26)[16] furnished endiandric acid B methyl ester (2-methyl ester)[14] identical with the methyl ester derived from natural endiandric acid B (2) (CH_2N_2) in all respects. Alkaline hydrolysis of 2-methyl ester leads to endiandric acid B (2) (100%), identical with an authentic sample.[15]

These first total syntheses of endiandric acids A (1) and B (2) demonstrate the feasibility and power of electrocyclizations both in the laboratory and possibly in nature. In the following paper we describe total syntheses of endiandric acids C and D and the as yet undiscovered endiandric acids E–G.[17,18]

Registry No. (±)-**1**, 74591-03-0; (±)-**1** methyl ester, 74635-24-8; (±)-**2**, 76060-33-8; (±)-**2** methyl ester, 82730-19-6; (±)-**3**, 76060-34-9; (±)-**4**, 82679-68-3; (*E*,*E*)-**12**, 7199-98-6; (±)-**15**, 82679-70-7; **16**, 82679-71-8; **17**, 82706-17-0; (±)-**18**, 82679-72-9; (±)-**19**, 82679-73-0; (±)-**20**, 82679-74-1; (±)-**21**, 82679-75-2; (±)-**22**, 82679-76-3; (±)-**23**, 82679-77-4; (±)-**24**, 82679-78-5; (±)-**25**, 82679-79-6; (±)-**26**, 82679-80-9; (±)-**27**, 82679-69-4; (*E*)-diethylcinnamylphosphonate methyl triphenylphoranylidene, 52378-69-5; acetate, 2605-67-6.

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

(16) A small amount (5–10%) of the cis isomer was formed in this reaction and was chromatographically removed from the desired product. The olefination proceeds just as well (although less convenient) and with higher geometrical selectivity with $(MeO)_2P(O)CH_2COOMe$–NaH–THF.

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

(18) The work described in this and the following papers was partially presented at the 11th American Chemical Society Northeast Regional Meeting, Rochester, NY, October 1981, and the 183rd American Chemical Society National Meeting, Las Vegas, NV, March–April, 1982.

The Endiandric Acid Cascade. Electrocyclizations in Organic Synthesis. 2. Stepwise, Stereocontrolled Total Synthesis of Endiandric Acids C–G

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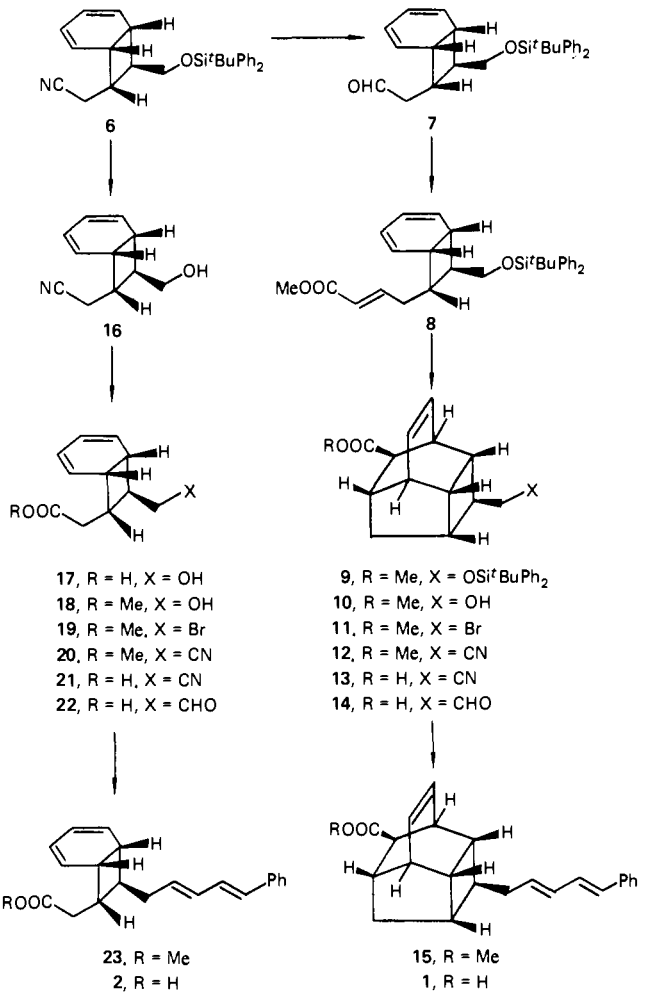
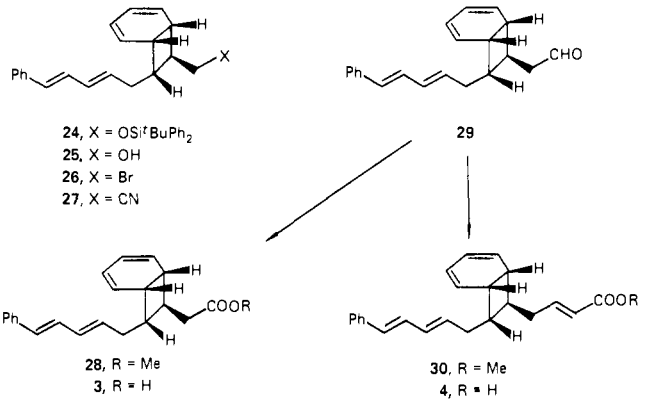
In the preceding communication[1] we described the total synthesis of endiandric acids A and B using electrocyclic reactions as key steps via a common intermediate. Our experimental findings strongly suggested that other members of the endiandric acid cascade such as endiandric acids E, F (**3**, **4**, Scheme II) and G (**5**, Scheme III) (see also Scheme I, paper 3 in this series[2]) could possess enough thermal stability to allow their existence in nature. In anticipation of their discovery in *Endiandra introrsa* (*Lauraceae*) and in order to aid the search for them, we undertook their total synthesis. We now detail in this paper stepwise and stereocontrolled total syntheses of endiandric acids C, D (**1**, **2**, Scheme I), E, F (**3**, **4**, Scheme II), and G (**5**, Scheme III) from the same central key intermediate **6** (Scheme I) described in the preceding article.[1]

The total syntheses of endiandric acids C (**1**) and D (**2**) proceeded along the lines of the retrosynthetic analysis outlined in the preceding paper[1] and is depicted in Scheme I. The aldehyde **7**, prepared from **6** as already described,[1] was condensed with $(MeO_2P(O)CH_2COOMe$–NaH (1.5 equiv of each, THF, 25 °C) to afford the α,β-unsaturated ester **8** (80% yield),[3] setting the stage

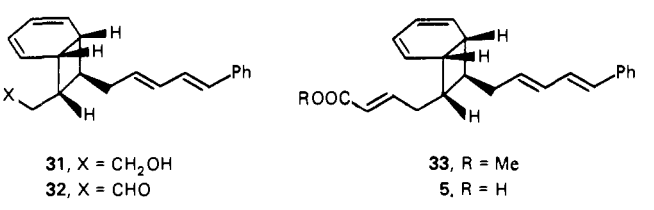
Scheme I. Total Synthesis of Endiandric Acids C (1) and D (2)



Scheme II. Total Synthesis of Endiandric Acids E (3) and F (4)



Scheme III. Total Synthesis of Endiandric Acid G (5)



for the construction of endiandric acid C framework via an intramolecular $\pi 4s + \pi 2s$ cycloaddition. Indeed, thermolysis of **8** (toluene, 110 °C, 12 h) led smoothly to structure **9** in 92% yield. Continuing with **9**, the following transformations were carried out, finally arriving at the requisite key intermediate **14**: (a) **9** → **10**

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

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

(3) Small amounts (<5%) of the corresponding *Z* isomer was also formed in this reaction and was removed from **8** chromatographically. Reaction of **7** with $Ph_3P{=}CHCOOMe$ (2.0 equiv, benzene, 25 °C) leads to similar results but with somewhat less geometrical selectivity. Similar observations were made in the preparations of **30** and **33**.

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(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$_2$P(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 (^{1}H 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 (^{1}H 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)$_2$P(O)CH$_2$COOMe-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)$_2$P(O)CH$_2$COOMe-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 ^{1}H NMR spectroscopy to be $E:Z \geq 20:1$. 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) ^{1}H 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)$_2$P(O)CH$_2$COOMe-NaH, 5927-18-4; *trans*-PhCH:CHCH$_2$P(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

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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 8πe conrotatory electrocyclization, followed by a 6πe 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.

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