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structure is detected automatically by unexpected values for the vicinal couplings.[2,12] Given the ease with which oligosaccharides can be fully *O*-acylated,[13] we draw attention to the substantial advantages of working with such derivatives in organic solvents.[14]

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Registry No. 1, 52211-61-7; **2**, 82892-18-0.

(12) Bothner-By, A. A. *Adv. Magn. Reson.* **1965**, *1*, 195–316.
(13) Wolfrom, M. L.; Thompson, A. *Methods Carbohydr. Chem.* **1973**, *2*, 211–215.
(14) Use may be made of solvent-induced shifts of minimize distortions arising through tight coupling.

The Endiandric Acid Cascade. Electrocyclizations in Organic Synthesis. 1. Stepwise, Stereocontrolled Total Synthesis of Endiandric Acids A and B†

K. C. Nicolaou,*‡ N. A. Petasis, R. E. Zipkin, and J. Uenishi

Department of Chemistry, University of Pennsylvania Philadelphia, Pennsylvania 19104

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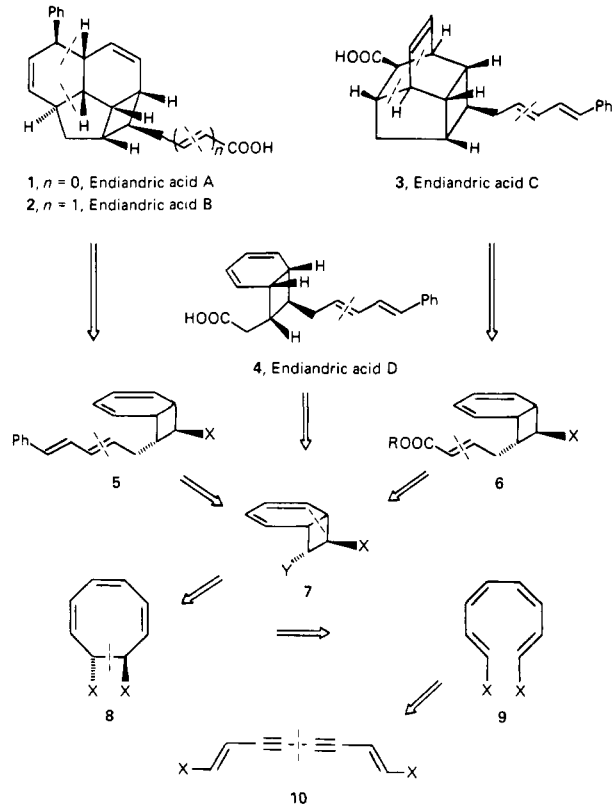
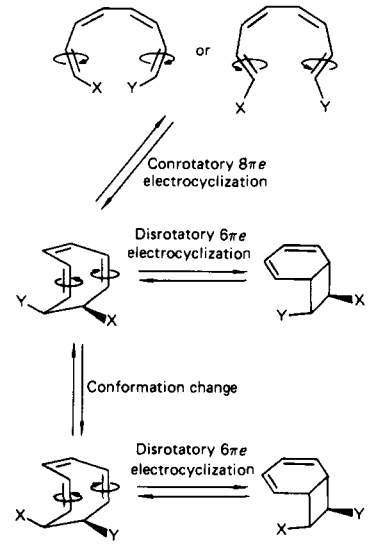
Endiandric acids A–D (**1–4**, Scheme I) were recently isolated from leaves of the Australian plant *Endiandra introrsa* (*Lauraceae*) and their structures firmly established by spectroscopic and X-ray crystallographic techniques.[1] Despite the presence of eight asymmetric centers in these novel polycyclic molecules, they occur in nature in racemic rather than enantiomeric forms, a rather unusual observation for naturally occurring compounds. This phenomenon taken together with the isolation of both types of structures (represented by A/B and C) from the same plant species led Black and his collaborators to propose a brilliant and provocative hypothesis for the "biogenesis" of these compounds in nature from achiral precursors by a series of nonenzymatic electrocyclizations.[1b] On the basis of this hypothesis and relying on well-known[2] but relatively unexplored, thermally allowed by the Woodward–Hoffmann rules,[3] electrocyclizations of the type shown in Scheme II, we devised stereocontrolled total syntheses of all four endiandric acids A–D (**1–4**, Scheme I). In this series of papers we report (a) a stepwise and stereocontrolled approach to these molecules culminating to the first total syntheses of endriandric acids A–D, (b) a "biomimetic" approach to these compounds providing an experimental test to Black's hypothesis, and (c) thermal stability studies leading to confirmation of the biogenetic hypothesis and predictions of the existence of other members of the endiandric acid cascade (endiandric acids E, F and G, see papers 2[4] and 4[6] in this series), which we have also synthesized. We begin with the retrosynthetic analysis of these complex polycyclic frameworks and the stepwise and sterecontrolled total synthesis of endiandric acids A and B (**1** and **2**, Scheme I).

In planning the synthesis of endiandric acids, we sought a general scheme that would allow the construction of each of these

Scheme I. Structures and Retrosynthetic Analysis of Endiandric Acids A–D



Scheme II. Thermally Allowed 8πe and 6πe Electrocyclizations (Woodward–Hoffmann Rules)



† This series of papers is dedicated to the memory of the late Professor Franz Sondheimer.
‡ 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] synthesized by us in 1981, and although found in *Endiandra 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) See for example: (a) Meister, H. *Chem. Ber.* **1963**, *96*, 1688. (b) Huisgen, R.; Dahmen, A.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 7130. (c) Marvell, E. N.; Seubert, J.; Vogt, G.; Zimmer, G.; Moy, G.; Siegmann, J. R. *Tetrahedron*, **1978**, *34*, 1323. (d) Harris, S. J.; Walton, D. R. M. *Tetrahedron* **1978**, *34*, 1037.

(3) (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; Vol. I, II.

(4) Paper 2: Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc.*, following in this issue.
(5) Paper 3: Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.*, following in this issue.
(6) Paper 4: Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.*, following in this issue.

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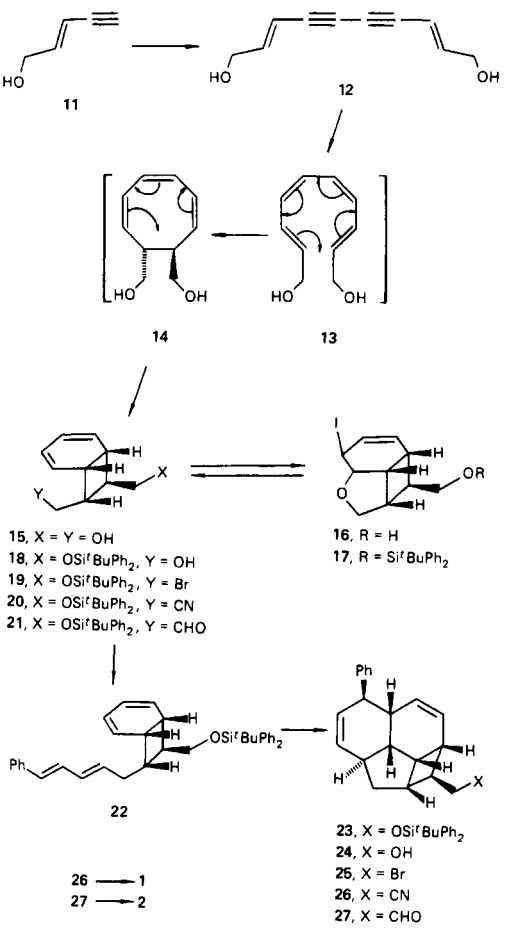
compounds in a selective manner from a central intermediate and, as mentioned above, relied heavily on electrocyclic reactions for stereocontrolled construction of rings and chiral centers. The principal strategic bond disconnections and complete retrosynthetic analysis of our first, stepwise approach to endiandric acids are illustrated in Scheme I. Thus, disassembling endiandric acids A (**1**), B (**2**), and C (**3**) by retrointramolecular $\pi 4s + \pi 2s$ cycloadditions (intramolecular Diels–Alder) as indicated leads to precursors **5** and **6**. Disconnections of precursors **5** and **6** at the marked olefinic bonds by a retro-Wittig-type reaction lead to the common bicyclic intermediate **7** where X and Y are appropriate appendages to allow for selective buildup of the required side chains. Similarly endiandric acid D (**4**) can be back-traced to the same key intermediate **7** as shown in Scheme I. Sequential opening of the bicyclo[4.2.0] central intermediate **7**, as indicated, leads to the cyclooctatriene intermediate **8** and thence to the acyclic tetraene **9**. The last disconnection arrives at a symmetrical structure (synthetically a highly desirable feature) with strict geometrical requirements. Finally, a simple interchange of the central *Z,Z*-diene unit with a diacetylenic grouping leads to the intermediate **10**, the construction of which from readily available starting materials becomes obvious. The three synthetically required cyclizations are well-known, thermally allowed by the Woodward–Hoffmann rules[3] electrocyclic processes. They are (i) an 8πe conrotatory electrocyclization (Scheme II), (ii) a 6πe disrotatory electrocyclization (Scheme II), and (iii) an intramolecular $\pi 4s + \pi 2s$ cycloaddition. This analysis establishes a central intermediate, thus providing synthetic routes to all endiandric acids and allows for the exploration of the complete endiandric acid cascade (Scheme I, paper 3 in this series[5]) and the synthesis of other stable members of this family of compounds.

In practice the above scheme was realized with remarkable success both in terms of efficiency and stereospecificity. Thus, when the diacetylenic diol **12** (Scheme III) (readily available from *trans*-pent-2-en-4-yn-1-ol (**11**) by acetylene coupling)[7] was mildly hydrogenated (Lindlar catalyst, CH_2Cl_2–CH_3OH–quinoline, 90:9.5:0.5, 25 °C, 3–6 h),[8] the bicyclic diol **15**[9] was obtained directly after column chromatography[10] (45–55% overall yield). The presumed intermediates **13** and **14** (Scheme III) in this sequence were not detectable under these conditions. Although direct discrimination of the two hydroxyls in **15** was not possible even with bulky protecting groups, the two functionalities were cleanly differentiated by iodo etherification (1.1 equiv of I_2, 2.2 equiv of K_2CO_3, CH_2Cl_2, −20 → 0 °C, 2 h) to afford **16** followed by silylation (1.5 equiv of *t*-$BuPh_2SiCl$, 3 equiv of imidazole, DMF, 25 °C, 2 h) giving **17** and reversal of the iodo etherification (3 equiv of Zn dust, AcOH, 25 °C) leading to the desired **18** in 70–80% overall yield (from **15**). The conversion of this monoprotected diol to the cyanide **20** proceeded uneventfully and in 95% overall yield (**18** → **19**: 2.0 equiv of CBr_4, 2.0 equiv of Ph_3P, CH_2Cl_2, 0 °C.[11] **19** → **20**: 1.5 equiv of NaCN, HMPA, 25 °C[12]). *This compound* (**20**) *served as a key intermediate for the stepwise and stereocontrolled total synthesis of all endiandric acids* (*A–G*). Reduction of **20** with Dibal (1.1 equiv, CH_2Cl_2, −78 °C) followed by mild acid hydrolysis led to the aldehyde **21**, required for the synthesis of endiandric acids A (**1**) and B (**2**).

The next operation was to construct stereoselectively a phenyl-substituted *E,E*-diene grouping on the endo side chain of the molecule in order to arrive at the designed precursor for the final $\pi 4s + \pi 2s$ intramolecular cyclization. To this end, the anion derived from diethyl cinnamylphosphonate (*trans*-PhCH=$CHCH_2P(O)(OEt)_2$) and LDA (2.0 equiv of each, THF, −78 °C, 15 min) was condensed with the aldehyde **21** (−78 → 25 °C, 24 h) to furnish **22** in a highly geometrically controlled manner (75% yield, *E*:*Z* ≥ 20:1 at the newly formed double bond).[13] The stage was now set for the final and crucial operation to complete the polycyclic framework of endiandric acids A (**1**) and B (**2**).

We were indeed delighted to observe an essentially quantitative conversion of **22** to **23**[14] at 110 °C (toluene, 5 h), with the indicated structural assignment proven by eventual conversion to the natural products (**1** and **2**) as follows. Desilylation of **23** (1.5 equiv of *n*-Bu_4NF, THF, 0 → 25 °C) led to **24** (100%), which was transformed to the bromide **25** (98%) and thence to the cyanide **26** (98%) as described above (for **18** → **19** → **20**). Finally hydrolysis of **26** (excess KOH, H_2O_2, H_2O, EtOH, 25 → 50 °C) proceeded smoothly to afford endiandric acid A (**1**) in 95% yield identical with authentic material[15] in all usual respects (^1H NMR, IR, mass spectroscopy, TLC, mp). The methyl esters (CH_2N_2) (1-methyl ester)[14] of the natural and synthetic endiandric acids A (**1**) were also identical by these criteria.[14] Reduction (1.1 equiv of Dibal, CH_2Cl_2, −78 °C, then acidic workup) of **26** followed by condensation of the resulting aldehyde **27** with Ph_3P=CHCOOMe (1.5 equiv, benzene, 25 °C, 85% overall yield from

Scheme III. Total Synthesis of Endiandric Acids A (**1**) and B (**2**)



(7) (a) Haynes, L. J.; Heilbron, I.; Jones, E. R. H.; Sondheimer, F. *J. Chem. Soc.* **1947**, 1583. (b) Heilbron, I.; Jones, E. R. H.; Sondheimer, F. *Ibid.* **1947**, 1586. (c) *trans*-Pent-2-en-4-yn-1-ol (**11**) is commercially available from Farchan Laboratories, Willoughby, OH.

(8) This Lindlar catalyst was supplied to us as a gift from Hoffmann La-Roche, Inc., Nutley, NJ, courtesy of Dr. John Partridge, and gave superior results to those obtained with commercial catalysts.

(9) All new compounds described in this and the following papers[4-6] were characterized by full spectroscopic and analytical or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials. Complete details will be disclosed in a forthcoming full account of this work.

(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(11) Kocienski, P. J.; Cernigliaro, G.; Feldstein, G. *J. Org. Chem.* **1977**, *42*, 353.

(12) Shaw, J. E.; Hsia, D. Y.; Parries, G. S.; Sawyers, T. K. *J. Org. Chem.* **1978**, *43*, 1017.

(13) The *E*:*Z* ratio was determined by ^1H NMR spectroscopy. It is interesting to note that while the anion of cinnamyldiphenylphosphine oxide (*trans*-PhCH=$CHCH_2P(O)Ph_2$) leads to a similar geometrical result, the corresponding triphenylphosphorane (*trans*-PhCH=CHCH=PPh_3) results in a 60:40 *E*:*Z* mixture.

(14) ^1H NMR, IR, and mass spectroscopic data are recorded in the supplementary material.

(15) Authentic natural samples of endiandric acids A (**1**) and B (**2**) were generously supplied to us by Professor D. St. C. Black, Monash University, Australia.

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

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

Department of Chemistry, University of Pennsylvania Philadelphia, Pennsylvania 19104

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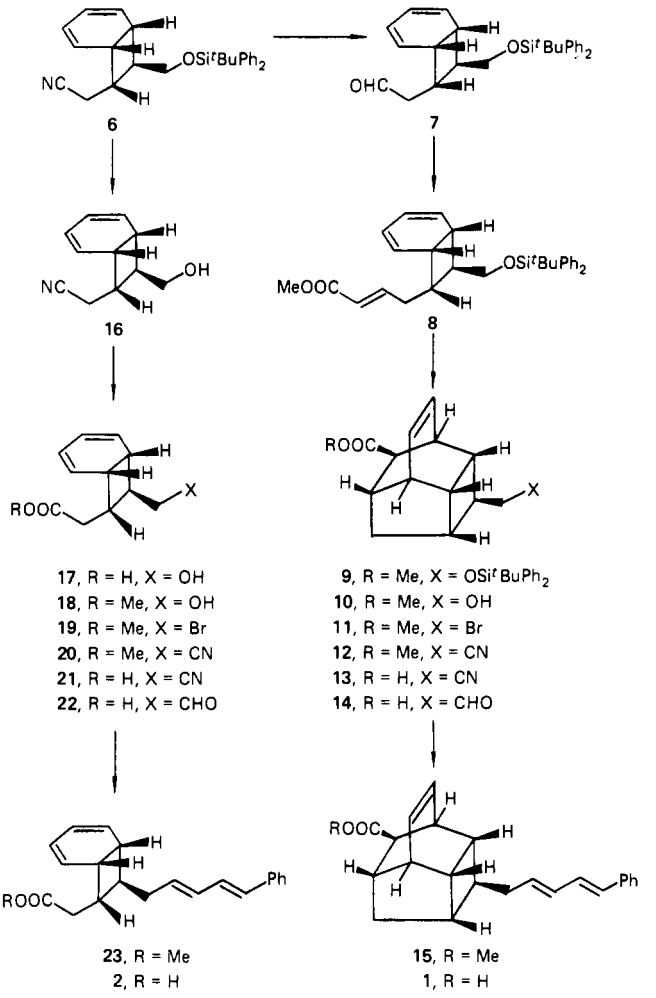
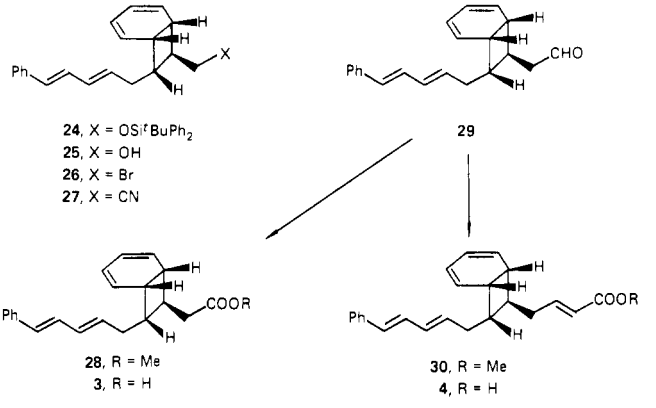
In the preceding communication[1] we described the total synthesis of endiandric acids A and B using electrocyclic reactions as key steps via a common intermediate. Our experimental findings strongly suggested that other members of the endiandric acid cascade such as endiandric acids E, F (**3**, **4**, 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

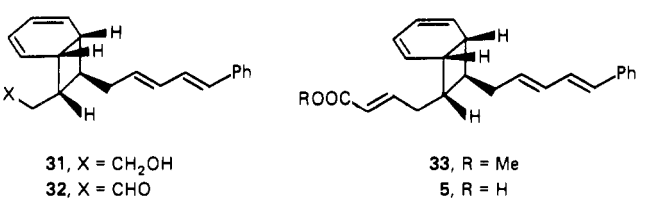
Scheme I. Total Synthesis of Endiandric Acids C (1) and D (2)



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**

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

(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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