Diastereomeric Atropisomers of the Tricyclo[9.3.1.$0^{3,8}$]pentadecane Ring System. Synthesis and Structural Studies

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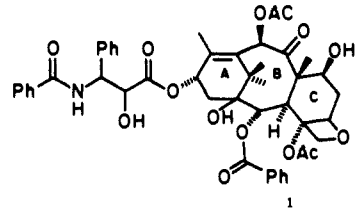
Abstract: Intramolecular Diels–Alder cycloaddition of trienone **7** yields a pair of atropisomers, *endo*- and *exo*-**6**. These diastereomeric conformational isomers are derivatives of the tricyclo[9.3.1.$0^{3,8}$]pentadecane ring system. The structures of the individual isomers have been unambiguously established by X-ray crystallography. Interconversion of *exo*- and *endo*-**6** requires rotation about five carbon–carbon single bonds. The barrier separating the two isomers was determined by a temperature dependence study of the rate of approach to equilibrium (E_a = 27.8 ± 1.0 kcal/mol, $\Delta S^{\ddagger}$ = 1.3 ± 0.8 eu). Lewis acid catalyzed intramolecular Diels–Alder cycloaddition of **7** ($ZnCl_2$, CH_2Cl_2, room temperature) was found to yield a single atropisomer (*endo*-**6**) in a rare example of an atropselective reaction.

The tricyclo[9.3.1.$0^{3,8}$]pentadecane ring system forms the basic substructural unit for a number of biologically important naturally occurring substances, including taxol (**1**), the principle cytotoxic and antileukemic constituent of *Taxus brevifolia* Nutt.[1] The ring system has attracted considerable interest from the synthetic chemistry community in recent years and a diversity of approaches to portions of or the entire taxane skeleton have emerged.[2]



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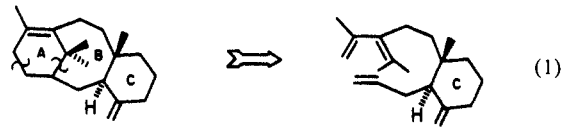
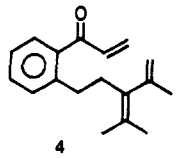
Several years ago we proposed a type **2** intramolecular Diels–Alder cycloaddition to simultaneously assemble the AB rings of the tricyclic skeleton (eq 1). This approach was first demonstrated



(1)

2 **3**

in the synthesis of the C-aromatic taxane derivative **5**, prepared by intramolecular Diels–Alder cycloaddition of trienone **4**. The



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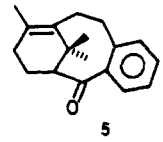

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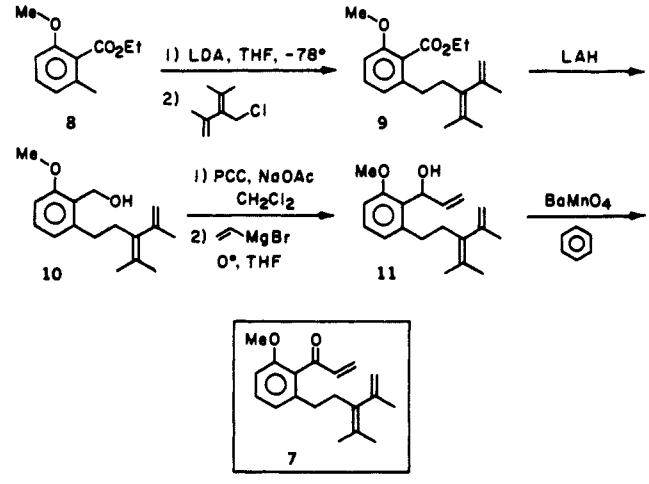
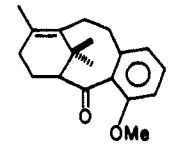
Scheme I



facility with which the C-aromatic taxane skeleton is assembled has prompted consideration of strategies that involve elaboration of these derivatives to the natural product skeleton. One approach requires the synthesis of methoxy derivative **6**. We envisioned



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this intermediate serving as a key precursor to taxane natural products, an approach which relies upon stereospecific incorporation of the C-8 methyl substituent. The synthesis of methoxy trienone **7**, its cycloaddition chemistry, and the remarkable conformational behavior of this ring system form the basis of the present report.

Results and Discussion

Synthesis of the Diels–Alder precursor **7** is outlined in Scheme I. After exploration of several alternatives, 2-carboethoxy-3-methylphenol was prepared by the procedure of Staunton and co-workers.[4] The phenol was converted to methoxy ester **8** by phase transfer methods.[5] Treatment of **8** with LDA at −78 °C[6] followed by 2,4-dimethyl-3-(chloromethyl)-1,3-pentadiene[3] gave

(1) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggan, P.; McPhail, A. I. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(2) (a) Trost, B. M.; Hiemstra, H. *J. Am. Chem. Soc.* **1982**, *104*, 886. (b) Holton, R. A. *Ibid.* **1984**, *106*, 5731. (c) Nagoaka, H.; Ohsawa, T.; Takata, T.; Yamada, Y. *Tetrahedron Lett.* **1984**, *25*, 5389. (d) Kojima, T.; Inouye, Y.; Kakisawa, H. *Chem. Lett.* **1985**, 323. (e) Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190. (f) Sakan, K.; Craven, B. M. *J. Am. Chem. Soc.* **1983**, *105*, 3732. (g) Brown, P. R.; Jenkins, P. R.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Chem. Commun.* **1984**, 253. (h) Kende, A. S.; Benechie, M.; Curran, D. P.; Fludzinski, P. *Tetrahedron Lett.* **1979**, 4513. (i) Inouye, Y.; Fukaya, C.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1117. (j) Andriamialisoa, R. Z.; Fetizon, M.; Hanna, I. *Tetrahedron* **1984**, *40*, 4285. (k) Berkowitz, W. F.; Perumattam, J.; Amarasekara, A. *Tetrahedron Lett.* **1985**, *26*, 3665. Berkowitz, W. F.; Amarasekara, A. S. *Tetrahedron Lett.* **1985**, *26*, 3663. (l) Neh, H.; Blechert, S.; Schnick, W.; Jansen, M. *Angew. Chem., Int. Ed. Eng.* **1984**, *23*, 905. (m) Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 203.

(3) Shea, K. J.; Davis, P. D. *Angew. Chem., Int. Ed. Eng.* **1983**, *22*, 419.

(4) Leeper, F. J.; Staunton, J. *J. Chem. Soc., Chem. Commun.* **1978**, 406.

(5) McKillop, A.; Fiaud, J.-C.; Hug, R. P. *Tetrahedron* **1974**, *30*, 1379.

(6) (a) Murphy, J. A.; Staunton, J. *J. Chem. Soc., Chem. Commun.* **1979**, 205. (b) Carpenter, T. A.; Evans, G. E.; Leeper, F. J.; Staunton, J.; Wilkenson, M. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1043.

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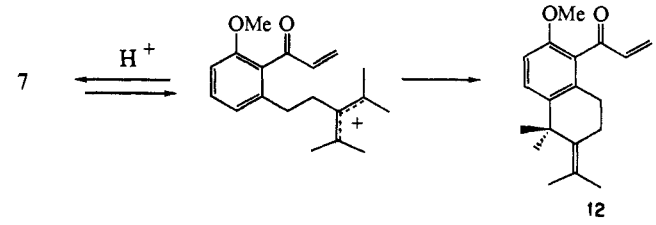
diene ester **9** in 60% yield. Elaboration of the carbomethoxy group to the enone was accomplished in four steps. These involve reduction to the benzylic alcohol **10** followed by PCC oxidation then treatment of the resulting aldehyde with vinyl magnesium bromide. The benzylic alcohol **11** was most efficiently oxidized by using $BaMnO_4$ in benzene. The overall sequence provided Diels–Alder precursor **7** in 30% yield from methoxy ester **8**. The thermal cycloaddition is accomplished by heating trienone **7** at 150 °C for 70 h (xylene, 0.1 M). Cycloadduct **6** is isolated in 80% yield. The thermal reactivity of **7** is very similar to that of **4**, thus the rate of cycloaddition is not influenced to any significant degree by the methoxy substituent.

We have previously established that derivatives of the tricyclo[9.3.1.$0^{3,8}$]pentadecane ring system are capable of existing in two low-energy conformations, *exo*-**5** and *endo*-**5**. For compound **5**, the barrier separating the conformational isomers was found to be $\Delta G^{\ddagger} = 16.5$ kcal mol.[7] It was not surprising therefore that the room temperature NMR spectra of cycloadduct **6** exhibited eight methyl resonances. This finding corresponds to a slow exchange of the endo and exo isomers on the NMR time scale. What was unanticipated however was the observation that the ratio of intensities of methyl signals varied as a function of the purification of the cycloadduct. This observation implied a nonequilibrium mixture of the two conformational isomers. Indeed both TLC and HPLC revealed two cycloaddition products which could be separated (isooctane/ethyl acetate, 35:1, 10μ porisil). Homonuclear ^{1}H double resonance and NOE experiments permitted tentative assignment of the two isomers, *endo*-**6** and *exo*-**6**. Particularly helpful was the chemical shift of the allylic methyl group (C-18), which is located at 0.80 ppm in *endo*-**6** and 1.60 ppm in *exo*-**6**. The chemical shift change results from a difference in proximity to the shielding region of the aromatic ring. The NMR assignments were confirmed by single-crystal X-ray structures of each isomer.[8] The ORTEP plots for the isomers are shown in Figure 1.

The X-ray data reveal the gross structural properties of the two conformations. In particular the "U"-shaped endo isomer situates the allylic methyl (C-18) over the aromatic ring and the extended exo isomer which locates the C-16 methyl group over the aromatic ring. The computed chemical shift differences, evaluated from X-ray crystallographic data and calculated shielding effects of the benzene ring,[9] agree extremely well with the experimental values.

The two isomers do not interconvert at room temperature. An equilibrium mixture of the diastereomers is obtained by heating an isooctane solution (150 °C) for 1 h. The equilibrium ratio of *endo*-**6**/*exo*-**6** is 2.78:1 yielding ($\Delta\Delta G^{\circ}_{endo/exo}$) 150 °C = 0.86 kcal/mol. By observing the approach to equilibrium of pure *endo*-**6** over a range of temperatures (50.1–89.9 °C) the activation energy and entropy of activation were evaluated ($E_a = 27.8 \pm 1.0$ kcal/mol, $\Delta S^{\ddagger} = 1.3 \pm 0.8$ eu). These results reveal that replacement of a hydrogen in **5** with a methoxy group raises the barrier to interconversion by over 10 kcal/mol. An explanation

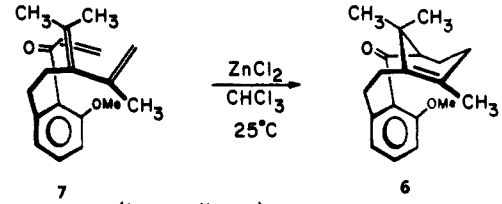
Scheme II



for this dramatic substituent effect arises from consideration of the dynamics of the interconversion. The carbonyl at C-2 must rotate past the ortho position of the aromatic ring. This factor alone is not expected to result in a dramatic increase of the barrier. However, as has been observed in 1,2,3-trisubstituted aromatic ketones,[10] the buttressing effect of the third aromatic substituent (C-8) amplifies the steric impediment to this torsion. The structural data support this analysis. The internal bond angles (C3–C4–O2) and (C2–C3–C4) for *exo*-**6** (114.1° and 117.2°) and *endo*-**6** (114.6 and 117.7°) reveal substantial crowding between the substituents at C4 and C5 (Figure 1). The magnitude of the barrier is nevertheless surprising since the methoxy substituent is also expected to *stabilize* the transition state for interconversion. This results from the fact that in both exo and endo isomers, the carbonyl group is orthogonal to the benzene ring.[11] In the interconversion between the two, the carbonyl group must pivot past the methoxy and at some point achieve coplanarity permitting resonance stabilization. The contribution of this resonance effect is not known; only the net effect of methoxy substitution on the barrier which is 11.3 kcal/mol.

The endo–exo interconversion requires torsion about five carbon–carbon single bonds. It is not possible at present to unequivocally establish if the bond rotations occur sequentially or in a synchronous manner. However, the influence of substituents on the barrier to rotation[7] suggest a *sequential* bond rotation with the potential energy maximum involving torsion about the C1–C2 and C2–C3 carbon–carbon bonds.

endo- and *exo*-**6** are diastereomeric atropisomers.[12] The Diels–Alder transition states leading to each isomer bear a diastereomeric relationship. Under thermal conditions for cycloaddition (150 °C), *endo*- and *exo*-**6** are equilibrated. To observe the *kinetic selectivity* for the cycloaddition, milder reaction conditions were explored. Treatment of trienone **7** with anhydrous $ZnCl_2$ (6–10 equiv, $CHCl_3$ 25 °C) for 2 h results in cycloaddition (80% isolated yield). Quite remarkably NMR analysis of the



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$(k_{ENDO}/k_{EXO})_{25°C} > 200:1$

$\Delta\Delta G^{\ddagger}_{(ENDO/EXO)_{25°C}} > 3.15$ kcal/mole

$\Delta G^{\circ}_{(ENDO/EXO)_{150°C}} = 0.86$ kcal/mole

crude reaction mixture revealed a kinetic selectivity $k_{endo}/k_{exo} > 200:1$ from which the energy difference for the two diastereomeric transition states is calculated to be $\Delta\Delta G^{\ddagger}_{25°C} = >3.15$ kcal/mol. Recalling that the free energy difference of the atropisomers is

(7) Shea, K. J.; Gilman, J. W. *Tetrahedron Lett.* **1983**, 657.

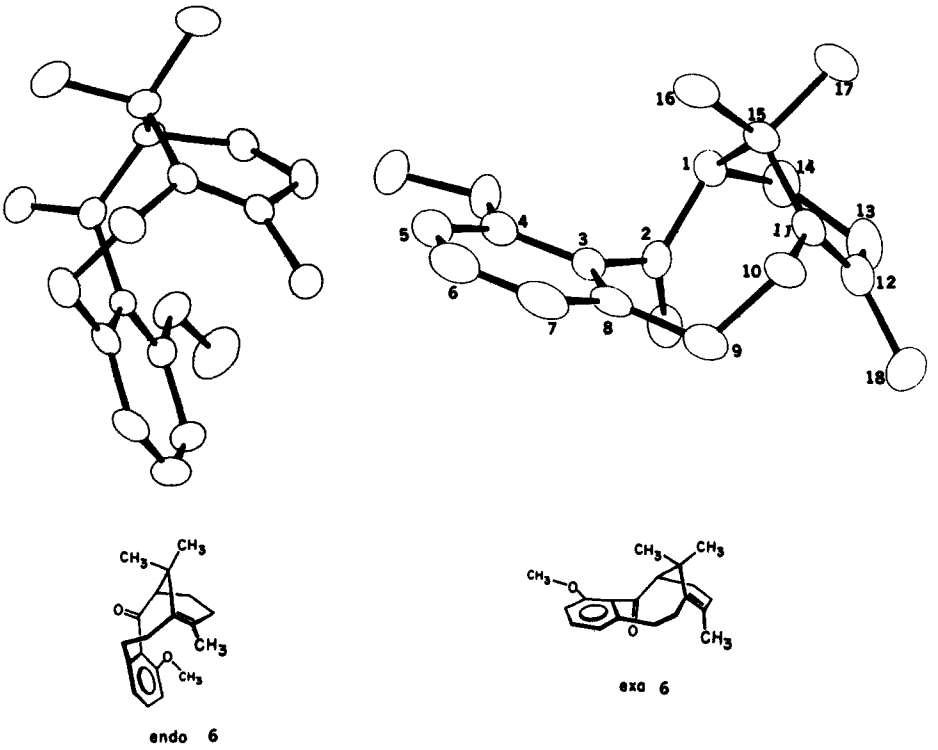
(8) (a) *endo*-**6**. X-ray structure data $C_{19}H_{24}O_2$, monoclinic, space group $P2_1/C$, $a = 14.474$ (5) Å, $b = 7.857$ (4) Å, $c = 14.296$ (5) Å, $\beta = 98.87$ (3), $U = 1606$ (1) Å^3, $Z = 4$. Intensity measurements were made on a Syntex $P2_1$ diffractometer, Mo Kα radiation λ $K_\alpha = 0.71073$ Å, graphite monochrometer. Intensities of 2209 reflections with $2\theta \leq 45°$ were measured; of these 1204 had intensities $I > 3\sigma(I)$. The structure was solved by direct methods (Multan 80) and refined by full-matrix least-squares calculations to $R = 0.059$, $R_w = 0.074$ (anisotropic thermal parameters for carbon and oxygen atoms experimentally determined). (b) *exo*-**6**. X-ray structure data $C_{19}H_{24}O_2$, monoclinic, space group $P21/a$, $a = 13.608$ (6) Å, $b = 7.793$ (2) Å, $c = 16.612$ (6) Å, $\beta = 115.59$ (3), $U = 1606$ (1) Å^3, $Z = 4$. Intensity measurements were made as in a. Intensities of 4058 reflections with $2\theta \leq 55°$ were measured; of these 1788 had intensities $I > 3\sigma(I)$. The structure was solved as in a and refined converged to $R = 0.070$, $R_w = 0.098$ (anisotropic thermal parameters for carbon and oxygen atoms). Tables of positional parameters, bond angles, interatomic distances, anisotropic temperature factors, and structure factors for both isomers are included as supplemental information.

(9) The calculated difference in chemical shift of Me-16 between the endo and exo isomers of **6** is 0.58 ppm (found 0.59 ppm) while the calculated value for Me-18 is 0.87 ppm (found 0.80 ppm). Bovey, F. A. *Nuclear Magnetic Resonance Spectroscopy*; Academic Press: New York, 1969; 264.

(10) (a) Sternhell, S. *Dynamic Nuclear Magnetic Resonance Spectroscopy*; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, *1975*; p 163. (b) Nakamura, N.; Ōki, M. *Bull. Chem. Soc. Jpn* **1972**, *45*, 2565. (c) Mislow, K. *Introduction to Stereochemistry*; W. A. Benjamin: New York, 1965; p 115.

(11) The angle between the least-squares plane of the aromatic ring and the carbonyl plane (defined by atoms O1–C2–C3) is 91.3° in *endo*-6 and 84.8° in *exo*-**6**.

(12) (a) Ōki, M. *Top. Stereochem.* **1983**, *14*, 1. (b) Ōki, M. *Acc. Chem. Res.* **1984**, *17*, 154.



endo 6

exo 6

Figure 1. ORTEP plots for endo-**6** and exo-**6** showing atomic numbering scheme.

only 0.86 kcal/mol, the Lewis acid catalyzed cycloaddition represents a situation where the product energy difference for the two competing reactions is substantially *amplified* in the transition states that lead to them. By comparison, the activation energy difference between the endo and exo transition states of **4** ($\Delta\Delta G^{\ddagger}_{-70°C}$ = 1.70 kcal/mol) is very similar to the differences in thermodynamic stability of the cycloadduct products ($\Delta\Delta G°_{(endo/exo)25°C}$ = 1.24 kcal/mol).[13] Factors that may account for this enhanced stereoselectivity are currently under investigation.

It is interesting to note that initial attempts to induce the Diels–Alder cycloaddition with $ZnCl_2$ in CH_2Cl_2 resulted in formation of cycloadduct **6** in addition to a side product, tetrahydronaphthalene **12**. We believed that **12** could arise from proton impurities in the Lewis acid. A mechanism for its formation is outlined in Scheme II. The proposed reaction is initiated by diene protonation followed by alkylation of the aromatic ring.

The presence of **12** created uncertainty as to what fraction, if any, of the cycloaddition product **6** arises from proton catalysis. This issue is particularly timely in light of the recent reports by Gassman and co-workers of proton catalysis in Diels–Alder reactions.[14] Several experiments were carried out to establish if the ratio of products could be influenced by the choice of reaction conditions and to see if cycloadduct **6** could be formed under protic conditions. The results are summarized in Table I.

$ZnCl_2$ in CH_2Cl_2 produces mixtures of cycloadduct **6** and tetrahydronaphthalene **12**. The amount of **12** is *increased* upon addition of trifluoroacetic acid (TFA). Indeed, TFA alone in CH_2Cl_2 results in formation of **12** as the major reaction product. Purified samples of $ZnCl_2$ in $CHCl_3$ gave *only* cycloadduct **6**. The addition of TFA to this reaction did however result in formation of significant amounts of **12**. The formation of **6** at room temperature in the presence of TFA implies a proton catalyzed intramolecular Diels–Alder reaction. The results at present do not permit a distinction between a step-wise or ionic mechanism for these catalyzed cycloadditions.

The diastereoselective (atropselective) Diels–Alder synthesis of *endo*-**6** provides an opportunity for utilizing conformational control in the elaboration of this isomer to the taxane natural products. Efforts along these lines are presently underway.

Table I. Influence of Reaction Conditions on Product Distribution

solv/temp	$ZnCl_2$ (equiv)	TFA (equiv)	time (h)	ratio[a] 6:12
CH_2Cl_2, *d*	10		4.5	70:30
CH_2Cl_2, *d*	10	5	2	50:50
CH_2Cl_2, *d*		5	0.5	16:84[b]
CH_2Cl_2, −60 → 0 °C		5	3	13:87[b]
$CHCl_3$, d	10		2	100:0
$CHCl_3$, d		5	18	70:30[c]

[a] Determined by GC. [b] In addition to **6** and **12**, side products amounting to approximately 25% of the mass balance were also detected. [c] Extensive side reactions were observed. [d] Room temperature.

Experimental Section

Ethyl 2-Methyl-6-methoxybenzoate (8). 2-Carbethoxy-3-methylphenol[6] (44.8 g, 247 mmol) was added to a solution of H_2O (300 mL), NaOH (27 g, 675 mmol), and benzyltriethylammonium chloride (5.2 g, 22.8 mmol). After the solution became homogeneous, CH_2Cl_2 (300 mL) was added. During vigorous stirring, dimethyl sulfate (27 mL, 286 mmol) was slowly added. Stirring was continued for 5 h at room temperature. Separation and extraction of the aqueous layer (CH_2Cl_2) followed by concentration yielded a residue that was added to H_2O (200 mL) and extracted with ether. The ether layers were combined and washed with 3 M NH_4OH, 2 M NaOH, and saturated brine solution. After drying ($MgSO_4$) and concentration, distillation gave anisole **8**, bp 90 °C (3 mm), 39.3 g, 82%.

3-(Chloromethyl)-2,4-dimethyl-1,3-pentadiene. To a solution of DMF (100 mL) containing LiCl (6.1 g, 143 mmol) and collidine (17.3 g, 143 mmol) was added 2,4-dimethyl-3-(hydroxymethyl)-1,3-pentadiene[3] (10.0 g, 79.4 mmol). The reaction was cooled to 0 °C, and methanesulfonyl chloride (16.4 g, 143 mmol) was slowly added with vigorous stirring. After 1.3 h the reaction was quenched with cold H_2O (100 mL) and extracted with ether. The ether extracts were washed with cold saturated cupric nitrate (3 × 75 mL), $NaHCO_3$, and brine. Drying ($MgSO_4$) and evaporation gave 10.2 g of crude allylic chloride. Bulb-to-bulb distillation gave 7.4 g (64%) of chlorodiene: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 4.95 (m, 1 H, vinyl), 4.67 (m, 1 H, vinyl), 4.08 (s, 2 H, CH_2Cl), 1.77 (t, 3 H, *J* = 1.2 Hz, CH_3), 1.73 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 144.5, 134.3, 133.3, 115.2, 44.3, 22.9, 22.3, 20.0 ppm; IR (film) 1663 m (C=C), 1630 m (C=C) cm^{-1}.

Ethyl 2-[4-Methyl-3-(methylethenyl)-3-pentenyl]-6-methoxybenzoate (9). To a THF solution of lithium diisopropyl amide (2.6 mmol) at −78 °C was added dropwise methoxy ester **8** (500 mg, 2.6 mmol) in THF (8

(13) Shea, K. J.; Gilman, J. W. *J. Am. Chem. Soc.* **1985**, *107*, 4791.
(14) (a) Gassman, P. G.; Singleton, D. A., *J. Am. Chem. Soc.* **1984**, *106*, 6085. (b) Gassman, P. G.; Singleton, D. A. *Ibid.* **1984**, *106*, 7993.

mL).[6] The solution was stirred for 1 h (deep red color) then added to the above chlorodiene (30 mL, 380 mg, 2.6 mmol) in THF (5 mL) at −78 °C. This solution stirred 2 h at −78 °C and then warmed to room temperature. After quenching (NH_4Cl) and extraction (CH_2Cl_2), the combined organic layers were dried ($MgSO_4$). Concentration gave after chromatography (1:1, CH_2Cl_2/petroleum ether, silica gel: 230/400, R_f 0.6) the diene ester **9** (410 mg, 80%): ^1H NMR ($CDCl_3$, 250 MHz) δ 7.25 (d of d, 1 H, J = 8.4, 7.7 Hz (Ar H)), 6.82 (d, 1 H, J. = 7.7 Hz (Ar H)), 6.75 (d, 1 H, J = 8.4 Hz (Ar H)), 4.97 (m, 1 H (vinyl)), 4.60 (m, 1 H, (vinyl)), 4.37 (q, 2 H, J = 7.2 Hz (OCH_2CH_3)), 3.80 (s, 3 H, (OCH_3)), 2.56 (m, 2 H (benzylic-CH_2)), 2.35 (m, 2 H (allylic-CH_2)), 1.78 (m, 3 H (CH_2)), 1.67 (s, 3 H ($C{=}C(CH_3)CH_3$)), 1.37 (t, 3 H, J = 7.2 Hz (OCH_2CH_3)) ppm; ^{13}C NMR ($CDCl_3$, 62.89 MHz) δ 168.5 (C=O), 156.5, 146.5, 141.1, 136.1, 130.3, 126.1, 124.2, 121.8, 113.6, 108.8, 61.3, 56.1, 33.5, 32.6, 22.9, 21.9, 14.4 ppm; IR ($CDCl_3$, 0.052 mm) 3070 m, 2920 m, 1710 s, 1680 s, 1270 s cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.45; H, 8.67. Found: C, 75.40; H, 8.70.

2-[4-Methyl-3-(methylethenyl)-3-pentenyl]-6-methoxybenzyl Alcohol 10. The diene ester **3** (2.67 g, 8.8 mmol) in ether (100 mL) was added dropwise to a solution of $LiAlH_4$ (0.72 g, 19 mmol, 2.1 equiv) in Et_2O (250 mL) at reflux. The reaction refluxed for 1 h and then was cooled to 0 °C and quenched by addition of H_2O (2.6 g), NaOH (2.6 g, 10% aqueous), H_2O (7.8 g), and $MgSO_4$ (8 g). After stirring at room temperature for 15 min, the suspension was filtered through a bed of $MgSO_4$. The ether soluiion was dried ($MgSO_4$) and concentrated to give after chromatography (SiO_2: 230/400, CH_2Cl_2), the benzyl alcohol **10** (2.14 g, 93%): ^1H NMR ($CDCl_3$, 250 MHz) δ 7.72 (d, 1 H, J = 7.7 Hz), 7.65 (d, 1 H, J = 8.3 Hz), 7.11 (t, 1 H, J = 8 Hz), 4.90 (m, 1 H (C=C-(H)H)), 4.65 (s, 2 H (CH_2OH)), 4.55 (m, 1 H (C=C(H)H)), 3.75 (s, 3 H (OMe)), 2.60 (, 2 H (($CH_2CH_2C{=}$)), 2.35 (s, 1 H (OH)), 2.20 (m, 2 H ($CH_2CH_2C{=}$)), 1.73 (m, 3 H ($H_2C{=}CCH_3$)), 1.59 (s, 3 H (geminal methyl)), 1.58 (s, 3 H (geminal methyl)); ^{13}C NMR ($CDCl_3$, 62.89 MHz) δ 158.45 (C=O), 146.6, 162.64, 136.2, 128.7, 127.2, 125.9, 121.5, 113.6, 108.4, 57.30, 55.60, 33.96, 32.26, 22.86, 21.85, 19.75 ppm; IR (film) 3450, 3095, 2920, 1585, 1470, 1270, 1020 cm^{-1}; high resolution mass spectrum, m/e (EI, 70 eV) calcd for $C_{17}H_{24}O_2$ 260.1860, obsd 260.1887.

2-[4-Methyl-3-(methylethenyl)-3-pentenyl]-6-methoxybenzaldehyde. A soluiion of **10** (2.14 g, 8.2 mmol) in CH_2Cl_2 (80 mL) was added dropwise to a suspension of anhydrous sodium acetate (660 mg, 8.0 mmol, 0.98 equiv) and PCC (3.6 g, 16.5 mmol, 2.0 equiv) in CH_2Cl_2 (250 mL) at 0 °C. This mixture stirred for 1.5 h then filtered through Florosil. Evaporation of solvent in vacuo gave the benzaldehyde (1.71 g, 80%). Typically, **10** was used without further purification: ^1H NMR ($CDCl_3$, 250 MHz) δ 10.63 (s, 1 H (C(O)H)), 7.4 (t, 1 H, J = 7.8 Hz), 6.83 (d, 1 H, J = 3.7 Hz), 6.81 (d, 1 H, J = 2.8 Hz), 5.0 (m, 1 H (C=CHH)), 4.63 (m, 1 H (C=CHH)), 3.9 (s, 3 H (OCH_3)), 2.95 (m, 2 H (benzylic)), 2.33 (m, 2 H), 1.84 (s, 3 H ($C(CH_3){=}CH_2$)), 1.68 (s, 6 H ($C{=}C(CH_3)_2$)); IR ($CDCl_3$, 0.052 mm) 3162, 3072, 2900, 2860, 1670, 1595, 1470, 1270 cm^{-1}; ^{13}C NMR ($CDCl_3$, 62.89 MHz) δ 191.8, 163.0, 146.4, 146.3, 136.1, 134.4, 125.8, 123.4, 123.2, 113.3, 109.0, 55.7, 32.9, 32.8, 22.7, 21.8, 19.6 ppm; high resolution mass spectrum, m/e (EI, 70 eV) calcd for $C_{17}H_{22}O_2$ 258.1619, found 258.1628.

1-[2-[4-Methyl-3-(methylethenyl)-3-pentenyl]-6-methoxyphenyl]-2-propen-1-ol (11). To a solution of the above aldehyde (1.71 g, 6.62 mmol) in THF (40 mL) at 0 °C was added dropwise vinyl magnesium bromide (26.5 mL, 4 equiv, 1 M) in THF (125 mL). The reaction stirred at 0 °C for 1 h and was quenched with NH_4Cl (50 mL) and H_2O (50 mL). The aqueous layer was extracted (Et_2O), and the combined organics were dried ($MgSO_4$) and concentrated to give the alcohol **11** (1.87 g, 99%). Typically, **11** was used without further purification; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.18 (t, 1 H, J = 7.9 Hz), 6.84 (t, 2 H, J = 7.8 Hz), 6.25 (m, 1 H, (C(H)=CH_2)), 5.38 (m, 1 H (CH(OH)), 5.12 (m, 2 H, (C(H)CH_2)), 5.00 (m, 1 H ($C(CH_3{=}CH$H$)$), 4.65 (m, 1 H (C=CHH)), 4.02 (d, 1 H, J = 11.1 Hz (OH)), 3.86 (s, 3 H (OCH_3)), 2.65 (m, 2 H (CH_2), 2.31 (m, 2 H), 1.81 (s, 3 H ($C(CH_3){=}CH_2$)), 1.69 (s, 6 H ($C{=}C(CH_3)_2$)) ppm; IR ($CDCl_3$, 0.0052 mm) 3520, 3125, 3060, 2915, 1578, 1460, 1210 cm^{-1}; ^{13}C NMR ($CDCl_3$, 62.89 MHz) δ 157.8, 146.4, 141.3, 140.6, 136.0, 128.3, 126.8, 123.0, 114.2, 113.5, 109.4, 71.3, 55.5, 33.4, 32.4, 22.8, 21.7, 19.6 ppm; high resolution mass spectrum calcd for $C_{19}H_{26}O_2$ 286.1933, found 286.1928.

1-[2-[4-Methyl-3-(methylethenyl)-3-pentenyl]-6-methoxyphenyl]-2-propen-1-one (7). A benzene (50-mL) solution containing **11** (4.39 g, 15.0 mmol) was added dropwise to a benzene (200-mL) solution containing $BaMnO_4$ (28.4 g, 103 mmol, 7 equiv). This mixture was refluxed for 4 h then filtered through a bed of Celite. Evaporation of solvent in vacuo gave after chromatography the trienone **7**, (silica gel: 230/400, 1:1, CH_2Cl_2/petroleum ether), 3.65 g, 91%: ^1H NMR ($CDCl_3$, 250 MHz) δ 7.28 (t, 1 H, J = 8.0 Hz), 6.84 (d, 1 H, J = 7.7 Hz), 6.77 (d, 1 H, J = 9.2 Hz), 6.61 (m, 1 H (COCH=CH_2)), 5.97 (m, 2 H (COCHCH_2)), 4.94 (m, 1 H (C=CHH)), 4.56 (m, 1 H (C=CHH)), 3.76 (s, 3 H (OCH_3)), 2.45 (m, 2 H), 2.26 (m, 2 H), 1.76 (s, 3 H ($C(CH_3{=}CH_2)$), 1.66 (s, 6 H ($C{=}C(CH_3)_2$)) ppm; IR ($CDCl_3$, 0.062 mm) 3120, 2910, 3020, 1650, 1570, 1460, 1250 cm^{-1}; ^{13}C NMR ($CDCl_3$, 62.89 MHz) δ 198.2, 156.6, 146.2, 141.4, 138.5, 136.8, 130.5, 130.1, 128.5, 125.9, 113.4, 108.4, 44.5, 33.5, 31.9, 22.6, 21.7, 19.6 ppm; high resolution mass spectrum, m/e (EI, 70 eV) calcd for $C_{19}H_{24}O_2$ 284.1776, found 284.1772.

Thermal Cyclization of Trienone 7. A solution of **7** (800 mg, 3.0 mmol) in toluene (100 mL) was sealed in a Carius tube with methylene blue (2 mg) and heated at 150 °C for 70 h. The solution was filtered through a bed of Celite to give after recrystallization (pentane) the tricyclic ketone **6** (640 mg, 2.4 mmol, 80%).

endo-**6**: ^1H NMR (C_6D_6, 500 MHz) δ 6.85 (t, 1 H, (H-2)), 6.56 (d, 1 H, (H-1)), 6.35 (d, 1 H, (H-3)), 3.19 (s, 3 H (OCH_3)), 2.78 (d, 1 H, (H-4)), 2.65 (m, 1 H (H-12)), 2.53 (m, 1 H (H-11)), 2.45 (m, 2 H (H-5, H-9)), 2.15 (m, 2 H (H-10, H-8)), 1.85 (m, 1 H (H-6)), 1.60 (m, 1 H (H-7)), 1.32 (s, 3 H (CH_3-16)), 1.02 (s, 3 H (CH_3-17)), 0.80 (s, 3 H (CH_3-18))); IR (CCl_4, 0.10 m) 3050, 2940, 1680, 1460, 1260, 1070 cm^{-1}; ^{13}C NMR (62.98 MH, $CDCl_3$) δ 213.9, 154.4, 138.0, 135.0, 133.1, 131.9, 128.5, 123.8, 109.2, 63.2, 56.0, 37.8, 33.6, 29.2, 29.0, 28.2, 24.9, 20.7, 18.2 ppm; UV λ_{max} = 280; ϵ_{endo} = 5.5 × 10^{-3} 1 mol^{-1}/cm^{-1}; high resolution mass spectrum calcd for $C_{19}H_{24}O_2$ 284.1776, found 284.1771.

exo-**6**: ^1H NMR (C_6D_6, 500 MHz) 7.0 (t, 1 H, J = 8 Hz (H-2)), 6.66 (d, 1 H, J = 8 Hz (H-1)), 6.40 (d, 1 H, J = 8 Hz (H-3)), 3.15 (s, 3 H (OCH_3)), 2.88 (d, 1 H, J = 2.4 Hz (H-4)), 2.82 (d of t, 1 H, J = 2.8, 13 Hz (H-9 or H-10)), 2.75 (6 t, 1 H (H-6)), 2.55 (d, 1 H (H-9 or H-10)), 2.38 (d of d, 1 H (H-11)), 2.25 (m, 1 H (H-8)), 2.18 (m, 1 H (H-7)), 2.10 (t, 1 H (H-12)), 1.79 (m, 1 H (H-5)), 1.60 (s, 3 H (CH_3-18)), 1.020 (s, 3 H (CH_3-17)), 0.73 (s, 3 H (CH_3-16)) ppm; ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 208.0, 156.1, 139.3, 139.2, 133.8, 132.7, 129.5, 123.9, 109.7, 60.2, 56.1, 38.1, 36.2, 29.8, 29.4, 29.0, 27.1, 20.2, 19.5 ppm; IR (CCl_4, 0.052 mm) 3050, 2940, 1680, 1460, 1250, 1070, cm^{-1}; UV λ_{max} = 280; ϵ_{exo} = 6.4 × 10^3 1·mol^{-1} cm^{-1}; high resolution mass spectrum calcd for $C_{19}H_{24}O_2$ 284.1776, found 284.1771.

Zinc Chloride Cyclization of 7. Synthesis of Cycloadduct 6. A solution of trienone **7** (2.56 g, 9.01 mmol) in $CHCl_3$ (400 mL) was charged with powdered anhydrous $ZnCl_2$ (12.3 g, 90.1 mmol, 10 equiv). The mixture stirred for 2 h at 25 °C. The reaction was quenched with $NaHCO_3$ and H_2O and extracted (CH_2Cl_2). The combined organic layers were dried ($MgSO_4$), concentrated, and purified by column chromatography (silica gel: 230/400, CH_2Cl_2, R_f 0.4) to give **6** (2.1 g, 80%).

Conformational Stability of *endo*-6 in the Presence of $ZnCl_2$. *endo*-**6** (30 mg, 0.1 mmol) in $CHCl_3$ (10 mL) containing $ZnCl_2$ (17 mg, 1.05 equiv, 10 equiv) at 25 °C was stirred for 24 h. No equilibration to *exo*-**6** was observed.

An identical experiment was performed with exo-**6**. No equilibration to the endo isomer was observed after 24 h.

1,1-Dimethyl-2-(1-methyl-1-ethenyl)-5-(1-oxo-2-vinyl)-6-methoxy-3,4-dihydronaphthalene (12) from 1-[2-[4-Methyl-3-(methylethenyl)-3-pentenyl]-6-methoxyphenyl]-2-propen-1-one (7). To a stirred solution of dienenone **7** (10 mg) in CH_2Cl_2 (6 mL) was added trifluoroacetic acid (5 equiv). The reaction was stirred at room temperature for 3 h at which time no starting material remained. The reaction was quenched with $NaHCO_3$ (20 mL) and extracted (CH_2Cl_2) to give tetrahydronaphthalene **12** by HPLC separation (isooctane/ethyl acetate (35:1): ^1H NMR ($CDCl_3$, 250 MHz) δ 7.40 (d, 1 H, J = 8.8 Hz), 6.81 (d, 1 H, J = 8.8 Hz), 6.60 (d, 1 H, J_{cis} = 9.95 Hz, J_{trans} = 14.95 Hz (=CH)), 6.02 (d, 1 H, J = 1 Hz (=CH)), 6.00 (d of d, J_{gem} = 1.3 Hz, J_{vic} = 2 Hz (=CH)), 3.76 (s, 3 H (OMe)), 2.47 (m, 2 H), 2.35 (m, 2 H), 1.92 (s, 3 H (ME)), 1.74 (s, 3 H (Me)), 1.54 (s, 6 H (Me)) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 199.6, 154.3, 143.0, 139.1, 137.8, 137.5, 131.2, 129.1, 127.1, 124.0, 110.0, 56.4, 40.7, 31.4, 29.5, 28.2, 24.2, 24.0 ppm; IR (CCl_4) 3070 w (Ar CH), 2950 s (aliphatic CH), 1665 s (C=O), 1590 s and 1475 s (C=C), 1270 s (CO) cm^{-1}; high resolution mass spectrum calcd for $C_{19}H_{24}O_2$ 284.1776, found 284.1760.

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Supplementary Material Available: Tables of positional parameters, anisotropic temperature factors, bond angles, and interatomic distances for *endo*-**6** and *exo*-**6** (8 pages). Ordering information is given on any current masthead page.