates from suitable and stable precursors and observing their chemical fate. In this communication, we describe the total synthesis of such stable precursors and in the following paper[5] disclose their conversion

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

(1) (a) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C.; Fallon, G. D.; Gatehouse, B. M. *J. Chem. Soc., Chem. Commun.* **1980**, 162. (b) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C. *Ibid.* **1980**, 902. (c) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C.; Fallon, G. D.; Gatehouse, B. M. *Aust. J. Chem.* **1981**, *34*, 1655. (d) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C. *Ibid.* **1982**, *35*, 557. (e) Bandaranayake, W. M.; Banfield, J. E.; Black, D. St. C.; Fallon, G. D.; Gatehouse, B. M. *Ibid.* **1982**, *35*, 567. (f) Endiandric acid D was predicted as a natural product in 1980[1b] and synthesized by us in 1981, and although found in *Endriandra introrsa* (*Lauraceae*) in the same year by Black's group, its structure was not determined until 1982 (personal communication); see also: Banfield, J. E.; Black, D. St. C.; Johns, S. R.; Willing, R. I. *Ibid.*, in press.

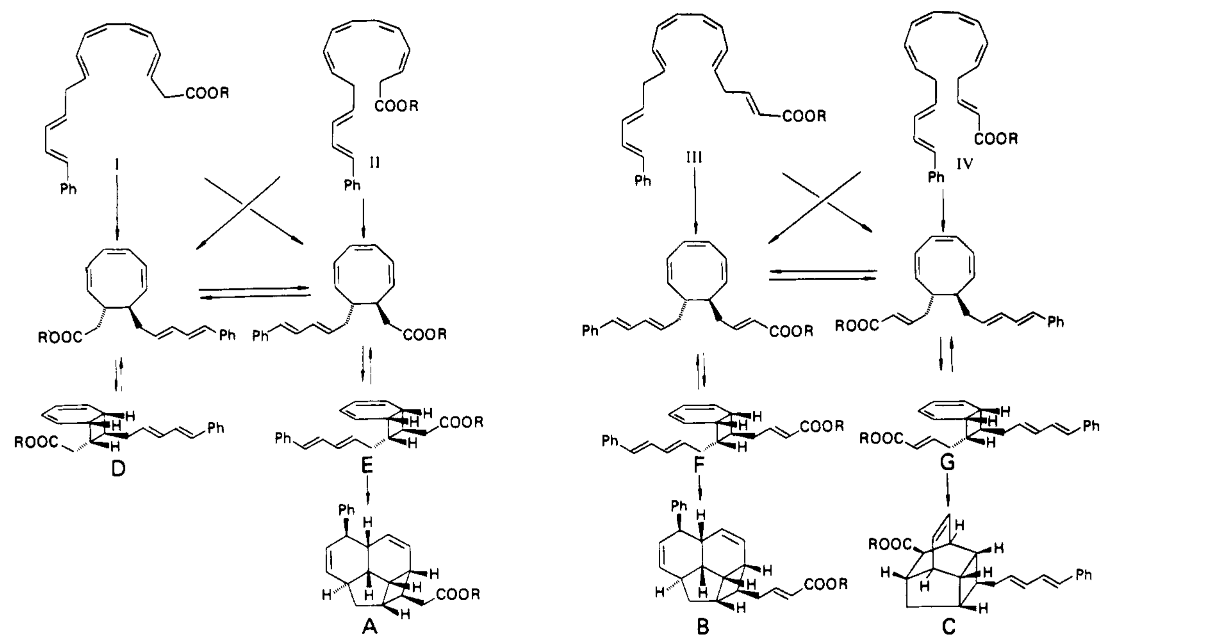
(2) (a) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie–Academic Press: New York, 1971. See also: (b) Lehr, R. E.; Marchand, A. P. "Orbital Symmetry"; Academic Press: New York, 1972. (c) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, 1976. (d) Marchand, A. P.; Lehr, R. E., Eds.; "Pericyclic Reactions"; Academic Press: New York, 1977; Vols. I, II.

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

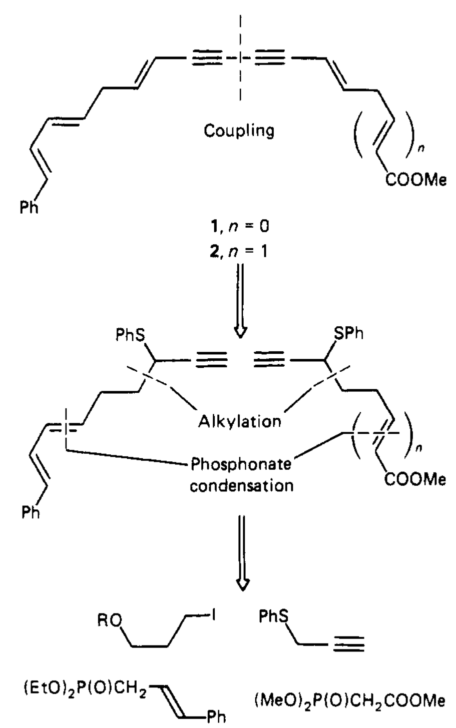
(4) Paper 2: Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc.*, preceding paper in this issue.

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

**Scheme I.** Endiandric Acid Cascade




**Scheme II.** Retrosynthetic Analysis of Acetylenic Precursors 1 and 2

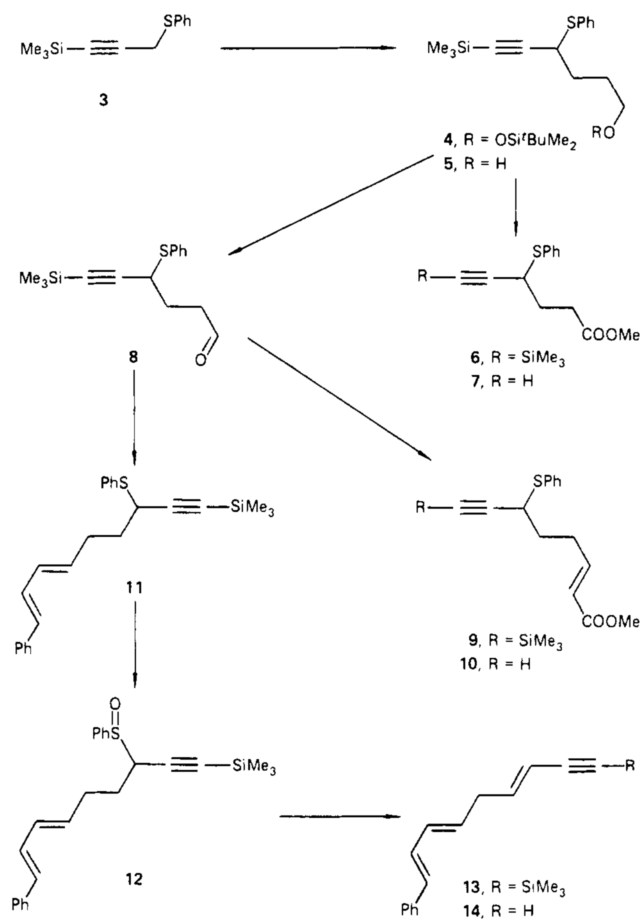



to the various members of the endiandric acid cascade.

When the synthesis of suitable polyunsaturated pregenitors of the endiandric acid cascade was designed, the following considerations served as guidelines: (a) the central *Z,Z*-diene grouping should be masked as a diacetylene unit until the last step in order to avoid possible premature $8\pi e$ electrocyclization; (b) since the Black hypothesis invokes either *E,E* or *Z,Z* or both geometries for the outer olefinic bonds of the tetraene system, a synthesis allowing for the construction of both types of compounds was sought; (c) for higher stability, chromatographic convenience, and $^1H$ NMR observation, the methyl esters, rather than the carboxylic acids themselves, were chosen as targets.

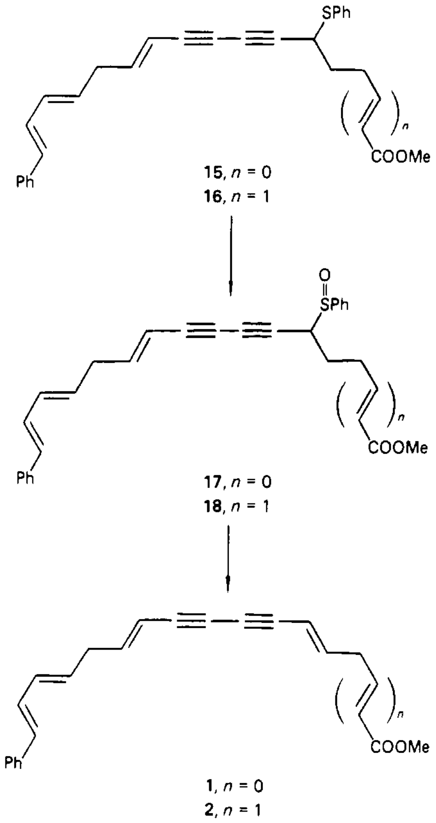
Scheme II depicts the final precursors (**1** and **2**) designed and synthesized in this study and outlines their retrosynthetic analysis. Thus, disconnection of the C–C bond linking the two acetylenic groupings in **1** and **2** (Scheme II) and functional group interchange of the two adjacent double bonds with phenylthio groups leads to terminal acetylenes. Further disconnection of strategic single and double bonds as shown indicates simple fragments as starting materials (Scheme II).

**Scheme III.** Synthesis of Key Intermediates 7, 10, and 14




The key intermediate terminal acetylenes required for the construction of compounds **1** and **2** were synthesized as outlined in Scheme III. Thus, alkylation of 1-(trimethylsilyl)-3-

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* $\alpha,\beta$-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 $^1$H 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 $^1$H 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 $^1$H 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 $^1$H 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 $^1$H 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 $^1$H 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) $^1$H 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

K. C. Nicolaou,*† N. A. Petasis, and R. E. Zipkin

*Department of Chemistry, University of Pennsylvania Philadelphia, Pennsylvania 19104*

*Received May 3, 1982*

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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