

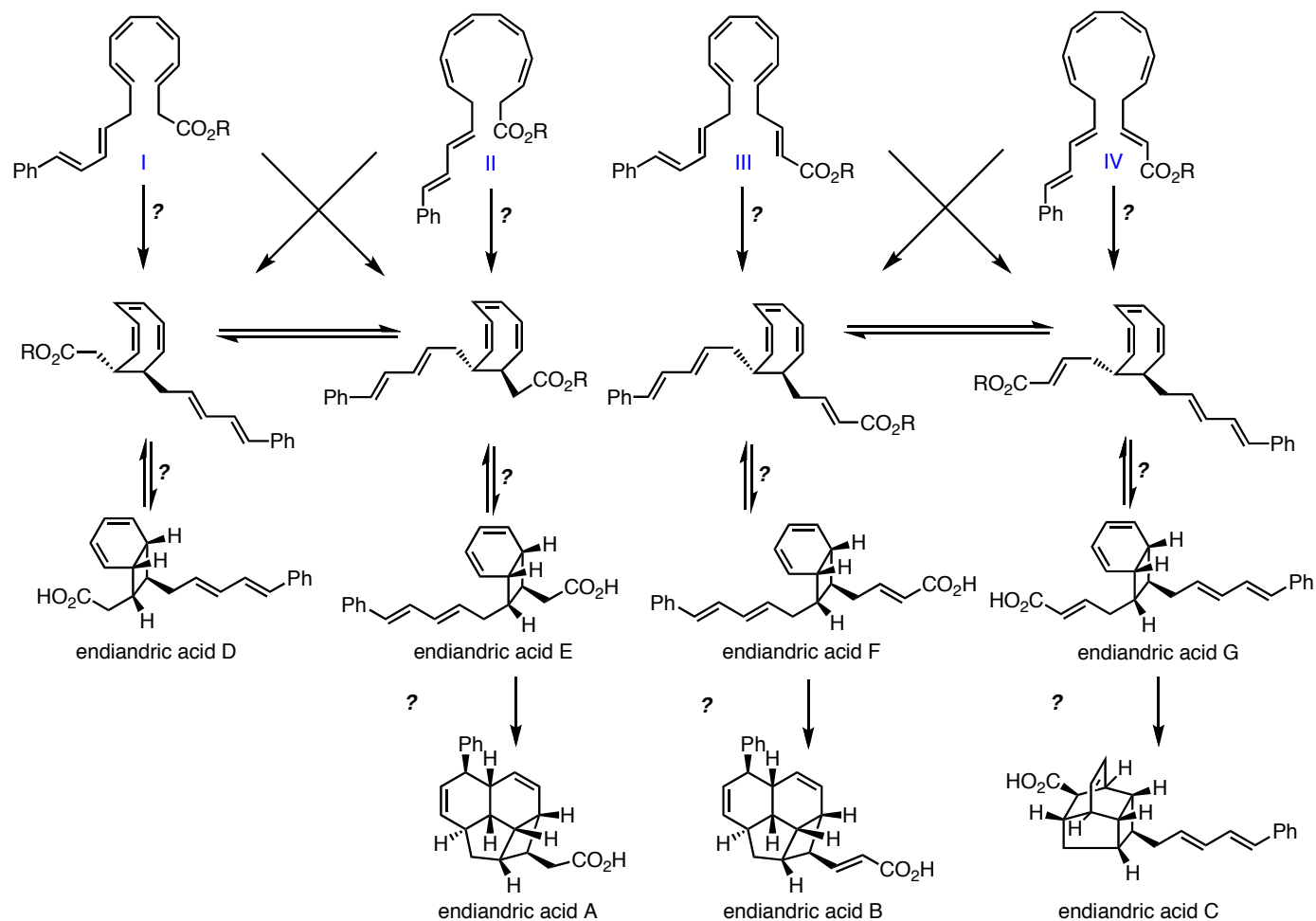
Chemistry 1310/2370 - Synthetic Organic Chemistry

Problem Set 3: Due Date 10/28/09

Name:

Read the attached summary of the 1982 synthesis of the Endiandric Acids A-D by the Nicolaou group, and answer the following questions:

a) For each of the 11 question marks below, indicate if the pericyclic reaction is a Diels-Alder reaction (**DA**), a conrotatory 8 π -electron electrocyclicization (**C8- π i**), or a disrotatory 6 π -electron electrocyclicization (**D6- π i**).



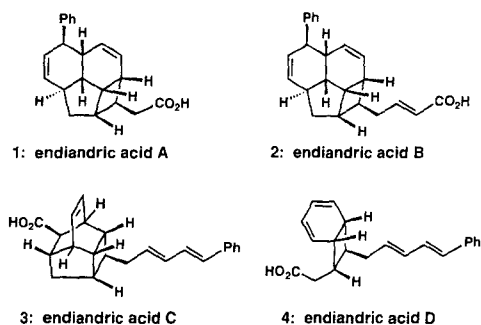
b) Show the steps that use a Glaser coupling.

c) Show the steps that use a Lindlar hydrogenation. What is the difference between a Lindlar hydrogenation and a classical hydrogenation?

d) Provide a mechanism for the conversion of an alcohol to a bromide with CBr_4 and Ph_3P .

e) List all reactions that involve oxidations, with the respective reagents.

f) List all reactions that involve reductions, with the respective reagents.



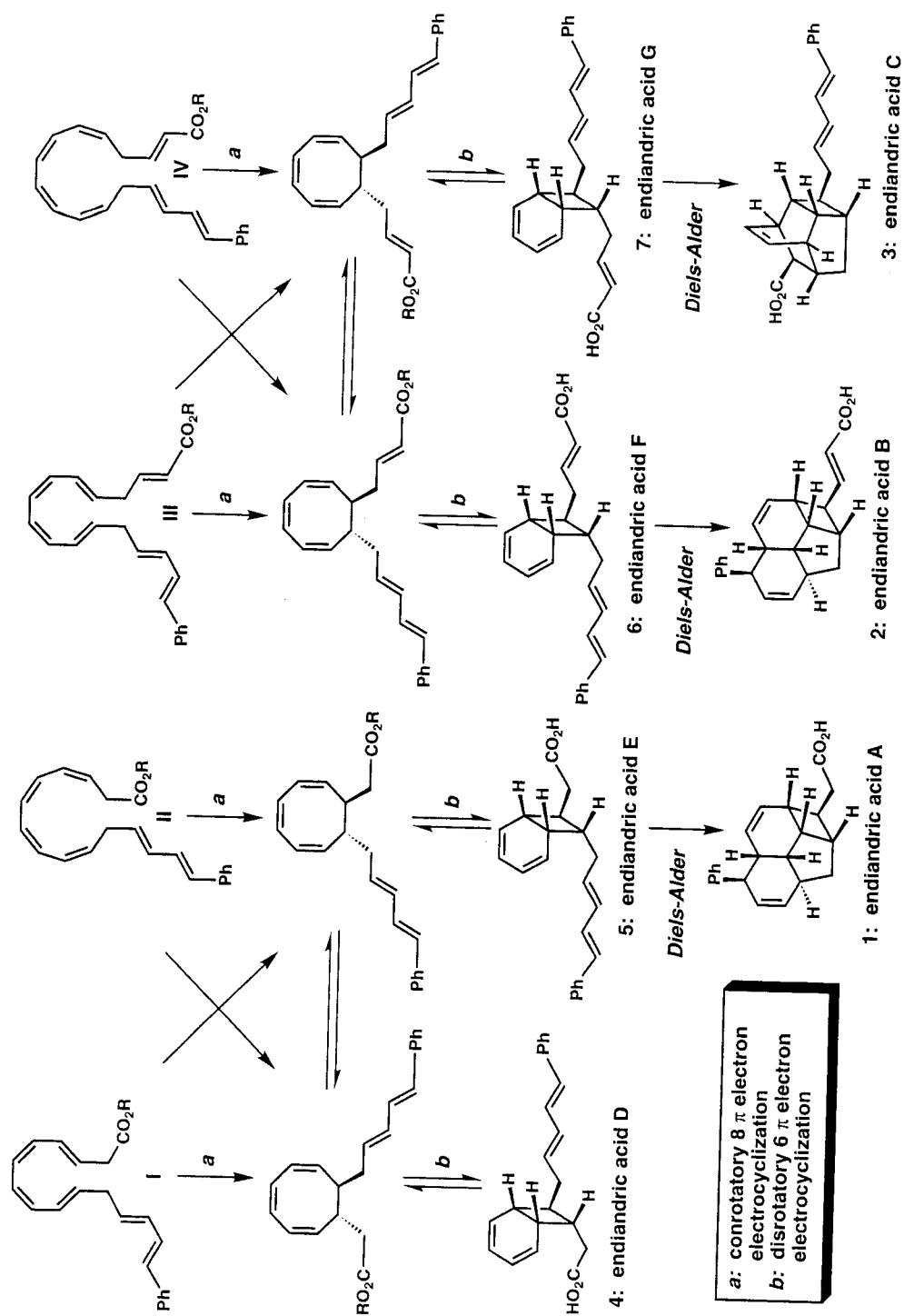
K. C. Nicolaou (1982)

Endiandric Acids A–D

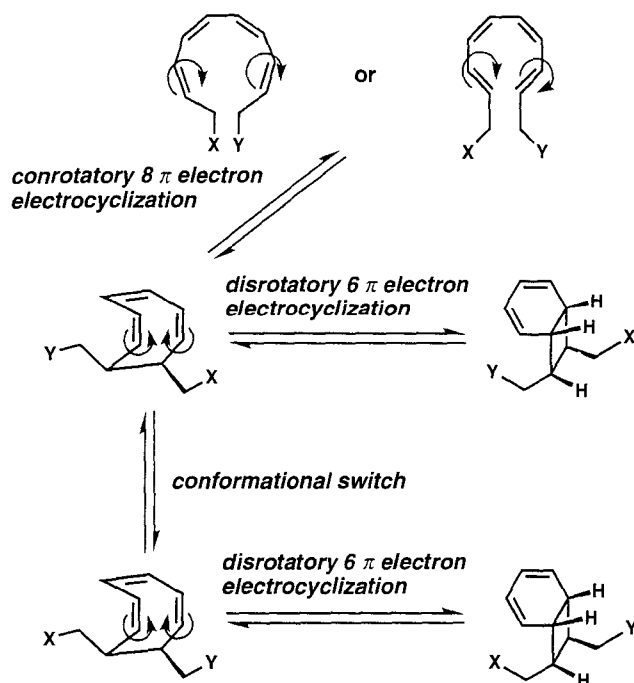
17.1 Introduction

The endiandric acids comprise a most notable class of secondary metabolites. Isolated in the early 1980s from the Australian plant *Endiandra introrsa* (Lauraceae) by D. St. C. Black's group,¹ these natural products are striking for their novel molecular architecture and their intricate structural interrelationships. Endiandric acids A (1), B (2), and C (3) contain four fused carbocyclic rings, a phenyl substituent and a carboxyl group. Despite containing eight stereogenic centers, the endiandric acids are found in nature as racemates, which is very unusual for chiral natural products. To explain this rather curious observation, Black proposed an intriguing hypothesis for the "biosynthesis" of these molecules from achiral polyunsaturated precursors through a series of *nonenzymatic* electrocyclizations (see Schemes 1 and 2). The Black hypothesis postulates the cascade of reactions shown in Scheme 1 as the pathway by which endiandric acids A–D are formed in nature. Thus endiandric acids E (5), F (6), and G (7) were proposed as immediate precursors to tetracyclic endiandric acids A (1), B (2), and C (3) respectively; the conversion being effected by an intramolecular Diels–Alder reaction. Endiandric acid D (4) cannot undergo an intramolecular Diels–Alder reaction, and so it does not form a corresponding tetracycle. An additional striking feature of the hypothesis of Black and coworkers is that endiandric acids D–G (4–7) could arise from sequential electrocyclizations of achiral polyenes I–IV through the intermediacy of 1,2-*trans*-disubstituted cyclooctatrienes (Scheme 1).

The molecular frameworks of the endiandric acids were unprecedented at the time of their discovery. Intrigued by these unique structures and Black's hypothesis for their biogenetic origin, the



Scheme 1. The endiandric acid cascade (R = H, Me).

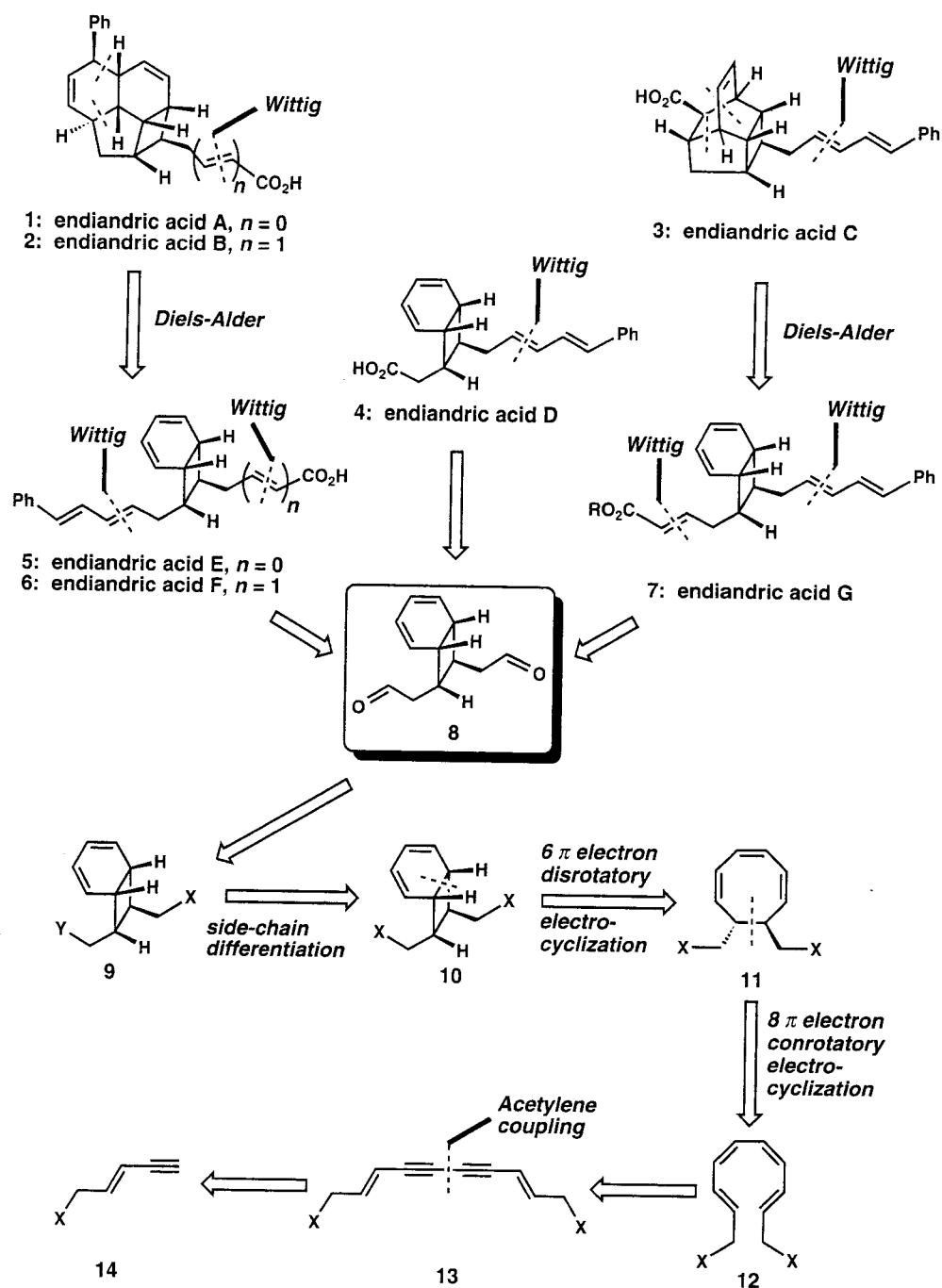


Scheme 2. Thermally allowed 8π electron and 6π electron electrocyclizations (Woodward-Hoffmann rules).

Nicolaou group initiated a program directed towards their total synthesis.²

17.2 Retrosynthetic Analysis and Strategy

The elegant and provocative biosynthetic hypothesis proposed by Black and coworkers guided the retrosynthetic analysis of the endiandric acids. The most logical and productive retrosynthetic disconnection of endiandric acids A (**1**), B (**2**), and C (**3**) appeared to be the one suggested by the biosynthetic hypothesis involving a retro Diels-Alder reaction as shown in Scheme 3. The forward transformation, the intramolecular Diels-Alder reaction, is, of course, well documented in the literature.³ A potential advantage of this strategy is that it leads to bicyclic endiandric acids E (**5**), F (**6**), and G (**7**). These compounds are closely related to a fourth endiandric acid unknown at the time of this planning, but anticipated to be a naturally occurring member of the family, namely endiandric acid D (**4**). Thus, the first subtargets became the four structu-



Scheme 3. Retrosynthetic analysis of endiandric acids A-G.

rally related endiandric acids D–G, all of which could conceivably arise from a common intermediate, dialdehyde **8** (Scheme 3) or its equivalent. Wittig-type or other olefination reactions would be required to achieve the construction of **4–7** from **8**. Differentiation of the two aldehyde functions in **8** would almost certainly be needed to achieve selectivity. Generalized intermediate **9** presents itself as a more practical precursor (one of the two substituents X and Y is an aldehyde and the other is a masked aldehyde). At this point, it was recognized that some degree of symmetry could be introduced into the precursor intermediates. Symmetry has always been a fascinating feature of many human endeavors, organic synthesis included. Symmetry can enhance the aesthetic appeal of a synthesis and can increase its efficiency, provided, of course, that differentiation of the symmetrical functionalities can be achieved at the appropriate point in the sequence. In the present case, intermediate **9** was considered as a differentiated derivative of compound **10**, a generic structure in which both appendages are terminated by the same group X. Two electrocyclization reactions operating on **10** in the retro direction lead to conjugated tetraene **12** via cyclooctatriene **11**. Further functional group manipulation provides **13** as a plausible precursor which, in addition to maintaining the same symmetry, is amenable to a direct synthesis from the commercially available enyne **14** (X=OH). In the synthetic direction, the conversion of intermediate **12** to the endiandric acids entails three tandem pericyclic reactions, two of which are electrocyclizations ($8\pi e^-$ and $6\pi e^-$) and one which is an intramolecular [4+2] cycloaddition. The two electrocyclic reactions are thermally allowed by the Woodward–Hoffmann rules⁴ and proceed in a stereospecific manner as shown in Scheme 2. Thus, in order to obtain the desired *trans* disubstituted [4.2.0] bicyclic product, the *trans/cis/cis/trans* or the *cis/cis/cis/cis* tetraenes must be used. When the two substituents (X and Y) are the same, the two bicyclic products are, of course, the same.

Although the above-mentioned electrocyclization reactions were well studied prior to the discovery of the endiandric acids, their utilization in the total synthesis of complex molecules had not been demonstrated. The endiandric acids, therefore, offered an irresistible opportunity to explore the utility of electrocyclization reactions in synthesis. The successful studies disclosed below demonstrate that these reactions can provide concise solutions to the challenge presented by complex polycyclic frameworks.

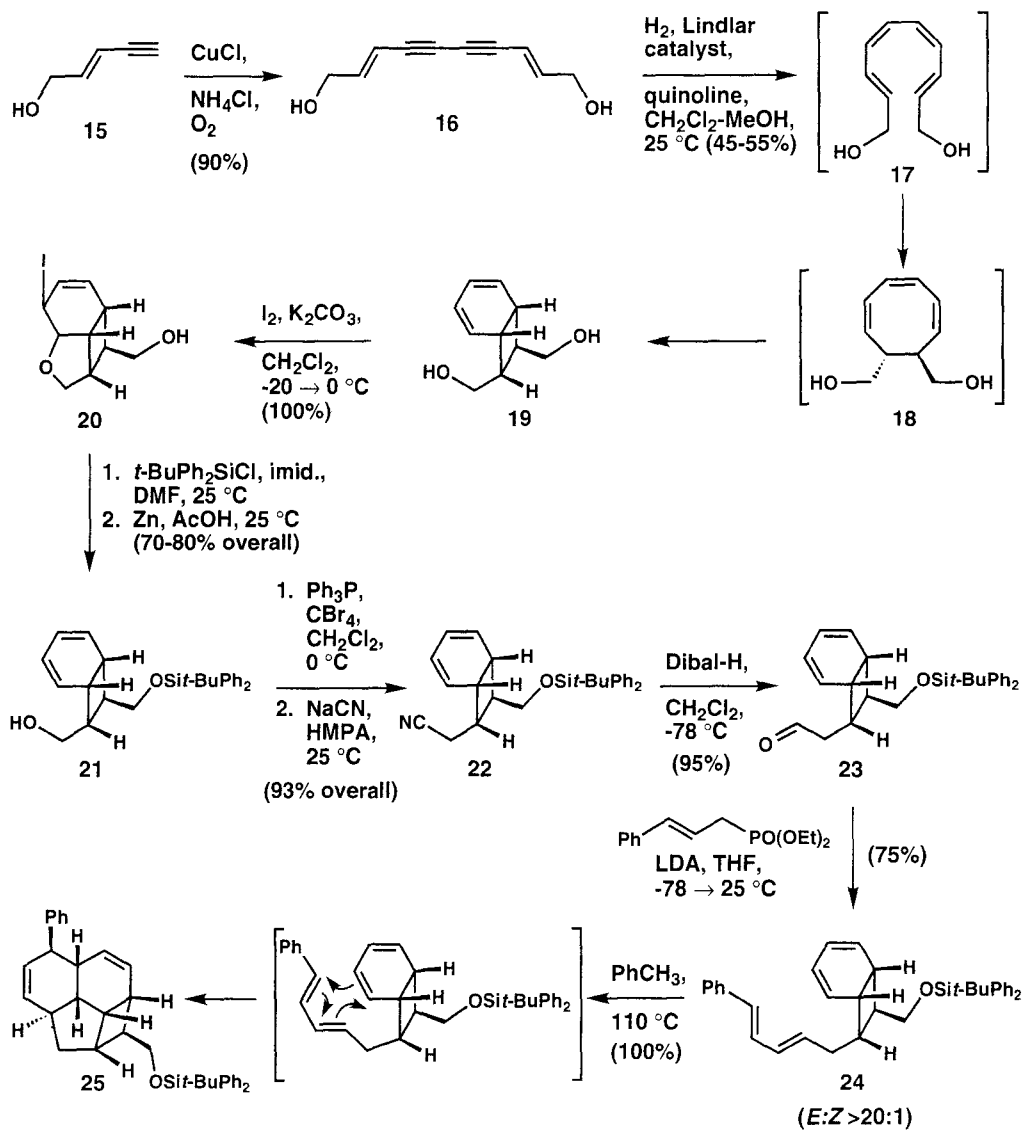
17.3 Total Synthesis

17.3.1 Stepwise, Stereocontrolled Total Synthesis of Endiandric Acids A-D (and E-G)

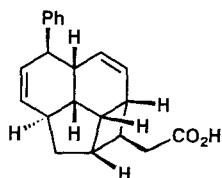
From the retrosynthetic analysis discussed above, a plan for a stepwise and stereocontrolled total synthesis of all the endiandric acids was evolved. The execution of the synthesis proceeded smoothly and delivered the target molecules efficiently and stereospecifically (see Schemes 4-7). Thus, subjection of commercially available *trans*-pent-2-en-4-yn-1-ol (**15**) to a classical Glaser acetylene coupling⁵ provides diacetylene **16** in 90 % yield (see Scheme 4). Partial hydrogenation of **16** (Lindlar catalyst, quinoline) results in the formation of tetraene **17**. The intermediacy of **17** is, however, only brief, for it participates in sequential $8\pi e^-$ conrotatory and $6\pi e^-$ disrotatory electrocyclizations to give bicyclic [4.2.0] system **19** in 45-55 % overall yield (see **17** \rightarrow **18** \rightarrow **19**). Unfortunately, the two hydroxyl groups in **19** could not be differentiated even with bulky reagents, and a special maneuver had to be devised for their sequential manipulation. You will note that the *endo*-oriented hydroxyl group in **19** resides in proximity to one of the π bonds in the six-membered ring. It was, therefore, anticipated that this unique spatial relationship could permit a facile iodoetherification reaction, thereby allowing a selective internal protection of the *endo* hydroxyl. Indeed, treatment of diol **19** with iodine and potassium carbonate provides, in quantitative yield, iodo ether **20**. Silylation of the remaining hydroxyl group in **20** with *tert*-butyldiphenylsilyl chloride under standard conditions, followed by reductive opening of the ether ring with Zn dust in acetic acid, gives the desired monoprotected hydroxy silyl ether **21** in 70-80 % overall yield from diol **19**. Treatment of alcohol **21** with CBr_4 and Ph_3P , followed by displacement of the resulting bromide with sodium cyanide in HMPA affords the nitrile **22** in 93 % yield. This nitrile (**22**) served admirably as a common intermediate for the stepwise and stereocontrolled total synthesis of all the endiandric acids (A-G).

The key intermediate **25** was prepared efficiently from aldehyde **23**, obtained by reduction of nitrile **22** with Dibal-H. Treatment of **23** with the lithium salt of *trans*-diethyl cinnamylphosphonate furnishes compound **24** in 75 % yield and with a 20:1 ratio of *E*:*Z* olefin stereoisomers. The stage is now set for the final and crucial operations to complete the molecular skeletons of endiandric acids A and B.

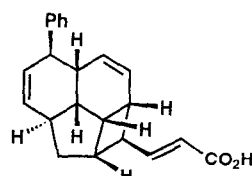
Gratifyingly, when compound **24** is refluxed in a solution of toluene at 110°C , it undergoes quantitative [4+2] cycloaddition to polycyclic system **25**. The indicated stereochemistry of **25** was anticipated on the basis of the *trans,trans* geometry of the phenyl-diene system in precursor **24** and the presumed preference for an *exo* transition state geometry. These assumptions were vindicated by the eventual conversion of **25** to endiandric acids A (**1**) and B (**2**).



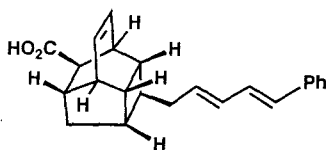
Scheme 4. Synthesis of intermediate 25.



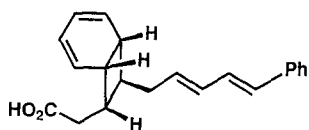
1: endiandric acid A



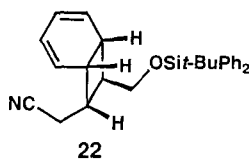
2: endiandric acid B



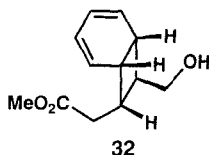
3: endiandric acid C



4: endiandric acid D



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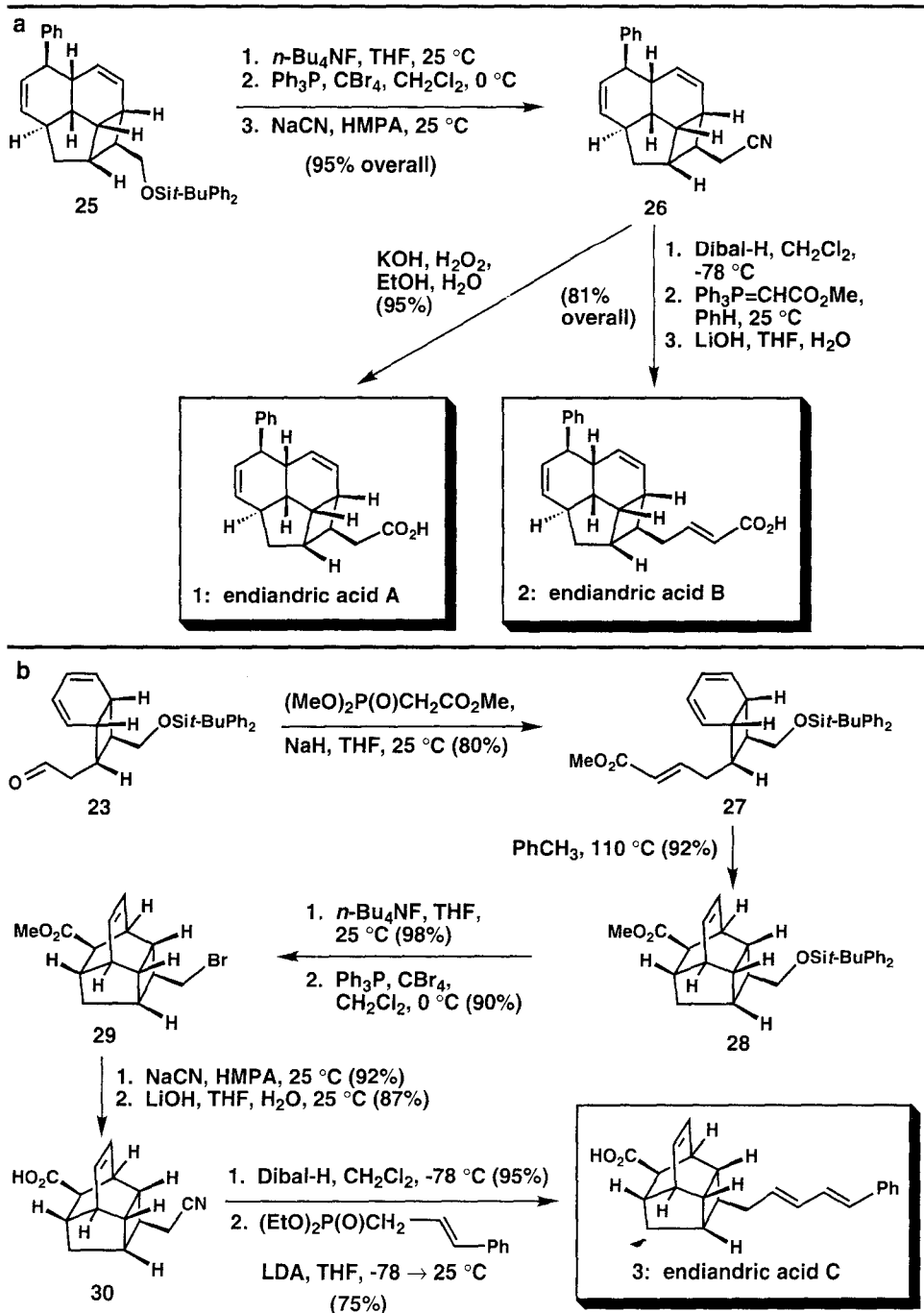


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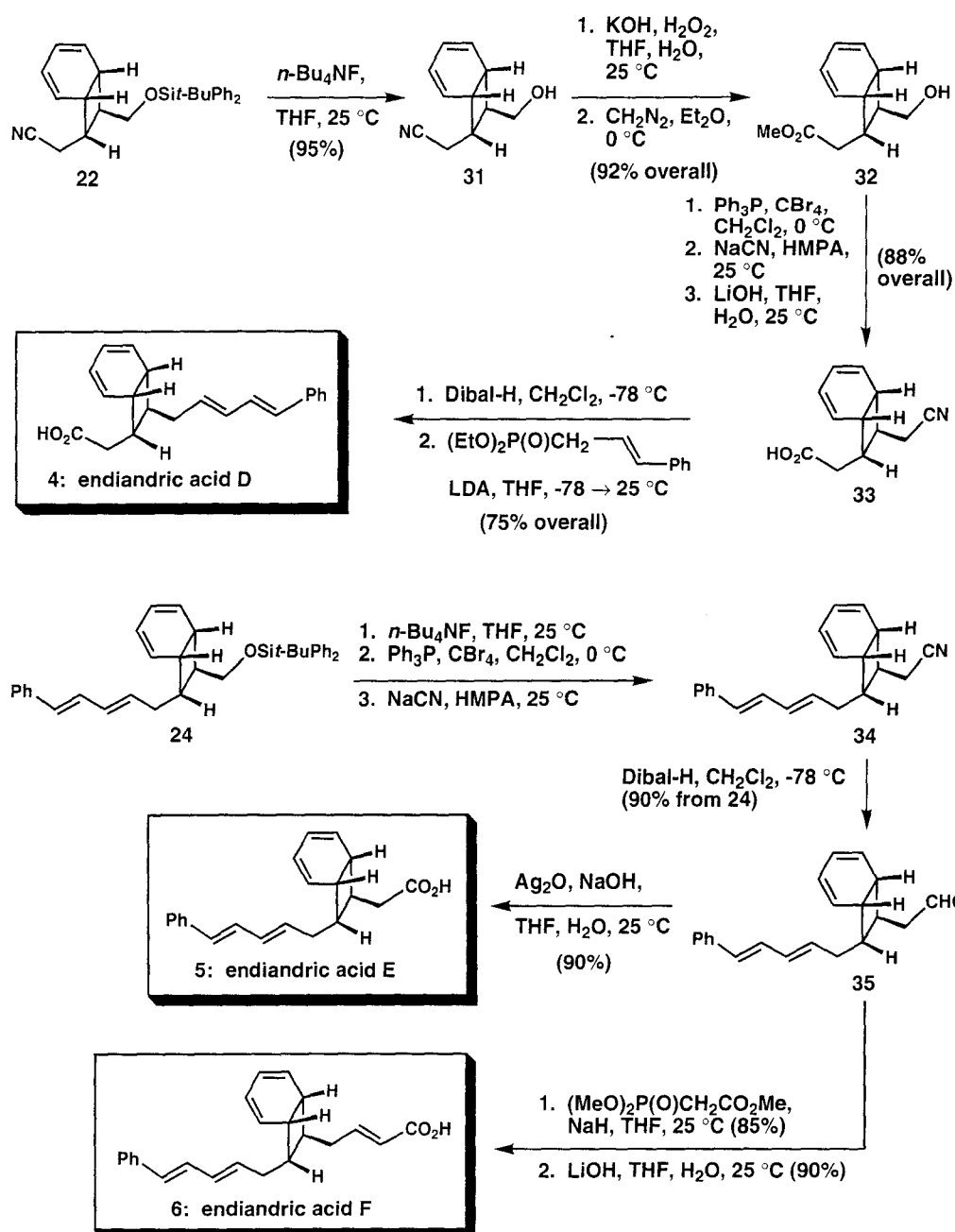
The final drive towards the target molecules proceeded as follows (see Scheme 5a). The silyl group is removed with fluoride ion and the resulting alcohol is converted to the corresponding bromide and then to the nitrile **26** (95 % overall yield). Finally, hydrolysis of the nitrile grouping in **26** with basic hydrogen peroxide at 25–50 °C furnishes, in 95 % yield, endiandric acid A (**1**). For the synthesis of endiandric acid B (**2**), nitrile **26** is taken through a different route. First, it is reduced with Dibal-H to afford the aldehyde which is then treated with $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ to afford the methyl ester of endiandric acid B in 81 % overall yield. Finally, endiandric acid B (**2**) was obtained from its methyl ester in quantitative yield by saponification with lithium hydroxide.

Endiandric acid C (**3**) can be synthesized from aldehyde **23** according to Scheme 5b. In contrast to the construction of endiandric acids A and B, only an isolated olefin is needed on the *endo* side chain of the molecule that can engage the 1,3-cyclohexadiene moiety in an intramolecular Diels–Alder reaction.³ Treatment of the anion derived from the action of sodium hydride on $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$ with aldehyde **23** gives, stereoselectively and in 80 % yield, the *E* α,β -unsaturated ester **27**. Refluxing compound **27** in toluene solution accomplishes the formation of the endiandric acid C framework **28** via the expected $[\pi 4_s + \pi 2_s]$ cycloaddition reaction in 92 % yield. Completion of the synthesis requires a series of steps by which the side chain on the cyclobutane ring can be homologated through an olefination reaction. Thus, desilylation of **28** with fluoride ion generates the corresponding alcohol (98 %) which can then be converted to bromide **29** by the action of $\text{Ph}_3\text{P}-\text{CBr}_4$ (90 %), and then to the corresponding nitrile by displacement of the bromide with cyanide ion (92 % yield). In order to provide protection for the carboxyl group during the impending Dibal-H reduction of the nitrile, the methyl ester is hydrolyzed to the corresponding carboxylic acid (**30**) with lithium hydroxide in 87 % yield. The reduction of **30** with excess Dibal-H proceeds smoothly in methylene chloride at low temperature and affords, upon workup, the desired aldehyde in 95 % yield. Finally, condensation of this substance with the anion derived from deprotonation of *trans* diethyl cinnamylphosphonate with LDA affords endiandric acid C (**3**) in 75 % yield.

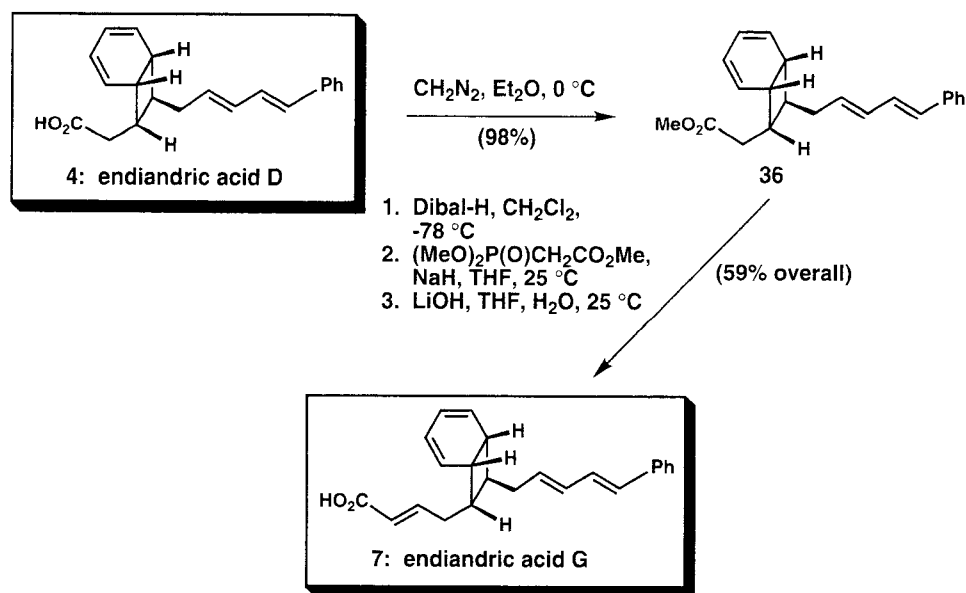
Although the “biosynthetic” cascade hypothesis predicts the co-occurrence of endiandric acids D (**4**) and A (**1**) in nature, the former compound was not isolated until after its total synthesis was completed in the laboratory (see Scheme 6). Our journey to endiandric acid D (**4**) commences with the desilylation of key intermediate **22** to give alcohol **31** in 95 % yield. The *endo* side chain is then converted to a methyl ester by hydrolysis of the nitrile to the corresponding acid with basic hydrogen peroxide, followed by esterification with diazomethane to afford intermediate **32** in 92 % overall yield. The *exo* side chain is then constructed by sequential bromination, cyanide displacement, ester hydrolysis (**33**), reduction, and olefination (**4**) in a straight-



Scheme 5. Syntheses of endiandric acids A (1) and B (2) (a), and C (3) (b).



Scheme 6. Syntheses of endiandric acids D (4), E (5) and F (6), and G (7).



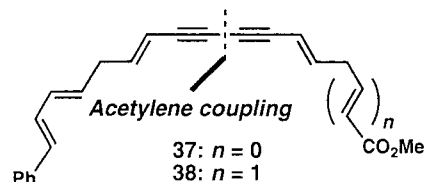
Scheme 6. Syntheses of endiandric acids D (4), E (5) and F (6), and G (7) (continued).

forward manner as already discussed for similar intermediates above.

The "biogenetic" scheme for endiandric acids also predicts the plausible existence in nature of endiandric acids E (5), F (6), and G (7). Even though they are still undiscovered, their synthesis has been achieved (Scheme 6). For endiandric acids E and F, key intermediate **24** is converted, by conventional means, to aldehyde **35** via intermediate **34**. Oxidation of **35** with silver oxide in the presence of sodium hydroxide results in the formation of endiandric acid E (5) in 90% yield, whereas elaboration of the *exo* side chain by standard olefination (85% yield) and alkaline hydrolysis (90% yield) furnishes endiandric acid F (6). The construction of the remaining compound, endiandric acid G (7), commences with the methyl ester of endiandric acid D (36) and proceeds by partial reduction to the corresponding aldehyde, followed by olefination and hydrolysis with aqueous base as shown in Scheme 6.

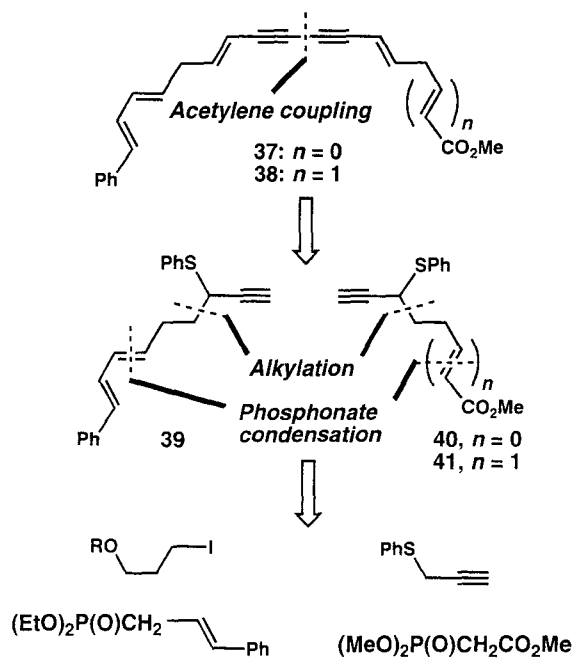
17.3.2 "Biomimetic", One-Step Approach to Endiandric Acids A–D (and E–G)

Through a display of a series of electrocyclization reactions, the Nicolaou group demonstrated the "biomimetic", one-step synthesis of the endiandric acids involving the cascade of reactions proposed by Black. The polyunsaturated compounds **37** and **38** (Scheme 7) were designed for their relative stability and potential to serve as

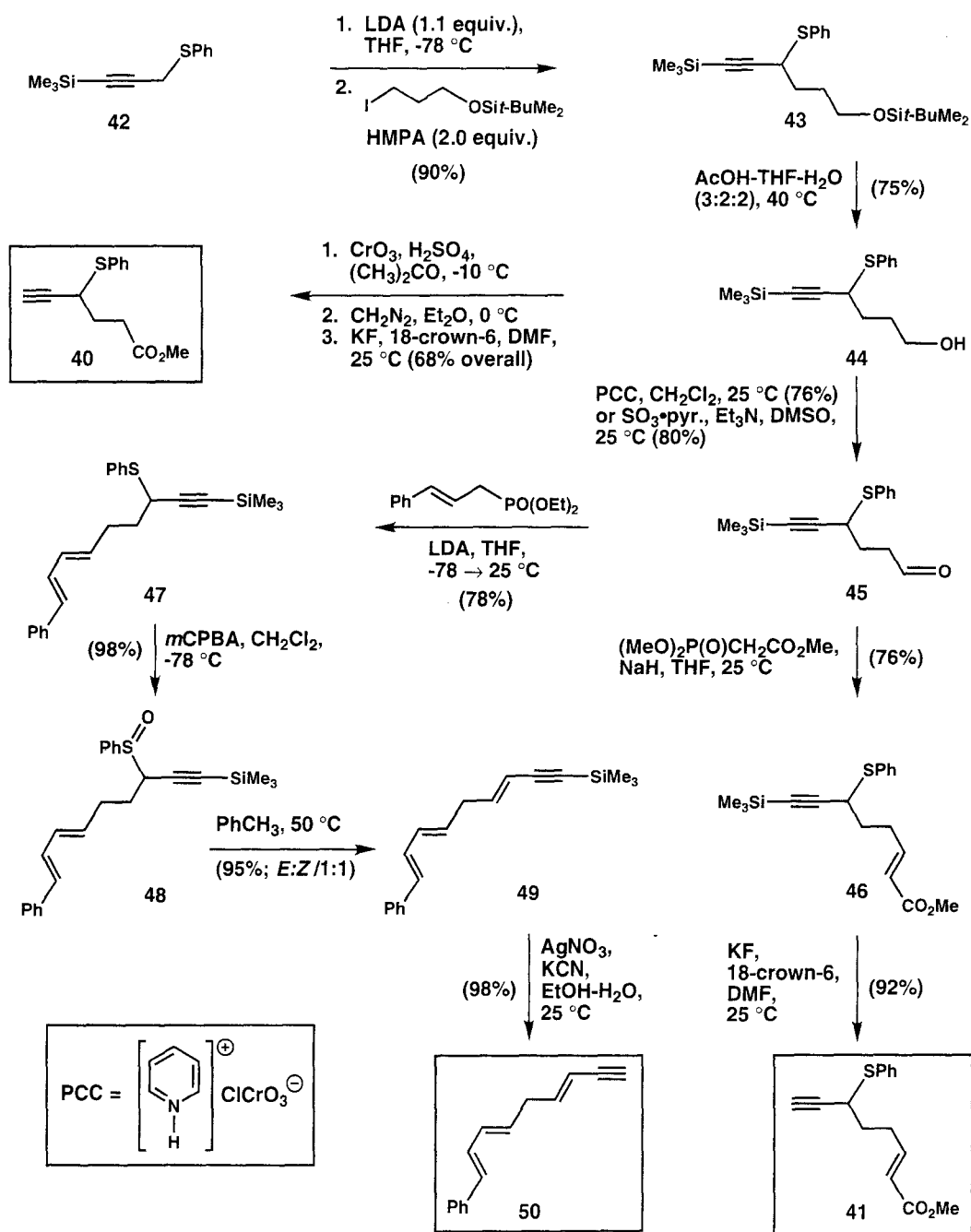


precursors to the required polyolefinic substances upon mild hydrogenation over Lindlar catalyst. Scheme 7 outlines, in retrosynthetic format, the general features of the strategy for the synthesis of these polyunsaturated molecules. Thus, disconnection of the carbon-carbon bond between the two acetylenic groups in **37** and **38** and functional group interchange by converting the two adjacent double bonds to single bonds carrying phenylthio groups leads to the terminal acetylenes **39–41**. In the synthetic direction, oxidation of sulfur to the corresponding sulfoxide followed by *syn*-elimination is expected to generate the desired *E* double bond in each compound. Two important reactions for carbon-carbon bond formation are then called upon to allow tracing of these intermediates (**39–41**) to simple starting materials as shown in Scheme 7. The use of heteroatoms (sulfur and phosphorus) in organic synthesis is amply demonstrated in these constructions. Alkylations of sulfur-stabilized anions and sulfoxide *syn*-eliminations are used to form, sequentially, single and double carbon-carbon bonds; phosphonate-aldehyde condensations are used to form olefinic bonds.

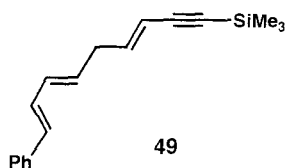
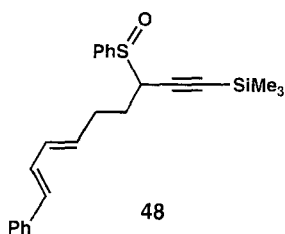
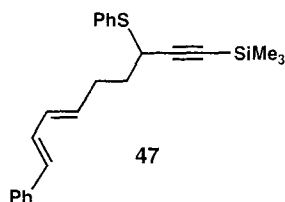
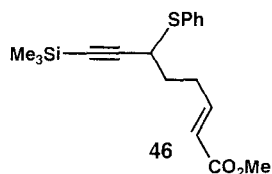
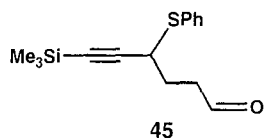
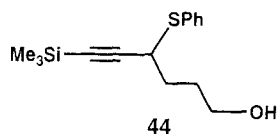
Scheme 8 summarizes the construction of the requisite building blocks **40**, **41**, and **50**. Alkylation of the lithio derivative of 1-(trimethylsilyl)-3-phenylthio-1-propyne (**42**) with 3-iodo-1-(*tert*-butyldimethylsilyloxy)propane in the presence of HMPA affords compound **43** in 90% yield. Selective desilylation of the protected alcohol is achieved by warming **43** to 40°C in AcOH-THF-H₂O



Scheme 7. Retrosynthetic analysis of polyunsaturated precursors **37** and **38**.



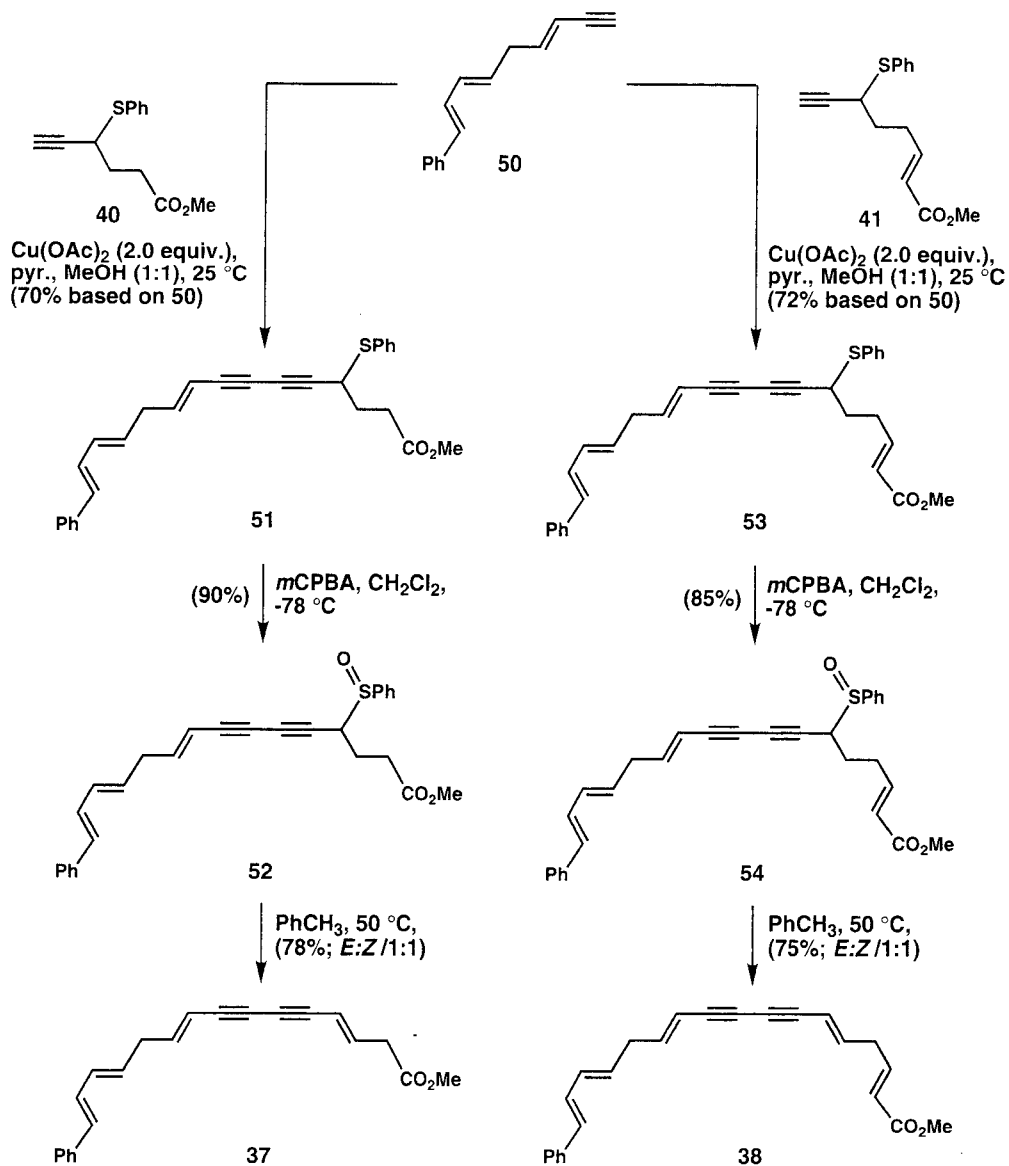
Scheme 8. Syntheses of intermediates 40, 41, and 50.

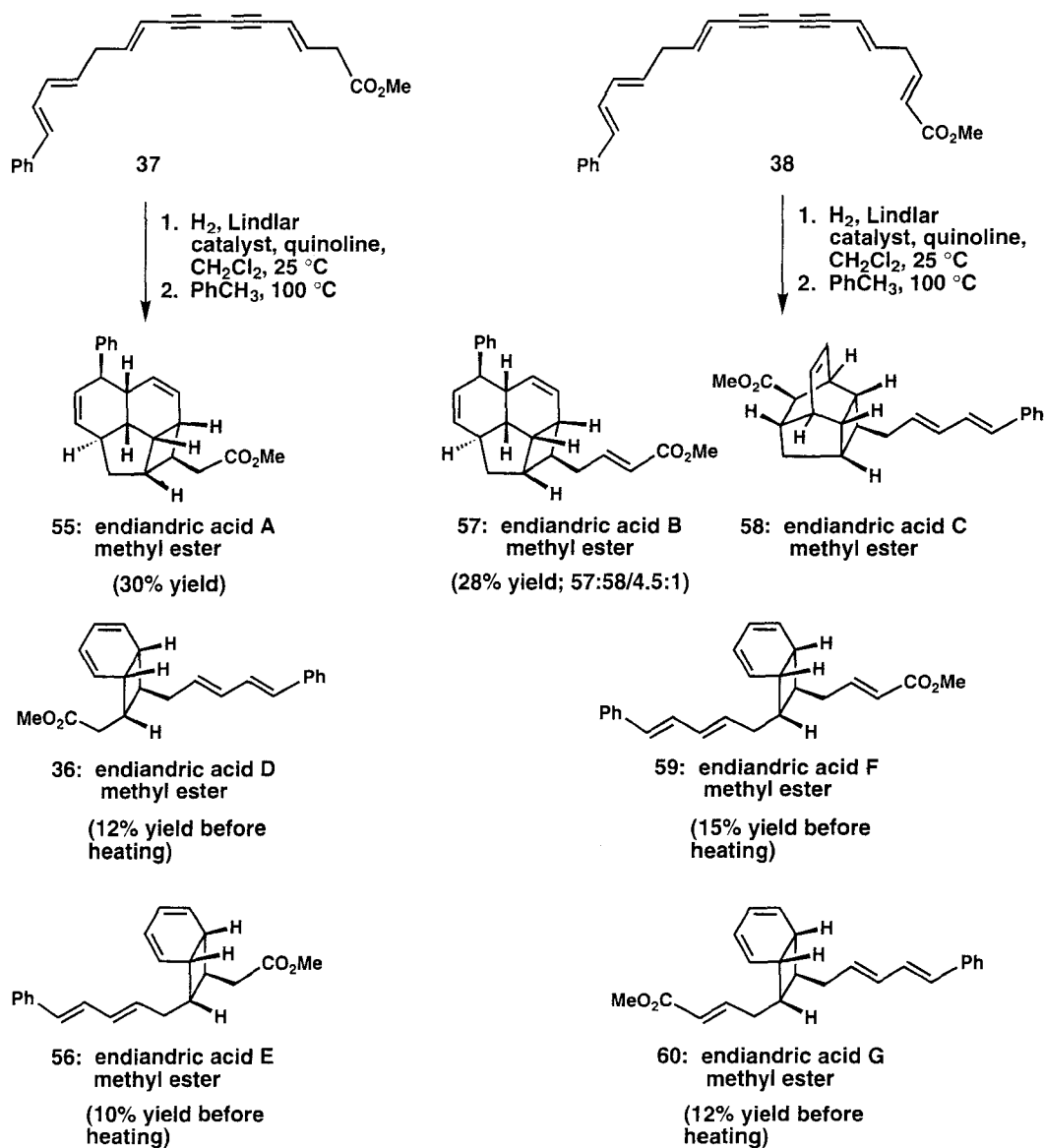


(3:2:2), affording alcohol **44** in 75% yield. Jones oxidation of **44** to the corresponding carboxylic acid is possible under carefully controlled conditions leading, after esterification (CH_2N_2) and deprotection of the acetylene ($\text{KF}/18\text{-crown-6}$), to terminal acetylene methyl ester **40** in 68% overall yield. Taken in a slightly different direction, primary alcohol **44** can be oxidized with pyridinium chlorochromate (PCC) in methylene chloride (76%) or alternatively with $\text{SO}_3 \cdot \text{pyr}/\text{Et}_3\text{N}$ in DMSO (80%) to the corresponding aldehyde **45**, a common precursor to both key intermediates **41** and **50**. Thus, standard olefination of **45** with the appropriate phosphonate reagent furnishes the *E* α,β -unsaturated methyl ester **46** stereoselectively and in 76% yield. Finally, removal of the silyl group from **46** with fluoride ion results in the formation of terminal acetylene **41** in high yield. On the other hand, reaction of **45** with the appropriate cinnamyl phosphonate reagent produces, stereoselectively and in 78% yield, diene **47**, the phenylthio group of which can be smoothly oxidized with *m*CPBA to afford the corresponding sulfoxide (**48**) in 98% yield as a 1:1 diastereoisomeric mixture. The anticipated *syn*-elimination is accomplished when **48** is heated in a solution of toluene at 50°C, furnishing a mixture of *E* and *Z* olefins (*ca.* 1:1) in 95% total yield. The pure *E* isomer **49** can be desilylated with $\text{AgNO}_3\text{--KCN}$ in aqueous ethanol to afford the desired terminal acetylene **50** in 98% yield.

With the required building blocks in hand, the targeted precursors **37** and **38** can be assembled as follows (see Scheme 9). A classical Glaser acetylene coupling reaction [$\text{Cu}(\text{OAc})_2/\text{pyr.}\text{--MeOH}$] is utilized to join compound **50** with the more readily available **40** (five-fold excess), leading to diacetylene **51** in 70% isolated yield (based on **50**). Selective oxidation of the sulfur atom in **51** with *m*CPBA affords the corresponding sulfoxide (**52**) as a mixture of diastereoisomers in 90% total yield. Thermally induced *syn*-elimination introduces the necessary unsaturation leading to a mixture of *E* and *Z* geometrical isomers, in 78% total yield, from which the pure *E* compound **37** is obtained after silica gel chromatography. In a similar fashion, and in similar yields, compound **38** can be synthesized from **50** and **41** (Scheme 9), setting the stage for the much anticipated triggering of the endiandric acid cascade and its experimental verification.

With the availability of suitable precursors, a systematic study of the endiandric acid cascade now became possible (see Scheme 10). The first experiment to be undertaken was the mild hydrogenation of the diacetylenic precursor **37** under carefully monitored conditions employing Lindlar catalyst and quinoline, followed by brief heating of the resulting mixture at 100°C in toluene. Gratifyingly, it was possible to isolate endiandric acid A methyl ester (**55**) from this mixture in 30% yield. The power of this cascade can only be fully appreciated when one recognizes that in a single operation, a simple achiral polyene is converted into the complex tetracyclic framework of endiandric acid A methyl ester with complete control over eight stereogenic centers! The apparent absence of endiandric

Scheme 9. Syntheses of intermediates **37** and **38**.



Scheme 10. “Biomimetic” syntheses of endiandric acids A–G.

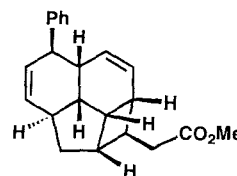
acid D methyl ester (**36**) in this reaction mixture is puzzling at first, but easily explained (and experimentally confirmed) on further reflection as discussed below. Examination of the reaction mixture in the above experiment *before heating* revealed the presence of both endiandric acids D and E methyl esters (**36** and **56**, respectively) which were isolated in 12 and 10% yields, respectively. Under these conditions, however, the conjugated tetraenes and cyclooctatrienes postulated in this cascade (see Scheme 1) were not observed, presumably due to their rapid conversion to the bicyclo [4.2.0] systems at ambient temperatures.

In a similar fashion, the selective hydrogenation of the extended diacetylene **38**, followed by brief heating at 100°C, allowed the isolation of endiandric acid B methyl ester (**57**) and endiandric acid C methyl ester (**58**) in a combined yield of 28% and in a ratio of ca. 4.5:1 (see Scheme 10). Once again, in this remarkable sequence we witness the generation of the two seemingly unrelated and complex polycyclic structures of endiandric acids B and C by assembly of four new rings and eight stereocenters from a prochiral, open-chain precursor in a stereospecific manner. Endiandric acid F and G methyl esters (compounds **59** and **60**) respectively, could be isolated in ca. 15 and 12% yield, provided the complete operation was conducted at ambient temperature. As expected, the postulated conjugated tetraene and cyclooctatriene systems were not observed, apparently due to their rapid conversion to bicyclic compounds even at ambient temperatures (see Scheme 1).

With the demonstration of the pathways described above it became abundantly clear that the formation of endiandric acids in nature from polyunsaturated achiral precursors is quite feasible without the participation of enzymes, as Black had so insightfully suggested in 1980.

The kinetics of certain paths of this fascinating cascade were further studied by NMR spectroscopy. Thus, thermally induced transformations of the methyl esters of endiandric acids D–G were conveniently observed in [D₈]-toluene at 70°C by following the ¹H NMR signal corresponding to the methyl ester group in these systems. Under these conditions, endiandric acid E methyl ester (**56**) was observed to undergo: (a) reversible isomerization to endiandric acid D methyl ester (**36**); and (b) irreversible intramolecular [$\pi 4_s + \pi 2_s$] cycloaddition (Diels–Alder reaction) to endiandric acid A methyl ester (**55**) with a half-life ($t_{1/2}$) of ca. 1.3 h (at 70°C) (Figure 1a). Eventually, all the material is transformed, and endiandric acid A methyl ester (**55**) is formed in high yield. Similar observations were made with endiandric acid D methyl ester (**36**) as shown in Figure 1b. Its half-life at 70°C was determined to be ca. 3.8 h, endiandric acid A being formed essentially in quantitative yield. This finding explains the absence of endiandric acid D methyl ester (**36**) in the hydrogenation–thermolysis experiment discussed above.

The thermally induced reactions of endiandric acids F and G methyl esters (**59** and **60**) were followed in a similar fashion



55: endiandric acid A methyl ester

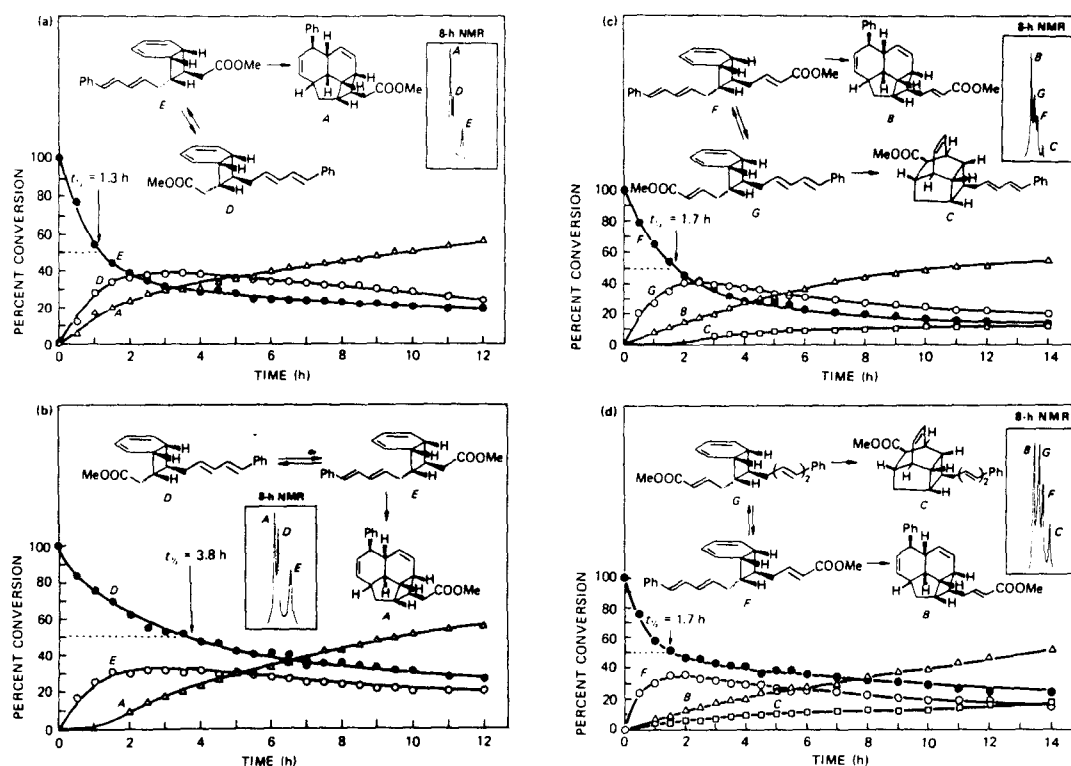
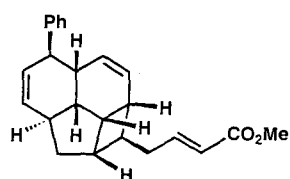
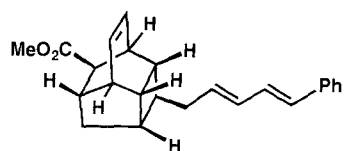


Figure 1. Thermolysis of the methyl esters of endiandric acids E (**56**) (a), D (**36**) (b), F (**59**) (c), and G (**60**) (d) at 70 °C in $[D_8]$ toluene. Data obtained by 1H NMR spectroscopy ($COOCH_3$) at 250 MHz. (from ref. 2d)



57: endiandric acid B methyl ester



58: endiandric acid C methyl ester

(Figure 1c,d). It was found that **59** and **60** are mutually interconvertible, and that both are eventually converted into compounds **57** (endiandric acid B methyl ester) and **58** (endiandric acid C methyl ester), respectively. Interestingly, compound G (**60**) was completely consumed with a half-life ($t_{1/2}$) of ca. 1.7 h (70 °C) producing endiandric acids B and C methyl esters (B and C) in a ratio of ca. 4.5:1, while compound F (**59**) was transformed to the same compounds (B and C, ca. 3.7:1 ratio) also in high yield and with a half-life ($t_{1/2}$) of ca. 1.7 h (70 °C). Apparently, the observed isomerizations $E \leftrightarrow D$ and $F \leftrightarrow G$ proceed by thermally allowed openings of the bicyclo[4.2.0] systems to cyclooctatriene systems, which undergo rapid conformational changes and reclose back to a mixture of the bicyclo[4.2.0] frameworks (see Scheme 1). It was, therefore, concluded by extrapolation of these results, that these chemical phenomena could take place in nature, albeit at slower rates.

17.4 Conclusion

The studies on the total synthesis of endiandric acids demonstrated a number of important principles of organic chemistry and provided experimental support for the rather daring hypothesis by Black regarding to their natural origin. Thus, the evolution of a highly challenging bicyclo[4.2.0] system by consecutive electrocyclizations ($8\pi e^-$ and $6\pi e^-$) demonstrates the power of such reactions in organic synthesis. The use of phosphonate condensation reactions proved quite powerful in constructing, in a stereocontrolled fashion, the required olefins, which provided the precursors to the final intramolecular [4+2] cycloaddition reactions *en route* to the target molecules. The "one-pot" construction of these targets through the endiandric acid cascade represents a remarkable and encouraging achievement in synthesis, particularly if one considers the stereospecificity of the chemical events which is, of course, encoded in the geometry of the double bonds involved in these remarkable, stereocenter-generating processes.

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