Sequential Diels–Alder Reactions on a 1,3,7,9-Tetraene: An Efficient and Stereoselective Route to the Perhydrophenanthrene Skeleton

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A novel, efficient, and stereoselective route to the perhydrophenanthrene skeleton is described utilizing sequential Diels–Alder reactions of methyl {(trimethylsilyl)ethynyl}acrylate with a 1,3,7,9-tetraene (bis-diene).

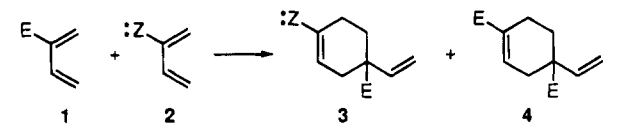
Introduction

The perhydrophenanthrene skeleton is extremely common in natural product chemistry, being embodied in particular in the carbon framework of steroids and most triterpenoids. Many synthetic methodologies have been developed to construct this core structure among which the Robinson annelation and the intramolecular Diels–Alder cycloaddition stand as some of the most successful.[2] We report herein the full details of our initial investigation of a novel approach to this skeleton that utilizes sequential Diels–Alder reactions on a bis-diene.

The cross Diels–Alder cycloaddition (CDAC) involving two different dienes, one acting as the diene and the other as the dienophile, is an aspect of the DAC reaction which has not found many synthetic applications,[3,4] mainly because in such reactions the final product is often a mixture of all possible structural, regio-, and stereoisomers, including self-dimerization. The few selective CDACs found in the literature often involve a butadiene substituted with an electron-withdrawing group (EWG) at the 2 and/or 3 position such as **1** and electron-rich dienes such as **2** (Scheme 1).[3,4] The EWG at position 2 on diene **1** increases the dienophilicity of the C1–C2 double bond whereas the electron-releasing group (ERG) at any position increases the enophilicity of the diene toward a normal DAC. Good yields of the cross cycloadduct **3** are obtained from these CDACs and the regioselectivity is usually very high (typically only one isomer (**3**) can be detected). Invariably, it is the olefin bearing the EWG substituent that reacts as the dienophile. The strong dienophilic character of the C1–C2 alkene in **1** is evidenced by its preference toward self-dimerization to give **4** rather than to react with methyl acrylate.[5]

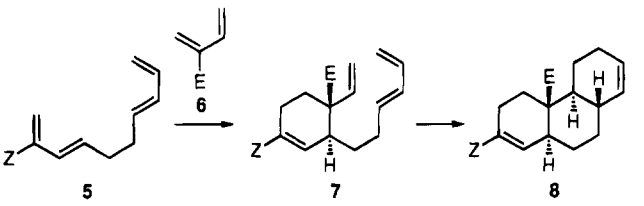
On the basis of the above discussion, we believed that it would be possible to adjust the electronic properties of

Scheme 1



E = Electron-withdrawing group, Z= Electron-releasing group

Scheme 2



E=electron-withdrawing group, Z=electron-releasing group

each of the three diene units in **5** and **6** in order to favor one of the 18 possible [4 + 2]-cycloadditions (not accounting for regio- and stereoisomers) as shown in Scheme 2. It was expected that the cycloadduct **7** would be favored, arising from an attack of the C_1–C_2 olefinic bond in **6** on the electron-rich diene. The regio- and stereochemistry of this adduct was expected to be as shown based on the Frontier Molecular Orbital (FMO) theory.[6] Then, an intramolecular Diels–Alder cycloaddition (IMDAC) on **7** would close the perhydrophenanthrene ring system. The IMDAC should proceed via an *exo* transition state for steric reasons to give the final tricyclic compound **8** having the stereochemistry present in most steroids and terpenoids (vide infra). This approach has several advantages, besides its potential efficiency and stereoselectivity. First, the tricyclic structure will contain strategically positioned functionality which may be useful for further elaboration of the intermediates into natural products. Secondly, many functional groups could be placed on the dienophile–diene units prior to assembly without compromising the key Diels–Alder reactions. This may include the challenging C11-hydroxy group of the corticosteroids. Thirdly, there is a wealth of technologies for the construction of dienes which contributes to the strength of this approach. But more importantly, the angular C10-ester group that would be produced by this approach provides a versatile appendage for the elaboration of the A-ring of the polycyclic intermediates into any of the main types of A-rings found in steroids (eq 1). In the case of the natural and unnatural

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(1) Present adress: Université de Sherbrooke, Département de Chimie, Sherbrooke, Qc, Canada, J1K 2R1.

(2) See Ho, T.-L. in *Carbocycle Construction in Terpenes Synthesis*; VCH Publishers: New York, 1988.

(3) For examples see: (a) Johnstone, R. A. W.; Quan, P. M. *J. Chem. Soc.* **1963**, 935. (b) Stewart, C. A., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 4815. (c) Houk, K. N.; Luckus, L. J. *J. Org. Chem.* **1973**, *38*, 3836. (d) Franck-Neumann, M.; Martina, D.; Brion, F. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 864. (e) Bellville, D. J.; Nathan, L. B. *J. Am. Chem. Soc.* **1982**, *104*, 2665.

(4) (a) Martina, D.; Brion, F. *Tetrahedron Lett.* **1982**, *23* (8), 865. (b) Chou, S.-S. P.; Tsai, C.-Y. *J. Org. Chem.* **1988**, *53*, 5305. (c) Chou, T.; Hung, S.-C. *J. Org. Chem.* **1988**, *53*, 3020.

(5) Ten equivalents of methyl acrylate is required to suppress dimerization. See McIntosh, J. M.; Sieler, R. A. *J. Org. Chem.* **1978**, *43*, 4431.

(6) Fleming, I. in *Frontier Orbitals and Organic Chemical Reactions*, Wiley & Sons: New York, 1976, and references therein.

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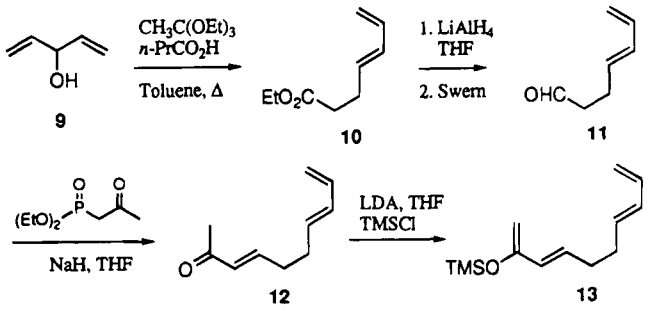
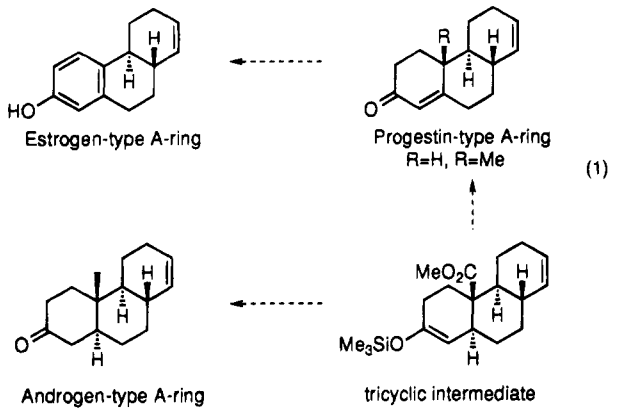
Scheme 3



progestins, for example, an oxidation of the enol ether and a reduction or decarboxylation of the C10-ester, respectively, would be required. In turn, standard oxidation of the resulting A-ring where R = H would produce the estrogen-type A-ring. Simple hydrolysis of the enol ether and reduction of the C10-ester would give entry to the androgen-type A-ring.



Results and Discussion

To test the viability of this approach, the model bis-diene **13** was prepared in six steps from acrolein and vinylmagnesium bromide (Scheme 3). The initial 1,2-addition furnished the commercial 1,4-pentadien-3-ol (**9**) in 87% yield. The orthoester Claisen rearrangement[7] proceeded in refluxing toluene to give 73% of the diene-ester **10** which was reduced to the aldehyde **11** (via the alcohol and oxidation) and condensed with the anion of diethyl 2-oxopropylphosphonate to afford a 63% yield of the (*E*)-α,β-unsaturated ketone **12** ($J_{C3=C4}$ = 16.7 Hz) for three steps. The kinetic enolate of **12** was generated with LDA in THF and trapped with trimethylsilyl chloride to give the desired bis-diene **13** in 81% yield after distillation.

2-Carbomethoxy-1,3-butadiene (**14**) can be generated *in situ* by a number of methods.[8] When the precursor 2-carbomethoxy-2,5-dihydrothiophene 1,1-dioxide[5] was heated to reflux in toluene in the presence of the bis-diene **13**, only the cyclodimer **15** was isolated (Scheme 4). Diene **14** is known to dimerize rapidly, even at 25 °C.[8] However, its preference for dimerization over its

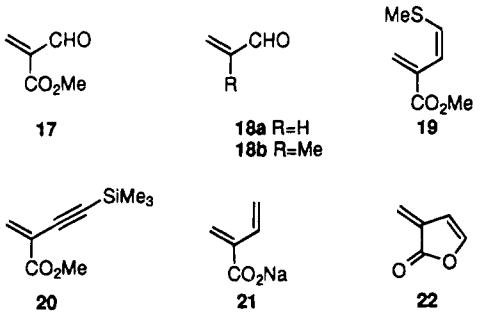
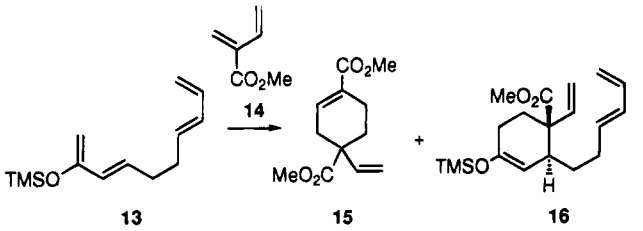


Figure 1. Possible substitutes for diene **14**.

Scheme 4



cross Diels–Alder reaction with **13** was a surprise. We have investigated this phenomenon in more detail and those results are reported elsewhere.[9] Even a slow addition of the sulfolene precursor via a syringe pump did not lead to synthetically useful amounts of the desired adduct **16**. Another method of generating **14**, in the presence bis-diene **13** at room temperature, also failed to provide acceptable amounts of **16**.[8a] We were therefore compelled to use a substitute for **14**, one in which dimerization would be impaired or impossible.

Many candidate molecules were considered to replace diene **14** (Figure 1). All have advantages and disadvantages. We first elected acrolein (**18a**) to serve as the substitute, mainly because of its ready availability and its known reactivity in the Diels–Alder reaction. The carbonyl of acrolein can act as a masked double bond thus avoiding the potential for nonselective CDACs one would expect if 1,3-butadiene was used as the diene. One disadvantage of using acrolein in this strategy is that it lacks the versatile ester group (vide supra). The analog **17** with the ester group was not selected because of the difficulties in its preparation and handling and because of potential problems of *endo*- vs *exo*-stereoselectivity in its intermolecular Diels–Alder reaction. Instead, we surmised that the use of either methacrolein or acrolein would serve as the equivalent of **17** for the construction of steroids with and without an angular methyl group.

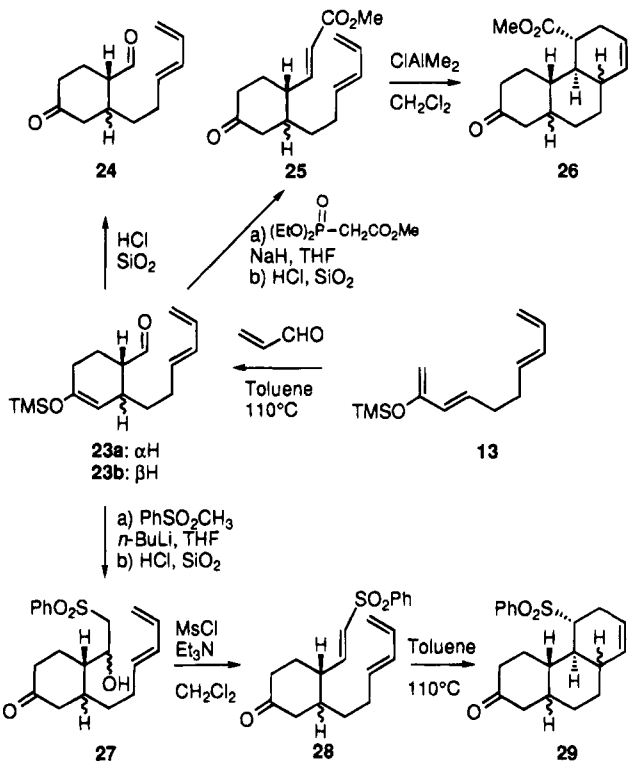
Nonetheless, when acrolein and bis-diene **13** were heated in toluene at 160 °C (sealed tube) for 1 h, we obtained the cycloadducts **23a** and **23b** in 49% yield (Scheme 5). The silyl enol ether underwent partial hydrolysis upon purification by column chromatography on silica gel. It was therefore more practical to characterize this compound as the hydrolyzed product. To that effect, the crude cycloadducts **23**, prior to purification, was stirred in ethyl acetate in the presence of silica gel and a drop of concentrated hydrochloric acid. The crude isolate, after acid hydrolysis, consisted of a 2:1 mixture of the *endo*- and *exo*-cycloadducts **24a** and **24b** which, unfortunately, could not be separated. The stereochemistry of adducts **24** could not be secured by 2D NMR

(7) For a review of the Claisen Rearrangement see Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

(8) (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 795. (b) Poly, W.; Schomburg, D.; Hoffmann, H. M. R. *J. Org. Chem.* **1987**, *53*, 3701. (c) Sydnes, L. K.; Skattebøl, L.; Chapleo, C. B.; Leppard, D. G.; Svanholt, K. L.; Dreiding, A. S. *Helv. Chim. Acta* 1975, *58*, 2061. (d) Goldberg, O.; Dreiding, A. S. *Helv. Chim. Acta* **1976**, *59*, 1904. (e) Alanine, A. I. D.; Fishwick, C. W. G.; Jones, A. D.; Mitchell, M. B. *Tetrahedron Lett.* **1989**, *30*, 5653. (f) Jung, M. E.; Zimmerman, C. N. *J. Am. Chem. Soc.* **1991**, *113*, 7813.

(9) Spino, C; Crawford, J. *Can. J. Chem.* **1993**, *71*, 1094

Scheme 5



methods. Thus, the structure of the major isomer is speculative and based on the expectation of a predominance of an *endo* approach of acrolein. We had planned to solve this stereochemical problem at a later stage, after the tricyclic nucleus had been constructed, but since this particular route was ultimately abandoned (vide infra), the stereochemical assignment of **24a** and **24b** remains unsolved.

We first looked at transforming the aldehyde into a plain terminal alkene. However, effecting a Wittig reaction on aldehydes **23** or **24** with phosphoranes proved futile as only starting material was recovered. Enolization of the aldehyde is probably at the origin of this difficulty. On the other hand, the Wadsworth–Emmons reaction of **23** with methyl diethylphosphonoacetate, followed by hydrolysis of the silyl enol ether, produced a 2:1 mixture of the desired (*E*)-α,β-unsaturated esters **25** stereoselectively in 61% yield. The *trans* geometry of the newly formed alkene in **25** was easily deduced from its coupling constant (J = 15.7 Hz). Treating this 2:1 mixture of trienes **25** in dichloromethane at ambient temperature with dimethylaluminum chloride for 45 h caused an IMDAC to occur to give four isomeric cycloadducts **26** in a 1:1.5:1.8:3.5 ratio (GC analysis). Since the original ratio of esters **25** was 2:1, this must constitute a 1.5:1 and 2:1 selectivity in the intramolecular cycloaddition of each ester separately. Other methods, including the thermal reaction, lead to similar mixtures. Because of the low selectivity exerted in this reaction we decided not to characterize each adduct and therefore we do not know which of the isomers was predominant. Alternatively, reacting the aldehydes **23** with the anion of phenyl methyl sulfone in THF, followed by acid treatment, produced a mixture of alcohols **27** which could be dehydrated using standard conditions to give two (*E*)-α,β-unsaturated sulfones **28a** and **b** ($J_{C=C}$ = 15.3 Hz) in the expected ratio of 2:1. The intramolecular Diels–Alder reaction of **28** proceeded in refluxing toluene in 18 h and we isolated again a mixture of four isomeric tricyclic molecules **29** in a 1:2.8:5.3:2.5 ratio. Although the selectivity of this intramolecular cycloaddition was slightly better than the previous one (~2–3:1), it was not synthetically acceptable. It appeared that the *endo*-**A**, normally favored by secondary orbital overlap, had not been able to successfully compete against the sterically less demanding *exo*-**B** (Figure 2). We realized that using methacrolein instead of acrolein might well increase the amount of aldehyde *endo*-cycloadduct in the intermolecular Diels–Alder as well as provide the necessary destabilization of the *exo*-**B** in the intramolecular cycloaddition. Nevertheless, the resulting perhydrophenanthrene intermediates could only lead to steroids and triterpenoids possessing an angular methyl group. It thus seemed sensible to try a second alternative to diene **14** which would incorporate the ester substituent at C_{10} (steroid numbering). The C_{10}-ester is likely to destabilized the corresponding *exo*-**D** effectively while giving a higher degree of flexibility in its transformation to steroid-type A-rings (Figure 2).

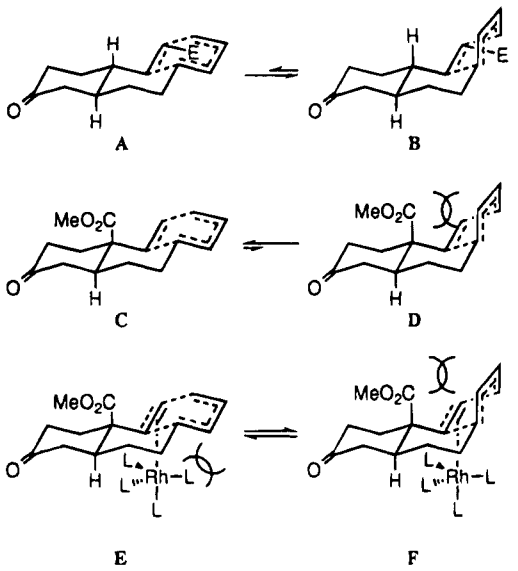
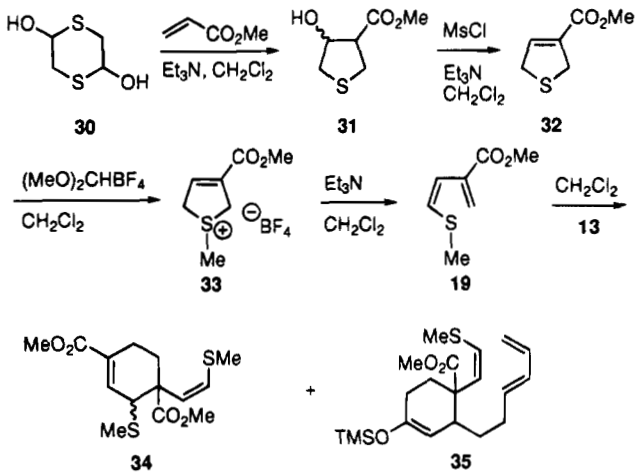


Figure 2. Transition states for the IMDAC reactions of **25**, **28**, **38**, and **40**.

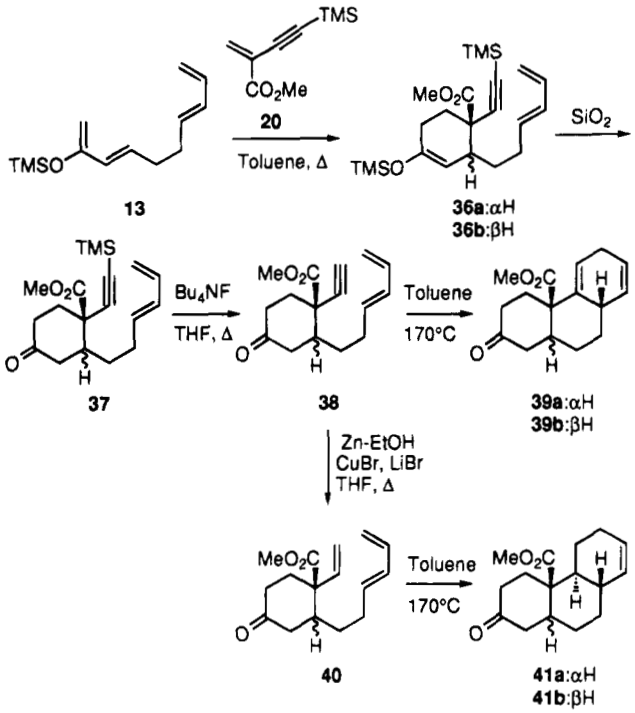
1-(Methylthio)-3-carbomethoxy-1,3-butadiene (**19**) was the second replacement for **14** that attracted our attention (Figure 1). It featured the ester functionality and a versatile (*Z*)-vinyl sulfide group which could be either oxidized to the sulfone for alkene activation or reductively removed. Compound **19** can be synthesized in four steps from methyl acrylate and 2,5-dihydroxy-1,4-dithiane in 36% overall yield (Scheme 6). The known dihydrothiophene **32** was prepared from methyl acrylate following the method of Belleau.[10] Its reaction with either of trimethyloxonium tetrafluoroborate or Borch's salt[11] gave a 94% yield of the sulfonium salt **33**. Treatment with triethylamine in dichloromethane effected a mild elimination to give exclusively the *Z*-diene **19**. Compound **19** cyclodimerizes slowly in solution (4–5 days) but rapidly when concentrated (90 min) and must therefore be used immediately.[9] When **19** was stirred for 5 days in a dichloromethane solution containing bis-diene **13**, a cycloaddition occurred to afford, as the sole product, the

(10) Honek, J. F.; Mancini, M. L.; Belleau, B. *Synth. Commun.* **1984**, *14*, 483.
(11) Borch, R. F. *J. Org. Chem.* **1969**, *34*, 627.

Scheme 6



Scheme 7



dimer **34** in 89% yield and none of the desired cross-cycloadduct **35**. This result was surprising since molecule **19** experiences a severe steric interaction between the methyl sulfide and the methylene in the *cisoid* conformation required for the DAC. We are currently investigating the reactivity of molecule **19**.

Finally, we decided to look at a third alternative to diene **14**, namely 3-carbomethoxy-1-(trimethylsilyl)-3-buten-1-yne (**20**) (Figure 1). Enyne **20** was, in retrospect, the perfect candidate to replace **14**. Not only can it not cyclodimerize because of the triple bond, but it should retain a similar dienophilicity to **14** and show an increased propensity for the *endo*-approach in its intermolecular DAC because of the bulky trimethylsilyl group. Moreover, the triple bond can be reduced to the alkene or serve as the dienophile in the IMDAC to afford a tricyclic adducts with a C_9-C_{11} double bond (steroid numbering). The latter could be used for the introduction of C_{11}-substituents, including the C_{11}-oxygen functionality present in corticosteroids. We prepared the trimethylsilyl enyne **20** in 76% yield from the palladium-catalyzed coupling of methyl 2-bromoacrylate and (trimethylsilyl)-acetylene.[12] The product was also contaminated with ca. 20% of the starting bromoacrylate. The TMS group stabilizes **20** toward polymerization, facilitates its handling and increases the ester-*endo*-selectivity of the intermolecular DAC by steric crowding. Still, the moderate yield of **20** in this reaction is thought to be a reflection of its propensity to polymerize. This mixture underwent a facile CDAC with bis-diene **13** over a 16 h period in refluxing toluene to yield the cycloadduct **36** as a 5.8:1 mixture of *endo*:*exo*-isomers (Scheme 7). Several chromatographies of **36** were needed in order to remove polymeric materials presumably emanating from the starting enyne and the bromoacrylate. In the process the silyl enol ether completely hydrolyzed to give the ketone **37** in 60% yield based on **13**. The stereochemistry of the major isomer could not be ascertained at this stage because of overlapping resonances in its ^{1}H-NMR spectra. We therefore decided to continue, confident that we would be able determine it at a later stage.

After removal of the TMS group with fluoride ion, we attempted the selective hydrogenation of the triple bond with Lindlar's catalyst. With two different sets of conditions and catalysts ($Pd/BaSO_4$, quinoline in EtOH and $Pd/CaCO_3$ in benzene), we obtained the preferential reduction of the internal double bond of the diene based on proton NMR. Despite this somewhat unexpected result, the desired transformation could be achieved with activated zinc in refluxing absolute ethanol for 72 h giving a 68% yield of the triene **40**.[13] This set the stage for the intramolecular cycloadditions. Compounds **38** and **40** underwent separate IMDACs in toluene at 170 °C in a sealed tube to give a 5:1 and 5.3:1 mixture of stereoisomers **39a**:**39b** and **41a**:**41b**, respectively. This essentially amounted to a completely stereoselective IMDAC in each case.[14] The major cycloadduct **39a** could be purified by crystallization (51% yield, >98% by GC) whereas the major isomer **41a** could be obtained in 64% yield after chromatography (>95% by GC). In the case of **39a**, a single crystal X-ray crystallographic analysis confirmed the proposed structure.[15] The analysis also confirmed the C5–C10 *trans* stereochemistry arising from the *endo* attack of the dienophile in the first intermolecular Diels–Alder reaction. The stereochemistry of **41a** was deduced from a NOE effect between the β-H at C1 and one of the hydrogens at C11 and by a coupling pattern for the α-H at C7 showing one small J = 4.3 Hz and three large J = 12.8 Hz (Figure 3).

The intramolecular [4 + 2]-cycloadditions thus proceeded via the transition state **C** as expected (Figure 2, center). The interaction between the ester group and the diene unit in **D** destabilizes it relative to **C**. The cycloaddition of alkyne **38** could also be achieved by bis-(triphenylphosphine)rhodium chloride catalysis at 50 °C in trifluoroethanol to give a 1:1 mixture of the two diastereomers **39a** and **39b**.[16] The lack of selectivity in this case can be explained by invoking a preferred

(12) Jeffery-Luong, T.; Linstrumelle, G. *Synthesis* **1983**, 32.

(13) Aerssens, M. H. P. J.; Van der Heiden, R.; Heus, M.; Brandsma, L. *Synth. Commun.* **1990**, *20*, 3421.

(14) The small discrepancy between the original 5.8:1 ratio of *endo*:*exo* isomers **37a** and **37b** can be explained by the incidental loss of one isomer in the following reactions.

(15) The author has deposited atomic coordinates for this structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

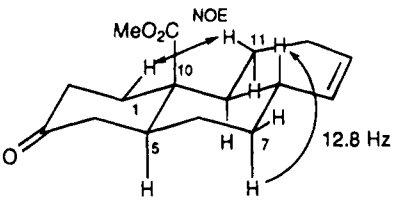


Figure 3. Evidence of the proposed structure of compound **41a**.

chelation of the rhodium on the triple bond *trans* to the ester group (Figure 2, bottom). This orientation of the catalyst creates steric interactions on either sides of the alkene making transition states **E** and **F** of near equal energy.

In conclusion we have developed a very expedient and stereoselective route to the perhydrophenanthrene ring system using a sequential Diels–Alder cycloaddition strategy. The method leads to polycyclic intermediates with adequate functionality around the rings system for further elaboration and should therefore be applicable to the synthesis of a variety of triterpenoids. We are currently undertaking the total synthesis of steroids and triterpenoids using this strategy and the results of our efforts will be reported in due course.

Experimental Section

All solvents were distilled from sodium–benzophenone with the exception of di- and tetrachloromethane and dimethyl sulfoxide which were distilled from calcium hydride. All reagents were used as is from the supplier unless otherwise stated. All reactions were performed under an atmosphere of argon unless otherwise stated. Flash column chromatography was done using Merck 60 silica gel, 230–400 mesh. NMR spectra were taken in $CDCl_3$ at 250 or 360 MHz, and IR spectra were recorded in $CHCl_3$. Gas chromatography was performed on a DB-1 capillary column with FID detector.

Ethyl 4,6-Heptadienoate (10). 1,4-Pentadien-3-ol (5 g, 177 mmol), triethyl orthoacetate (227 mL, 1.24 mol), and propionic acid (2.60 mL, 35 mmol) were heated to reflux in toluene overnight. Toluene was then removed by rotary evaporation to yield a yellow oil which was subsequently distilled under vacuum (0.1 mmHg) to afford the ester **10** (bp 60–75 °C), which was further purified by a bulb-to-bulb (Kugelrohr) distillation to give 19.9 g (73%) of a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.26 (dt, 1H, J = 16.8, 10.2 Hz), 6.07 (m, 1H), 5.67 (m, 1H), 5.08 (dd, 1H, J = 16.8, 1.6 Hz), 4.96 (dd, 1H, J = 10.2, 1.6 Hz), 4.10 (q, 2H, J = 7.1 Hz), 2.39 (m, 4H), 1.24 (t, 3H, J = 7.1 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 172.8 (s), 138.6 (d), 132.6 (d), 131.9 (d), 115.6 (t), 60.2 (t), 33.8 (t), 27.2 (t), 14.1 (q). IR ($CHCl_3$, cm^{-1}) 1710 (br), 1590 (w). LRMS m/e (relative intensity): 155 (M + 1, 100), 119 (45), 109 (31), 81 (77), 67 (37). HRMS calcd for $C_9H_{14}O_2$: 154.0994, found: 154.1007. Anal. Calcd for $C_9H_{14}O_2$: C, 70.1; H, 9.15. Found: C, 70.02; H, 8.83.

4,6-Heptadienal (11). Ethyl 4,6-heptadienoate (14 g, 92 mmol), dissolved in 30 mL of THF, was added to a 0 °C solution of lithium aluminium hydride (3.5 g, 92 mmol) in 500 mL of THF. After stirring for 1 h, the reaction was quenched with distilled water. A solution of 1N HCl was added and the layers were stirred vigorously for 1 h. Following separation of the aqueous and organic layers, the aqueous layer was extracted three times with diethyl ether. The combined organic fractions were then dried over anhydrous magnesium sulfate and concentrated by rotary evaporation. The pure alcohol (8.54 g, 83% yield) was obtained by Kugelrohr distillation (60–70 °C at 0.1 mmHg). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.25 (dt, 1H, J = 16.8, 10.2 Hz), 6.06 (m, 1H), 5.65 (dt, 1H, J = 15.1, 6.9 Hz), 5.06 (dd, 1H, J = 16.8, 1.6 Hz), 4.93 (dd, 1H, J = 10.2, 1.6 Hz), 3.59 (t, 2H, J = 6.9 Hz), 2.11 (m, 3H), 1.63 (m, 2H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 137.0 (d), 134.3 (d), 131.3 (d), 114.9 (t), 61.7 (t), 31.8 (t), 28.7 (t). IR ($CHCl_3$), 3615 (s), 3470 (br), 1645 (m). LRMS m/e (relative intensity): 112 (M^+, 15), 93 (5), 79 (100). HRMS calcd for $C_7H_{12}O$: 112.0900, found: 112.0888. Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.01; H, 10.98.

Oxalyl chloride (7.28 mL, 78.5 mmol) was added to a −60 °C solution of dimethyl sulfoxide (5.92 mL, 78.5 mmol) in 500 mL of THF and the mixture was stirred for 15 min. 4,6-Heptadien-1-ol (8.0 g, 71.3 mmol) was then added slowly, and the mixture was allowed to stir for 15 min. Triethylamine (31.7 mL, 215 mmol) was then added, and the reaction was allowed to warm to rt and stirred for 30 min. 1 N HCl was added, the aqueous and organic phases were separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were then dried over anhydrous magnesium sulfate and concentrated by rotary evaporation to afford crude 4,6-heptadienal which was used without purification in the next reaction.

3,7,9-Decatrien-2-one (12). Dimethyl (2-oxopropyl)phosphonate (11.6 mL, 71.3 mmol) was added to a 0 °C solution of sodium hydride (3.34 g, 78.5 mmol) in 300 mL of THF, and the resulting mixture was stirred for 60 min. The crude 4,6-heptadienal (in 15 mL THF) was then added to the reaction via cannula. After stirring for 2 h, the reaction was quenched with water (to aid clarification, 1 N HCl was added as well). The aqueous and organic layers were then separated, the aqueous layer extracted with diethyl ether, and the combined organic layers were dried over anhydrous magnesium sulfate. Following concentration of the organic layers by rotary evaporation, the residue was chromatographed on silica gel (400 g) using a 9:1 mixture of hexanes:ethyl acetate as an eluent. The ketone **12** was isolated in a 79% yield (8.98 g, calculated from 4,6-heptadien-1-ol). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.65 (dt, 1H, J = 16.0, 6.5 Hz), 6.24 (dt, 1H, J = 16.7, 10.1 Hz), 5.95 (m, 2H), 5.53 (dt, 1H, J = 16.1, 6.9 Hz), 4.97 (dd, 1H, J = 16.7, 1.6 Hz), 4.85 (dd, 1H, J = 10.1, 1.6 Hz), 2.25 (m, 4H), 2.15 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 198.5 (s), 147.2 (d), 136.9 (d), 132.9 (d), 132.1 (d), 131.7 (d), 115.7 (t), 32.0 (t), 31.0 (t), 26.9 (q). IR ($CHCl_3$, cm^{-1}) 1670 (s), 1625 (s), 1250 (s). LRMS m/e (relative intensity): 150 (M^+, 12), 107 (20), 67 (100). HRMS calcd for $C_{10}H_{14}O$: 150.1045, found: 150.1058. Anal. Calcd for $C_{10}H_{14}O$: C, 79.94; H, 9.40. Found: C, 79.88; H, 9.32.

2-[(Trimethylsilyl)oxy]-1,3,7,9-decatetraene (13). *n*-Butyllithium (2.0 mL, 4.4 mmol) was added to a −78 °C solution of diisopropylamine (0.612 mL, 4.4 mmol) in 6 mL of THF. The mixture was stirred for 15 min, and then 3,7,9-decatrien-2-one (600 mg, 4.0 mmol) in 2 mL of THF was added over 5 min. After stirring at −78 °C for 25 min, chlorotrimethylsilane (0.760 mL, 6.0 mmol) was quickly added. The solution was then allowed to warm to rt and was stirred for 60 min. The reaction was worked up with ice-cold distilled water. Addition of a small amount of diethyl ether aided separation of the organic and aqueous layers. The aqueous layer was also extracted twice with ether. The combined organic fractions were then dried over anhydrous magnesium sulfate, filtered and concentrated by rotary evaporation. Purification was accomplished by Kugelrohr distillation (80–90 °C at 0.1 mmHg) to yield a colorless liquid in 81% yield (720 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.28 (dt, 1H, J = 16.7, 10.1 Hz), 5.98 (m, 3H), 5.68 (m, 1H), 5.08 (dd, 1H, J = 16.7, 1.6 Hz), 4.94 (dd, 1H, J = 10.1, 1.6 Hz), 4.22 (s, 2H), 2.19 (m, 4H), 0.20 (s, 9H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 154.8 (s), 137.1 (d), 134.2 (d), 131.4 (d), 130.7 (d), 128.1 (d), 115.0 (t), 94.5 (t), 32.1 (t), 31.7 (t), 0.02 (q). IR ($CHCl_3$, cm^{-1}) 1650 (m), 1590 (s). LRMS (m/z, relative intensity): 223 (M + 1, 100), 207 (48), 155 (74), 133 (37). HRMS calcd for $C_{10}H_{23}OSi$: 223.1518, found: 223.1517.

(3S*,4S*)-4-Formyl-3-(1,3-hexadien-6-yl)cyclohexan-1-one (24). 2-[(Trimethylsilyl)oxy]-1,3,7,9-decatetraene (222 mg, 1.0 mmol), acrolein (0.10 mL, 1.5 mmol), and hydroquinone (10 mg) were dissolved in 0.4 mL of toluene and placed in a glass tube which was subsequently sealed under vacuum. The sealed tube was then placed in a 160 °C oven for 60 min. The

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tube was then allowed to cool and opened at liquid nitrogen temperature, and the contents were removed. Most of the toluene and excess acrolein were removed under reduced pressure. Purification of the Diels–Alder adduct was accomplished by flash chromatography (3:1 hexanes:ethyl acetate on 25 g silica gel) to yield the silyl enol ether **23** in 55% yield which was contaminated with the hydrolyzed product **24**. In subsequent reaction, the silyl enol ether **23** was used as the crude, but for characterization purposes, the crude silyl enol ether was dissolved in 5 mL of ethyl acetate, to which 0.5 g silica gel and 2 drops of concentrated HCl were added. The hydrolysis reached completion after 90 min, at which point the mixture was filtered over approximately 10 g of silica gel using ethyl acetate as an eluent. After removal of the solvents by rotary evaporation, the residue was chromatographed over 10 g silica gel using a 3:1 mixture of hexanes:ethyl acetate as an eluent. The product **24** was collected as a pale yellow viscous oil in a 49% yield (46 mg). The two isomers formed in the reaction were found to be in a 3.4:1 ratio (by GC) which were inseparable by flash chromatography. Major isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.67 (d, 1H, J = 2.1 Hz), 6.25 (dt, 1H, J = 16.9, 10.2 Hz), 6.02 (dd, 1H, J = 15.0, 10.2 Hz), 5.56 (dt, 1H, J = 15.0, 7.0 Hz), 5.06 (dd, 1H, J = 16.9, 1.6 Hz), 4.93 (dd, 1H, J = 10.2, 1.6 Hz), 2.20–2.55 (m, 5H), 1.90–2.20 (m, 5H), 1.30–1.60 (m, 2H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 209.3 (s), 202.9 (d), 136.7 (d), 133.1 (d), 132.0 (d), 115.6 (t), 52.1 (d), 44. 2 (t), 38.9 (t), 36.1 (d), 33.4 (t), 29.1 (t), 23.7 (t). IR ($CHCl_3$, cm^{-1}): 2750 (w), 1720 (br, s), 1220 (br, m). LRMS m/e (relative intensity): 206 (M^+, 25), 188 (15), 67 (100). HRMS calcd for $C_{13}H_{18}O_2$: 206.1307, found: 206.1301. Minor isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.83 (bs, 1H), 6.25 (dt, 1H, J = 16.9, 10.2 Hz), 6.02 (dd, 1H, J = 15.0, 10.2 Hz), 5.56 (dt, 1H, J = 15.0, 7.0 Hz), 5.06 (dd, 1H, J = 16.9, 1.6 Hz), 4.93 (dd, 1H, J = 10.2, 1.6 Hz), 2.88 (m, 1H), 2.20–2.55 (m, 5H), 1.90–2.20 (m, 4H), 1.30–1.60 (m, 2H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 209.8 (s), 202.8 (d), 136.7 (d), 133.2 (d), 131.9 (d), 115.6 (t), 50.3 (d), 37.2 (d), 38.8 (t), 44.7 (t), 30.3 (t); 29.9 (t), 22.9 (t).

(3S*,4S*)-3-(1,3-Hexadien-6-yl)-4-{2-(methoxycarbonyl)-ethenyl}cyclohexan-1-one (25). To 5 mL of anhydrous THF was added sodium hydride (21 mg, 0.52 mmol, 60% dispersion in mineral oil). The mixture was then cooled to 0 °C and methyl diethylphosphonoacetate (0.094 mL, 0.49 mmol) was slowly added. The reaction was then allowed to stir for 1 h, and then aldehydes **23** (132 mg, 0.47 mmol) were slowly added. The mixture was then allowed to stir for 2 h at 0 °C. The reaction was quenched with 1 N HCl (which hydrolyzed the silyl enol ethers) and extracted with ethyl acetate. The combined organic fractions were then dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. Purification was accomplished by flash chromatography (3:1 hexanes:ethyl acetate on 15 g silica gel). A pale yellow viscous oil containing an inseparable mixture of isomers was obtained in 61% yield (75 mg). Major isomer: ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.09 (dd, 1H, J = 15.7, 7.6 Hz), 6.21 (dt, 1H, J = 16.9, 10.1 Hz), 5.92 (m, 1H), 5.90 (dd, 1H, J = 15.7, 1.3 Hz), 5.53 (m, 1H), 5.03 (dd, 1H, J = 16.8, 1.2 Hz), 4.91 (dd, 1H, J = 10.1, 1.2 Hz), 3.70 (s, 3H), 2.71 (m, 1H), 2.70–1.10 (m, 11H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 209.9 (s), 166.4 (s), 147.4 (d), 136.7 (d), 133.6 (d), 131.6 (d), 122.7 (d), 115.3 (t), 51.5 (q), 44.1 (t), 40.2 (d), 40.1 (d), 38.1 (t), 30.8 (t), 29.6 (t), 28.5 (t). IR ($CHCl_3$, cm^{-1}) 1725 (s), 1661 (m, sh). LRMS m/e (relative intensity): 262 (M^+, 100), 245 (10), 230 (25), 202 (90). HRMS calcd for $C_{16}H_{22}O_3$: 262.1570, found: 262.1576. Minor isomer: ^{1}H NMR (360 MHz, $CDCl_3$): δ 6.74 (dd, 1H, J = 15.7, 8.6 Hz), 6.21 (dt, 1H, J = 16.9, 10.1 Hz), 5.92 (m, 1H), 5.87 (dd, 1H, J = 15.7, 1.1 Hz), 5.53 (m, 1H), 5.03 (dd, 1H, J = 16.8, 1.2 Hz), 4.91 (dd, 1H, J = 10.1, 1.2 Hz), 3.69 (s, 3H), 2.70–1.10 (m, 12H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 209.8 (s), 166.4 (s), 150.5 (d), 136.7 (d), 133.6 (d), 131.5 (d), 122.0 (d), 115.3 (t), 51.5 (q), 45.2 (d), 44.7 (d), 41.3 (d), 39.8 (t), 33.9 (t), 31.0 (t), 28.7 (t).

3-Carbomethoxytricyclo[8.4.0]tetradec-5-en-12-one (26). To a solution of esters **25** (67 mg, 0.260 mmol) in 8 mL of dichloromethane was slowly added a 1.0 M solution of dimethylaluminum chloride in toluene (0.624 mL, 0.624 mmol). The reaction was then allowed to stir for 45 h at rt. Approximately 2 mL of 1 N HCl was then slowly added to the reaction mixture. Following separation of the organic and aqueous layers, the organic layer was extracted twice with ethyl acetate. The combined organic fractions were then dried over anhydrous magnesium sulfate and filtered. The solvent was removed by rotary evaporation, and the residue was chromatographed over 7 g silica gel using a 5:1 mixture of hexanes:ethyl acetate as eluent. The product was obtained as a mixture of four isomers (60 mg, 89%). The major isomer could be separated from the other isomers and obtained as a viscous liquid (26.6 mg, 40%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.65–5.50 (m, 1H), 5.45–5.35 (m, 1H), 3.60 (s, 3H), 2.43–2.20 (m, 3H), 2.05–1.15 (m, 14H). ^{13}C NMR (90 MHz, $CDCl_3$): δ (carbonyl singlet not seen for unknown reason), 171.0 (s), 132.4 (d), 123.6 (d), 51.5 (q), 45.5 (d), 41.9 (d), 41.7 (t), 37.1 (d), 36.1 (d), 35.3 (t), 31.9 (t), 31.2 (t), 28.3 (t), 26.5 (t), 26.3 (d). IR ($CHCl_3$, cm^{-1}) 1720 (s), 1429 (m). LRMS m/e (relative intensity) 262 (M^+, 83), 244 (10), 230 (30), 202 (70), 91 (100). HRMS calcd for $C_{16}H_{22}O_3$: 262.1569, found: 262.1581.

(3S*,4S*)-3-(1,3-Hexadien-6-yl)-4-(2-(phenylsulfonyl)-ethen-1-yl)cyclohexan-1-one (28). To a −78 °C solution of diisopropylamine (0.082 mL, 0.585 mmol) in 3 mL of THF was slowly added 2.2 M n-butyllithium (in hexanes, 0.265 mL, 0.585 mmol). The solution was allowed to stir at −78 °C for 15 min, and then methyl phenyl sulfone (97 mg, 0.624 mmol, in 1 mL of THF) was added over 5 min. The mixture was allowed to stir for 30 min, and then a solution of aldehydes **23** (108 mg, 0.39 mmol) in 1 mL of THF was added. The mixture was then slowly warmed to rt and stirred overnight. The reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The combined organic fractions were then dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue could be chromatographed over silica gel using a 3:1 mixture of hexanes:ethyl acetate as eluent to give a 44% yield of four inseparable isomeric silyl enol ethers (74 mg) and 33% (47 mg) of an inseparable mixture of four isomeric ketones. It was, however, more practical to treat the crude mixture of silyl enol ethers with a catalytic amount of concd HCl (1 drop) in ethyl acetate containing silica gel (roughly 1 mL per 100 mg product) to obtain a mixture of four isomeric ketones. Because of the complex mixture, this product was only characterized by proton NMR. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.85 (m, 2H), 7.60 (m, 3H), 6.25 (m, 1H), 5.90 (m, 1H), 5.60 (m, 1H), 5.40 (m, 1H), 5.05 (d, 1H, J = 16.9 Hz), 4.95 (dd, 1H, J = 10.1 Hz), 4.30 (m, 1H), 3.60 (m, 1H), 3.20–3.00 (m, 2H), 2.60–0.90 (m, 11H).

To a 0 °C solution of **27** (75 mL, 0.21 mmol) in 10 mL of dry dichloromethane were added triethylamine (0.050 mL, 0.346 mmol) and methanesulfonyl chloride (0.020 mL, 0.260 mmol). The mixture was then allowed to warm slowly to rt and was stirred for 16 h. The reaction was then quenched with 1 N HCl and extracted with ethyl acetate. The combined organic fractions were then dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. Purification was accomplished by silica gel flash chromatography (1:1 hexanes:ethyl acetate on 5 g of silica gel). The product was obtained as an inseparable 2:1 mixture of 2 isomers in 49% yield (36 mg) and 37% of starting material which was recycled. Major isomer: ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.85 (m, 2H), 7.60 (m, 3H), 7.10 (dd, 1H, J = 15.3, 7.3 Hz), 6.39 (dd, 1H, J = 15.3, 1.3 Hz), 6.21 (dt, 1H, J = 16.9, 10.1 Hz), 5.92 (m, 1H), 5.48 (m, 1H), 5.05 (dd, 1H, J = 16.9, 1.2 Hz), 4.95 (dd, 1H, J = 10.1, 1.2 Hz), 2.80 (m, 1H), 2.70–1.30 (m, 11H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 209.3 (s), 145.5 (d), 140.2 (s), 136.7 (d), 133.4 (d), 133.2(d), 132.2 (d), 131.7 (d), 129.3 (d), 127.4 (d), 115.5 (t), 45.1 (t), 41.3 (d), 40.0 (d), 39.6 (t), 30.6 (t), 29.5 (t), 27.6 (t). IR ($CHCl_3$, cm^{-1}) 1722 (s), 1446 (m). LRMS m/e (relative intensity): 344 (M^+, 5), 261 (20), 243 (40), 145 (70), 77 (100). HRMS calcd for $C_{20}H_{24}O_3S$: 344.1447, found: 344.1431. Minor isomer: ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.85 (m, 2H), 7.60 (m, 3H), 6.80 (dd, 1H, J = 15.1, 9.4 Hz), 6.39 (dd, 1H, J = 15.1, 1.3 Hz), 6.21 (dt, 1H, J = 16.9, 10.1 Hz), 5.92 (m, 1H), 5.48 (m, 1H), 5.05 (dd, 1H, J = 16.9, 1.2 Hz), 4.95 (dd, 1H, J = 10.1, 1.2 Hz), 2.80 (m, 1H), 2.70–1.30 (m, 11H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 209.1 (s), 149.0 (d), 140.1

(s), 136.7 (d), 133.4 (d), 133.2 (d), 131.6 (d), 131.5 (d), 129.3 (d), 127.4 (d), 115.5 (t), 44.1 (t), 43.9 (d), 39.8 (d), 38.2 (t), 33.8 (t), 30.3 (t), 28.5 (t).

3-(Phenylsulfonyl)tricyclo[8.4.0]tetradec-5-en-12-one (29). Sulfone **28** (58 mg, 0.168 mmol) was dissolved in 5 mL of toluene and heated to reflux for 18 h. After cooling, the toluene was removed by rotary evaporation, and the residue was chromatographed over 5 g of silica gel using 5:1 hexanes:ethyl acetate as eluent. The product was obtained as two sets of two inseparable isomers in yields of 52% (30 mg, ratio of isomers 2.8:1 by GC) and 30% (17 mg, ratio of isomers 2.2:1 by GC), respectively. Each set of isomers was separately recrystallized from an ethyl acetate/hexanes mixture giving 26 mg (45%) and 14 mg (24%) of the major and minor set, respectively, each obtained as white crystals. Major set of isomers: mp 198–202 °C dec. Major component: ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.85 (m, 2H), 7.60 (m, 3H), 5.62 (m, 2H), 3.42 (m, 1H), 3.08 (m, 1H), 2.59–1.10 (m, 15H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 210.2, 138.8, 133.6, 131.8, 129.3, 128.4, 122.9, 60.0, 48.2, 42.9, 41.0, 38.5, 37.5, 31.1, 30.3, 30.0, 29.4, 20.6. IR ($CHCl_3$, cm^{-1}) 3000 (w), 2910 (m), 2850 (w), 1700 (s), 1440 (m), 1300 (m, sh), 1210 (m, br), 1140 (s), 1070 (m), 900 (w), 670 (m, br). LRMS *m/e* (relative intensity): 344.1 (4), 202.1 (100), 145.1 (6), 91.1 (12), 51 (11). HRMS calcd for $C_{20}H_{24}O_3S$: 344.1447, found: 344.1433. Anal. Calcd for $C_{20}H_{24}O_3S$: C, 69.74; H, 1.02; O, 13.93. Found: H, 6.96; C, 69.15; O, 14.01. Minor component: ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.85 (m, 2H), 7.60 (m, 3H), 5.62 (m, 2H), 3.42 (m, 1H), 3.08 (m, 1H), 2.59–1.10 (m, 15H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 210.4, 138.5, 134.7, 133.5, 129.2, 129.1, 126.0, 65.0, 64.8, 48.3, 44.1, 43.6, 41.3, 40.1, 34.1, 31.3, 30.9, 24.6. Minor set of isomers: mp 196–199 °C dec. Major component: ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.85 (m, 2H), 7.60 (m, 3H), 5.55 (m, 2H), 3.54 (m, 1H), 3.10 (m, 1H), 2.60–1.20 (m, 15H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 211.7, 138.8, 133.8, 131.7, 129.2, 128.5, 122.1, 58.5, 44.4, 43.9, 39.3, 38.8, 37.3, 32.3, 29.4, 29.0, 27.3, 26.1. LRMS *m/e* (relative intensity): 344 (4), 203 (25), 202 (100). HRMS calcd for $C_{20}H_{24}O_3S$: 344.1447, found: 344.1428. Minor component: ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.85 (m, 2H), 7.60 (m, 3H), 5.55 (m, 2H), 3.54 (m, 1H), 3.10 (m, 1H), 2.60–1.20 (m, 15H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 212.8, 138.7, 134.2, 133.7, 129.3, 128.7, 125.0, 65.0, 44.5, 43.4, 42.9, 38.9, 38.4, 37.0, 33.5, 28.9, 26.9, 26.4.

***S*-Methyl-3-carbomethoxy-2,5-dihydrothiophene Tetrafluoroborate (33).** Dimethoxycarbonium tetrafluoroborate (699 mg, 4.32 mmol) was added to a solution of dihydrothiophene **32** in 3 mL of dry dichloromethane. After stirring 14 h, ethyl acetate was added and the mixture was stirred vigorously for 15 min. The suspension was allowed to settle and the top layer of ethyl acetate was carefully pipetted out. The oil was repeatedly washed in that fashion, each time allowing vigorous stirring with ethyl acetate. Upon sitting under high vacuum for 18 h the oil solidified into a white sticky solid. The solid was repeatedly washed with ethyl acetate and dried under high vacuum to yield 794 mg (94%) of the sulfonium salt **33** which could be used without further purification. ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.92 (bs, 1H), 4.45 (bt, 2H, J = 16.1 Hz), 4.16 (bt, 2H, J = 16.1 Hz), 3.75 (s, 3H), 2.80 (s, 3H). IR (KBr pellet, cm^{-1}) 1700 (s), 1050 (s).

(Z)-1-(Methylthio)-3-carbomethoxy-1,4-butadiene (19). Triethylamine (0.17 mL, 1.22 mmol) was added to a suspension of sulfonium salt **33** (100 mg, 0.41 mmol) in 2 mL of dry dichloromethane. It was stirred at rt for 30 min after which time the solid dissolved. The mixture was then filtered through a pad of silica gel, eluting with dichloromethane, ensuring that the product remained in solution at all times. The solvent was carefully evaporated at 25 °C under high vacuum (pump) while stirring until ~0.5 mL remained in the flask. Then dichloromethane was added (~2 mL) and the solvent was again evaporated under vacuum. This procedure was repeated two or three times (once, for purpose of spectral identification, this procedure was done with $CDCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.46 (s, 1H), 6.30 (s, 1H), 5.82 (s, 1H), 3.72 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 166.8 (s), 134.9 (s), 132.8 (d), 126.3 (d), 119.1 (t), 52.0 (q), 18.8 (q).

1,4-Dicarbomethoxy-3-(methylthio)-4-[2-(methylthio)-ethen-1-yl)]-1-cyclohexene (34). The diene **19** was dissolved in dichloromethane or in deuterated chloroform and allowed to stir or sit at room temperature for 5 days. Alternatively, the diene can be left neat at room temperature for 2 h. Then the solvent was evaporated and the product directly chromatographed on silica gel using a 15:1 mixture of hexanes–ethyl acetate as eluent to yield 89% of a 9:1 isomeric mixture of dimers **34**. Major isomer: ^{1}H NMR (360 MHz, $CDCl_3$): δ 6.98 (dt, 1H, J = 5.7, 1.0 Hz), 6.05 (d, 1H, J = 10.2 Hz), 5.45 (d, 1H, J = 10.2 Hz), 4.00 (bd, 1H, J = 5.7 Hz), 3.62 (s, 6H), 2.40–1.95 (m, 4H), 2.18 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 173.3 (s), 167.0 (s), 137.7 (d), 130.7 (d), 127.8 (s), 127.6 (d), 52.3 (q), 51.6 (q), 50.6 (s), 46.7 (d), 28.0 (t), 21.9 (t), 18.0 (q), 17.3 (q). IR ($CHCl_3$, cm^{-1}) 1735–1700 (bs), 1642 (m), 1595 (w), 1260 (bs). LRMS *m/e* (relative intensity) 316 (5), 269 (40), 158 (60), 143 (100). HRMS calcd for $C_{14}H_{20}O_4S_2$: 316.0803, found: 316.0764. Anal. Calcd for $C_{14}H_{20}O_4S_2$: C 53.15; H 6.38; S 20.23. Found: C, 52.96; H, 6.39; S, 20.18. Minor isomer: ^{1}H NMR (360 MHz, $CDCl_3$): δ 6.88 (bd 1H, J = 5.7 Hz), 5.94 (d, 1H, J = 10.2 Hz), 5.15 (d, 1H, J = 10.2 Hz), 3.67 (s, 3H), 3.64 (s, 3H), 3.49 (bd, 1H, J = 5.7 Hz), 2.40–1.95 (m, 4H), 2.17 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 172.9 (s), 167.0 (s), 135.3 (d), 131.0 (d), 130.2 (s), 126.5 (d), 51.8 (q), 51.7 (q), 51.5 (s), 49.4 (d), 22.4 (t), 21.5 (t), 17.3 (q), 16.4 (q).

Methyl 2-[2-(Trimethylsilyl)ethyn-1-yl]acrylate (20). To 10 mL of dry triethylamine were added 4-methoxyphenol (5 mg), copper(I) iodide (10 mg, 0.05 mmol), bis(triphenylphosphine)palladium(II) chloride (70 mg, 0.10 mmol), methyl 2-bromoacrylate (660 mg, 4 mmol), and trimethylsilyl acetylene (0.680 mL, 5 mmol) in that order. Following addition of the trimethylsilyl acetylene, the reaction mixture changed color (over approximately a 5 min period) from yellow to a greenish-blue and eventually to a reddish-brown. The flask was then wrapped in aluminum foil (to exclude light) and fitted with a condenser (to prevent loss of the volatile (trimethylsilyl)-acetylene). The mixture was then allowed to stir for 20 h. The resulting brown reaction mixture was then filtered, and the solid material washed with ethyl acetate. The filtrate was then concentrated by rotary evaporation, and the residue was chromatographed over 60 g of silica gel, using a 5:1 mixture of hexanes:ethyl acetate as eluent. The product was obtained in 76% yield as a yellow oil, but was contaminated with approximately 20% of the starting material. Approximately 5 mg of 4-methoxyphenol was added to the neat product before storage, to prevent polymerization. Alternatively, it can be stored as a solution in ethyl acetate. ^{1}H NMR (360 MHz, $CDCl_3$): δ 6.57 (d, 1H, J = 1.5 Hz), 6.09 (d, 1H, J = 1.5 Hz), 3.78 (s, 3H), 0.20 (s, 9H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 164.3 (s), 135.1 (s), 123.8 (t), 99.6 (s), 97.9 (s), 52.5 (q), −0.4 (q). IR ($CHCl_3$, cm^{-1}) 2258 (w), 2157 (w), 2057 (w), 1731 (s), 1442 (m). LRMS *m/e* (relative intensity) 182 (30), 179 (70), 167 (40), 113 (100). HRMS calcd for $C_9H_{14}O_2Si$ 182.0763, found: 182.0768.

(3*R,4*S**)-4-Carbomethoxy-3-(1,3-hexadien-6-yl)-4-{2-(trimethylsilyl)ethyn-1-yl}cyclohexan-1-one (37).** Into 6 mL of dry toluene were dissolved bis-diene **13** (95 mg, 0.4 mmol) and enyne **20** (88 mg, 0.4 mmol, containing ~20% methyl bromoacrylate). The mixture was then heated to reflux and stirred for 16 h. The toluene was then removed by rotary evaporation and the residue was chromatographed on 10 g silica gel using 5:1 hexanes:ethyl acetate as eluent. Repeated (two to three times) column chromatography was necessary to obtain the product **37** in a satisfactorily pure state as a mixture of isomers (in a 5.8:1 ratio) as a yellow viscous oil in a yield of 60% (96 mg). Major isomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.23 (dt, 1H, J = 16.9, 10.1 Hz), 6.00 (dd, 1H, J = 15.1, 10.2 Hz), 5.55 (m, 1H), 5.06 (dd, J = 16.9, 1.6 Hz), 4.94 (dd, 1H, J = 10.1, 1.6 Hz), 3.75 (s, 3H), 2.95 (dd, 1H, J = 14.0, 4.6 Hz), 2.75–1.80 (m, 11H), 1.60–1.10 (m, 2H), 0.15 (s, 9H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 209.7 (s), 171.2 (s), 136.9 (d), 133.3 (d), 131.9 (d), 115.4 (t), 104.8 (s), 89.5 (s), 52.7 (q), 46.9 (s), 43.4 (d), 41.3 (t), 37.5 (t), 30.2 (t), 30.0 (t), 29.6 (t), −0.1 (q). IR ($CHCl_3$, cm^{-1}) 2162 (w), 1722 (s), 1440 (m). LRMS *m/e* (relative intensity): 332 (M^+, 20), 317 (80), 273 (80), 73 (100). HRMS calcd for $C_{19}H_{28}O_3Si$: 332.1808. Found: 332.1798.

(3R*,4S*)-4-Carbomethoxy-4-ethynyl-3-(1,3-hexadien-6-yl)cyclohexan-1-one (38). To a 0 °C solution of tetra-*n*-butylammonium fluoride (0.33 mL, 0.33 mmol, 1 M in THF) in 4 mL of THF was slowly added silane **37** (118 mg, 0.33 mmol) in 1 mL of THF. The reaction was allowed to stir at 0 °C for 90 min, at which point 2 mL of brine was added. The organic and aqueous layers were separated, and then the aqueous layer was extracted three times with ethyl acetate. The combined organic fractions were then dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was then chromatographed over 12 g of silica gel using a 6:1 mixture of hexanes:ethyl acetate as eluent. The product was obtained as a viscous oil in 98% yield (92 mg) as a mixture of two isomers in a 5.5:1 ratio. Major isomer: ^{1}H NMR (360 MHz, $CDCl_3$): δ 6.22 (dt, 1H, J = 16.9, 10.1 Hz), 6.00 (dd, 1H, J = 15.0, 10.2 Hz), 5.55 (m, 1H), 5.06 (dd, 1H, J = 16.9, 1.6 Hz), 4.93 (dd, 1H, J = 10.1, 1.6 Hz), 3.76 (s, 3H), 2.83 (m, 1H), 2.70–1.90 (m, 9H), 1.60–1.15 (m, 2H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 209.5 (s), 171.0 (s), 136.7 (d), 133.0 (d), 131.9 (d), 115.5 (t), 83.2 (d), 72.7 (s), 52.9 (q), 45.9 (s), 43.4 (t), 41.2 (d), 37.3 (t), 30.4 (t), 29.8 (t), 29.5 (t). IR ($CHCl_3$, cm^{-1}) 3312 (s), 2160 (w), 1731 (s), 1442 (m). LRMS *m/e* (relative intensity) 260 (M^+, 85), 229 (60), 228 (60), 201 (95), 103 (100). HRMS calcd for $C_{16}H_{20}O_3$, 260.1413 found: 260.1412.

$\Delta^{2,3}$,$\Delta^{5,6}$-(1R*,7S*,10S*)-1-Carbomethoxytricyclo[8.4.0]-tetradeca-2,5-dien-12-one (39). Compound **38** (140 mg, 0.54 mmol) and 2.0 mg of methylene blue were dissolved in 3.0 mL of toluene and placed in a glass tube, which was then sealed under high vacuum (0.05 mmHg, at liquid nitrogen temperature). The tube was then placed in a 170 °C oven for 48 h. After cooling to rt, the tube was cooled to liquid nitrogen temperature and opened, and the contents were removed. The toluene was removed by rotary evaporation, and the residue was chromatographed over silica gel using a 9:1 mixture of hexanes:ethyl acetate as eluent. The product was isolated as two isomers in a 5:1 ratio (by NMR) in 64% yield; 51% (71 mg) of the major isomer in a pure form (colorless crystalline solid (mp 139–142 °C) after recrystallization from a mixture of hexanes and ethyl acetate) and 13% (9 mg) of the minor isomer (which was contaminated with the major isomer). Major isomer: ^{1}H NMR (360 MHz, $CDCl_3$): δ 5.65–5.58 (m, 2H), 5.53 (m, 1H), 3.68 (s, 3H), 2.98 (ddd, 1H, J = 15.4, 13.6, 1.0 Hz), 2.75 (m, 2H), 2.60–2.38 (m, 3H), 2.28–2.08 (m, 3H), 1.90–1.65 (m, 3H), 1.49 (ddt, 1H, J = 13.4, 4.1, 2.4Hz), 1.21 (dq, 1H, J = 4.3, 12.8 Hz). ^{13}C NMR (90 MHz, $CDCl_3$): δ 210.4 (s), 173.7 (s), 138.2 (s), 128.8 (d), 122.4 (d), 117.7 (d), 52.0 (q), 51.7 (s), 46.0 (d), 45.0 (t), 38.6 (t), 35.6 (t), 34.9 (t), 32.4 (t), 29.2 (t), 27.0 (t). IR ($CHCl_3$, cm^{-1}) 1718 (s), 1450 (m). LRMS *m/e* (relative intensity): 260 (M^+, 35), 201 (100). HRMS calcd for $C_{16}H_{20}O_3$ 260.1412, found: 262.1400. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.81; H, 7.75. Found: C, 74.03; H, 7.77.

(3R*,4S*)-4-Carbomethoxy-4-ethenyl-3-(1,3-hexadien-6-yl)cyclohexan-1-one (40). To 2 mL of dry ethanol were added acid-activated zinc dust (163 mg, 2.5 mmol) and 1,2-dibromoethane (3 μL). The mixture was gently heated until a vigorous reaction occurred (about 5 min), and then the flask was allowed to cool for 10 min. Another 3 μL of dibromoethane was added and allowed to react for 10 min. Then 560 μL of a 133 mg/mL CuBr and 200 mg/mL LiBr (74 mg, 0.27 mmol; 112 mg, 0.66 mmol respectively) solution in THF was slowly added. The mixture was heated to reflux for 20 min, accompanied by a change in color of the reaction mixture from gray to brown. The reaction mixture was allowed to cool for 5 min, and then alkyne **38** (130 mg, 0.5 mmol) in 1 mL of THF was added. The reaction was heated to reflux again, and allowed to stir, at reflux, for 72 h. The reaction mixture was allowed to cool, and then 3 mL of a saturated ammonium chloride solution was added. The organic and aqueous layers were separated, and then the aqueous layer was extracted twice with diethyl ether. The combined organic fractions were then dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was chromatographed over silica gel using a 9:1 mixture of hexanes: ethyl acetate as eluent. The product was isolated as a viscous oil in a 68% yield (88 mg). ^{1}H NMR (360 MHz, $CDCl_3$): δ 6.23 (dt, 1H, J = 16.9, 10.1Hz), 6.00 (dd, 1H, J = 15.0, 10.2 Hz), 5.92 (dd, 1H, J = 17.6, 10.8 Hz), 5.56 (m, 1H), 5.35 (d, 1H, J = 10.7 Hz), 5.19 (d, 1H, 17.6 Hz), 5.06 (dd, 1H, J = 16.9, 10.6 Hz), 4.93 (dd, 1H, J = 10.2, 1.6 Hz), 3.66 (s, 3H), 2.48–2.10 (m, 8H), 1.38–1.20 (m, 2H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 210.4 (s), 173.8 (s), 139.0 (d), 136.9 (d), 133.6 (d), 131.7 (d), 117.1 (t), 115.3 (t), 52.1 (q), 51.9 (s), 42.9 (t), 41.2 (t), 37.3 (t), 30.2 (t), 30.1 (t), 28.1 (t). IR ($CHCl_3$, cm^{-1}) 1722 (s), 1429 (m). LRMS *m/e* (relative intensity) 262 (M^+, 60), 230 (10), 202 (40), 47 (100). HRMS calcd for $C_{16}H_{22}O_3$: 262.1570. Found: 262.1568.

$\Delta^{5,6}$-(1R*,2S*,7R*,10S*)-1-Carbomethoxytricyclo[8.4.0]-tetradec-5-en-12-one (41). Compound **40** (58 mg, 0.22 mmol) and 0.5 mg of methylene blue were dissolved in 2.0 mL of toluene and placed in a glass tube, which was then sealed under high vacuum (0.05 mmHg, at liquid nitrogen temperature). The tube was then placed in a 170°C oven for 48 h. After cooling to rt, the tube was cooled to liquid nitrogen temperature and opened, and the contents were removed. The toluene was removed by rotary evaporation, and the residue was chromatographed over 6 g of silica gel using a 9:1 mixture of hexanes:ethyl acetate as an eluent. The product was isolated as two isomers in a 5.3:1 ratio (by NMR) in an 80% yield: 64% (37 mg) of the major isomer and 16% (9 mg) of the minor isomer (which was contaminated with the major isomer). Major isomer: ^{1}H NMR (360 MHz, $CDCl_3$): δ 5.60 (m, 1H), 5.37 (dd, 1H, J = 9.9, 1.9 Hz), 3.70 (s, 3H), 2.75 (ddd, 1H, J = 13.3, 6.1, 2.6 Hz), 2.49 (dt, 1H, J = 14.1, 1.0 Hz), 2.42–1.15 (m, 14H), 1.10 (dq, 1H, J = 4.3, 12.8 Hz). ^{13}C NMR (90 MHz, $CDCl_3$): δ 210.5 (s), 173.5 (s), 131.9 (d), 126.0 (d), 51.2 (q), 50.2 (s), 49.0 (d), 45.7 (d), 45.6 (t), 39.0 (t), 36.5 (d), 34.5 (t), 32.9 (t), 29.1 (t), 26.5 (t), 23.8 (t). IR ($CHCl_3$, cm^{-1}) 1722 (s), 1451 (m). LRMS *m/e* (relative intensity): 262 (M^+, 100), 230 (60), 203 (90), 202 (90). HRMS calcd for $C_{16}H_{22}O_3$ 262.1569, found: 262.1569. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.24; H, 8.46. Found: C, 73.03; H, 8.40.

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Supplementary Material Available: The ^{1}H NMR spectra of **24–26**, **28**, **29**, **37**, **38**, **40**, **41a** including an enlarged portion in the case of **41a**; the ^{13}C NMR, DEPT, COSY, NOESY, and ^{1}H–^{13}C correlated spectra of **41a**; ORTEP of **39a** (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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