H), 2.18-2.46 (m, 3 H), 3.34 (m, 1 H), 3.83 (dd, 1 H), 4.03 (dd, 1 H), 4.60 (m, 1 H), 5.72 (s, 1 H), 7.34-7.48 (m, 6 H), 7.61-7.68 (m, 4 H); FAB mass spectrum, m/e 563 ($M^+ + 1$); IR (CH_2Cl_2) 1823 (β-lactone), 1705 cm^{-1} (α,β-unsaturated δ-lactone).

(2′*R*,3′*R*,7*R*)-(*E*,*E*)-*tert*-Butyl 11-[3′-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-4′-oxo-2′-oxetanyl]-3,5,7-trimethyl-2,4-undecadienoate (21). To a refluxing solution of 16 mg (0.025 mmol) of **19** in 3 mL of CH_2Cl_2 in the presence of 100 μL (1.23 mmol) of pyridine was added dropwise a solution of 50 μL (0.69 mmol) of thionyl chloride in 1 mL of CH_2Cl_2 during 3 min. The mixture was then stirred for 5 min at refluxing temperature. The product was purified by preparative TLC (R_f 0.63, 20% EtOAc in hexane) to afford 14 mg (90%) of a mixture, which was then purified again via repeated development seven times on preparative TLC plates to give 4.2 mg (30%) of **21** (bottom band, top band was a mixture of other isomers): $[\alpha]_D$ +3.38° (c 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.83 (d, 3 H), 1.07 (s, 9 H), 1.19-1.57 (s + m, 15 H), 1.58-2.00 (s + m, 7 H), 2.09 (dd, 1 H), 2.10 (s, 3 H), 3.34 (q, 1 H), 3.83 (dd, 1 H), 4.04 (dd, 1 H), 4.60 (m, 1 H), 5.59 (s, 1 H), 5.68 (s, 1 H), 7.34-7.53 (m, 6 H), 7.60-7.70 (m, 4 H); FAB mass spectrum, m/e 619 ($M^+ + 1$); IR (CH_2Cl_2) 1820 cm^{-1} (β-lactone). Anal. Calcd for $C_{38}H_{54}O_5Si$: C, 73.75; H, 8.79. Found: C, 73.45; H, 8.70.

(2′*R*,3′*R*,7*R*)-(*E*,*E*)-11-[3′-(Hydroxymethyl)-4′-oxo-2′-oxetanyl]-3,5,7-trimethyl-2,4-undecadienoic Acid (L-659,699). To a solution of 10 mg (0.016 mmol) of **21** in 0.1 mL of THF was added 0.14 mL of 50% aqueous hydrofluoric acid. After stirring for 18 h at room temperature, the mixture was neutralized with saturated $NaHCO_3$ solution and then extracted with 3 × 10 mL of CH_2Cl_2. The organic phases were combined, dried and concentrated. The product was purified by preparative TLC to afford 4 mg (76%) of the synthetic L-659,699: $[\alpha]_D$ +27.4° (c 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.84 (d, 3 H), 1.10-1.57 (m, 6 H), 1.58-1.99 (s + m, 7 H), 2.10 (dd, 1 H), 2.25 (s, 3 H), 3.41 (q, 1 H), 4.00 (dd, 1 H), 4.07 (dd, 1 H), 4.61 (m, 1 H), 5.71 (s, 1 H), 5.75 (s, 1 H); FAB mass spectrum, m/e 325 ($M^+ + 1$); IR (CH_2Cl_2) 1815 cm^{-1} (β-lactone). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.59; H, 8.59.

Acknowledgment. Microanalytical data were obtained by the analytical Research Department of Merck Sharp and Dohme Research Laboratories.

A New General Synthetic Approach to Diterpenes: Application to Syntheses of (±)-Taxodione and (±)-Royleanone

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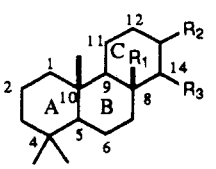
High-pressure Diels-Alder reactions of 1,3,3-trimethyl-2-vinyl-1-cyclohexenes **3a,b,i** with substituted 1,4-benzoquinones afford, in good yield, highly functionalized tricyclic ring systems which are found in many classes of naturally occurring terpenes. Notably, the reactions of **3a** are highly regio- and stereoselective. Efficient, formal syntheses of the antitumor diterpenes (±)-taxodione and (±)-royleanone are reported, which demonstrate the practical application of this new strategy for the preparation of varied terpene systems. Of particular interest is that the high-pressure reactions are accelerated by mild Lewis acids and the regio- and stereoselectivity of these reactions is also improved under the combined high-pressure/Lewis acid conditions in comparison to the high-pressure conditions alone. Indeed, in the reaction of **3a** with 2-methoxy-5-methyl-1,4-benzoquinone, $ZnBr_2$ is required to effect the Diels-Alder reaction even at 12 kbar, and endo adduct **12c** is formed stereoselectively in ≥90% yield. In contrast, low-temperature Ti(IV)-catalyzed reactions of diene **3a** with methoxy-substituted 1,4-benzoquinones at atmospheric pressure regioselectively produce dihydrobenzofurans **19** and **20**, apparently via alkylation of the quinone Ti(IV) complex by the diene followed by ring closure.

Introduction

The 4,4,10-trimethyl- and 4,4,8,10-tetramethylperhydrophenanthrene[1a] ring systems **1** and **2** form all, or part of, the basic carbocyclic framework of several classes of terpenes.[1] In addition, the B and C rings in many of the natural products incorporate carbonyl, hydroxyl, epoxide, and/or olefin moieties at various positions. Strategies for total synthesis of these terpenes most commonly employ consecutive Robinson annulation reactions or cation-olefin/arene cyclization reactions. An alternate, albeit obvious, strategy to molecules incorporating structures **1**/**2** with oxidized B/C rings is a Diels-Alder reaction of 1,3,3-trimethyl-2-vinylcyclohexene **3** with an appropriately substituted 1,4-benzoquinone (Scheme I). However, cycloaddition reactions of **3** are difficult to effect with many dienophiles, probably due to steric hindrance provided by three methyl groups on the diene, and relatively few synthetic approaches to natural products using this strategy have been reported.[2,3]



1, R_1=H, R_2,R_3=H or alkyl
2, R_1=CH_3, R_2,R_3=H or alkyl

† Lilly Grantee, 1989-1991.

(1) (a) In the interest of clarity, the standard terpene numbering scheme for **1** and **2** and derivatives is used in the Introduction and Results and Discussion sections. However, the systematic *Chemical Abstracts* names and numbering scheme are used in the Experimental Section, as recommended by the Editor. For reviews of structures and syntheses of di-, sester-, and triterpene ring systems, see: (b) Hanson, J. R. *Nat. Prod. Rep.* **1988**, *5*, 211. (c) Hanson, J. R. *Ibid.* **1986**, *3*, 123. (d) Connolly, J. D.; Hill, R. A. *Ibid.* **1985**, *2*, 1. (e) ApSimon, J. W.; Fyfe, K. E.; Greaves, A. M. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; Wiley-Interscience: New York, 1984; Vol. 6, p 85. (f) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Noze, S. *Natural Products Chemistry*; Academic Press: New York, 1974; Vol. 1. (g) Hanson, J. R. *Terpenoids and Steroids-Specialist Periodical Report of the Royal Society of Chemistry*; The Royal Society of Chemistry: London, 1971-1983; Vol. 1-12 and references cited in the above.

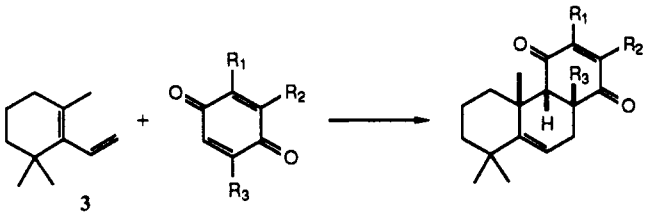
0022-3263/89/1954-5712$01.50/0

Table I. Diels–Alder Reactions of 1,3,3-Trimethyl-2-vinylcyclohexenes with 1,4-Benzoquinones

				conditions[a]			products, % yield			
entry	diene	quinone	catalyst (equiv)	pressure	time	temp, °C				
	3a	**11a**					**12a**	**13a**	**14a**	
1			–	6 kbar	14 days	rt[b]	32	14	16	
2			$SnCl_4$ (1)	1 bar	3 h	−40	69			
3			BF_3Et_2O (0.5)	1 bar	5 h	0	55	14		
4			–	12 kbar	1 h	rt	19	8		
5			$ZnBr_2$ (0.88)	12 kbar	1 h	rt	67	8		
	3a	**11b**					**12b**	**17b**		
6			–	7 kbar	14 days	rt	80			
7			–	12 kbar	5 days	rt	71	3		
8			–	12 kbar	14 days	rt	86	10		
9			$ZnBr_2$ (1.0)	11 kbar	15 h	rt	52			
	3a	**11c**					**12c**			
10			$ZnBr_2$ (1.1)	12 kbar	14 days	rt	92			
	3b	**11a**					**23**	**24**		
11			–	12 kbar	2 days	rt	38	~1		
	3b	**11b**					**26**	**27**	**30**	
12			–	12 kbar	10 days	rt	26	23		
13			$Eu(fod)_3$ (0.07)	12 kbar	18 h	rt	23	12	≤2	
14			$Yb(fod)_3$ (0.10)	12 kbar	18 h	rt	27	12	≤2	
	3i	**11a**					**25**			
15			–	12 kbar	8.5 days	rt	60			
	3i	**11b**					**28**	**29**		
16			–	12 kbar	13 days	rt	20	42		
17				12 kbar	4 days	rt	11	21		
18			$Eu(fod)_3$ (0.10)	12 kbar	3.5 days	rt	13	23		
19			$Yb(fod)_3$ (0.10)	12 kbar	4.5 days	rt	11	66		
	3a	**44**					**45**	**46**	**47**	**48**
20			–	6 kbar	14 days	rt	18	18	13	
21			–	12 kbar	5 days	rt	36	17	8	
22			$ZnBr_2$ (0.86)	12 kbar	5 days	rt	60	14	–	tr[c]
23			$ZnBr_2$ (0.62)	12 kbar	30 h	rt	53	14	–	nd[d]
24			$ZnBr_2$ (0.74)	12 kbar	2 days	rt	49	10	–	nd
25			$ZnBr_2$ (1.47)	12 kbar	2 days	rt	40	15	–	nd
26			$ZnBr_2$ (1.13)	12 kbar	5 days	rt	31	19	–	13

[a] All experiments were carried out in CH_2Cl_2. [b] rt = room temperature; [c] tr = trace; [d] nd = not determined.

Scheme I



Thermal Diels–Alder reaction of diene **3a** with dimethyl acetylenedicarboxylate (DMAD) to give **4** has been used often in synthesis of the drimane insect antifeedants (Scheme II).[2] Diene **3a** has been reported to react thermally with maleic anhydride, although different structures for the adduct have been suggested.[4,5] Reactions of enol ether **3b**[4] and dieneamines **3c/d**[6] with DMAD, maleic anhydride, dimethylfumarate, and methyl acrylate give adducts **5–8**, respectively. Dioxene **3e** reacts thermally with DMAD to produce **9** in 16% yield; however, the $EtAlCl_2$-catalyzed reaction of **3e** and DMAD gives **10**, presumably via a 2 + 2 adduct.[7] Attempted Diels–Alder reactions of the functionalized dienes **3f–j** under thermal or Lewis acid catalyzed conditions have generally failed.[2b] Several intramolecular variants of the Diels–Alder reactions discussed here are known (Scheme III).[8]

In this paper,[9] we report the details of our work on the stereo- and regioselective Diels–Alder reactions of dienes **3a,b,i** with various 1,4-benzoquinones, which establishes that the strategy outlined in Scheme I is effective for the preparation of diterpenes possessing structure **1** and should be applicable to higher terpenes which incorporate structure **2** as well. A relatively unusual solution[10] to the steric

(2) For a review of the application of this strategy to syntheses of drimane sesquiterpenes, see: (a) deGroot, A.; van Beek, T. A. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 1. See also: (b) Hollinshead, D. M.; Howell, S. C.; Ley, S. V.; Mahon, M.; Ratcliffe, N. M.; Worthington, P. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1579 and references cited therein. Diels–Alder reactions of 1,3-dimethyl-2-vinylbicyclo[4.1.0]hept-2-ene, a diene closely related to **3a**, have been reported. (e) Meinwald, J.; Sakaino, M. *Tetrahedron Lett.* **1987**, 3201.

(3) Approaches to rosmariquinone and the tanshinones, terpene systems related to **1** but which lack the angular C-10 methyl substituent, have been reported via Diels–Alder reactions of 6,6-dimethylvinylcyclohexene with quinones; see: (a) Knapp, S.; Sharma, S. *J. Org. Chem.* **1985**, *50*, 4996. (b) Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3318. (c) Lee, J.; Snyder, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 1522.

(4) Jalali-Naini, M.; Guillerm, D.; Lallemand, J.-Y. *Tetrahedron* **1983**, *39*, 749.

(5) Campos, J. A.; Garcia Jimenez, F. *Rev. Soc. Quim. Mex.* **1975**, *19*, 93.

(6) Snowden, R. L.; Wust, M. *Tetrahedron Lett.* **1986**, 699.

(7) Fetizon, M.; Goulaouic, P.; Hanna, I.; Prangé, T. *J. Org. Chem.* **1988**, *53*, 5672.

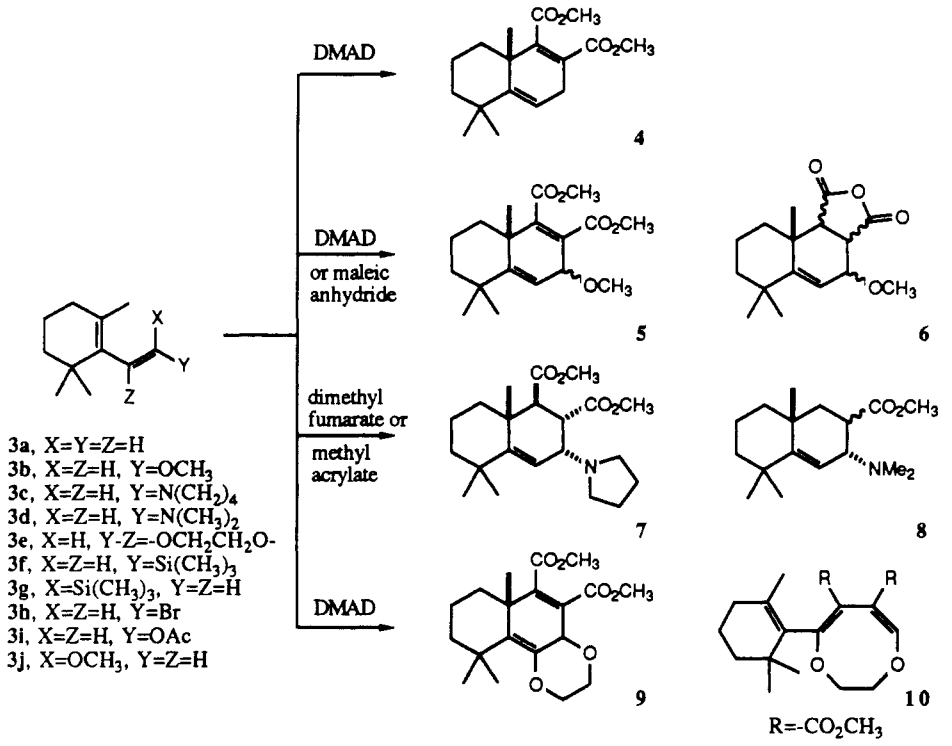
(8) (a) Jenkins, P. R.; Menear, K. A.; Barraclough, P.; Nobbs, M. S. *J. Chem. Soc., Chem. Commun.* **1984**, *1423*. (b) Nicolaou, K. C.; Li, W. S. *Ibid.* **1985**, 421. (c) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *Tetrahedron Lett.* **1985**, 3307. (d) Corey, E. J.; Da Silva Jardine, P.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672. (e) He, J.-F.; Wu, Y.-L. *Tetrahedron* **1988**, *44*, 1933.

(9) Preliminary accounts of this work have appeared: (a) Engler, T. A.; Naganathan, S.; Takusagawa, F.; Yohannes, D. *Tetrahedron Lett.* **1987**, 5267. (b) Engler, T. A.; Naganathan, S. *Ibid.* **1986**, 1015. The full experimental details of the work presented in these communications appear herein.

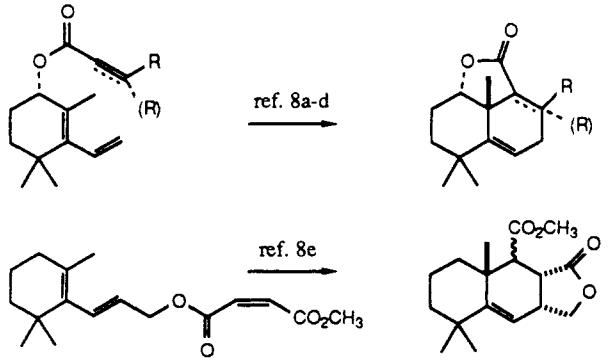
(10) For other reports of the use of the combination of Lewis acid catalysis and high pressure to effect difficult Diels–Alder reactions, see: (a) Jurczak, J.; Golebiowski, A.; Raczko, J. *Tetrahedron Lett.* **1988**, 5975. (b) Dauben, W. G.; Bunce, R. A. *Tetrahedron Lett.* **1982**, 4875 (cf. Trost, B. M.; O'Krongly, D.; Belletine, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595).

(11) An unusually high field singlet at 0.67 ppm in the 300-MHz ^1H NMR spectrum of the crude reaction mixture is characteristic of an α C-4 methyl group in ring C aromatic podocarpane diterpenes with cis AB ring fusions due to shielding of this methyl group by the aromatic ring; see: Martin, J. D. *Tetrahedron* **1973**, *29*, 2553, ref 21c and references cited therein.

Scheme II



Scheme III



problems encountered in the cycloaddition reactions was provided by the combined use of high-pressure and Lewis acid catalysis which led to faster reactions and increased stereo- and regioselectivity.

Results and Discussion

Model Studies. Initially, reactions of diene **3a**[2b] with 1,4-benzoquinones **11a–c** were examined to test the feasibility and the potential stereo- and regioselectivity of the anticipated Diels–Alder process (Scheme IV). The reactions were studied under both high pressure and Lewis acid catalyzed conditions.[9]

The pressure-promoted reaction of diene **3a** with 1,4-benzoquinone **11a** produced enedione **12a**, quinone **13a**, and hydroquinone **14a** (Scheme IV and Table I). Enedione **12a** was the exclusive 1:1 adduct formed from the $SnCl_4$-catalyzed reaction of the diene and the quinone, and the BF_3·Et_2O-catalyzed reaction of **3a** and **11a** gave a 4:1 mixture of enedione **12a** and quinone **13a**. An interesting observation made during the course of these studies was that mild Lewis acids accelerated the high-pressure Diels–Alder reactions and also improved the selectivity of the reaction (vide infra).[10] Thus, reaction of diene **3a** and quinone **11a** at 12 kbar for 1 h gave a 2.4:1 ratio of **12a**:**13a** in 27% yield (entry 4). However, under the same conditions in the presence of $ZnBr_2$, **3a** and **11a** produced a 8.4:1 ratio of **12a**:**13a** in 75% yield (entry 5). Products **12–14** were established as 4 + 2 adducts via chemical interconversion and transformation to known systems (Scheme V).[9a]

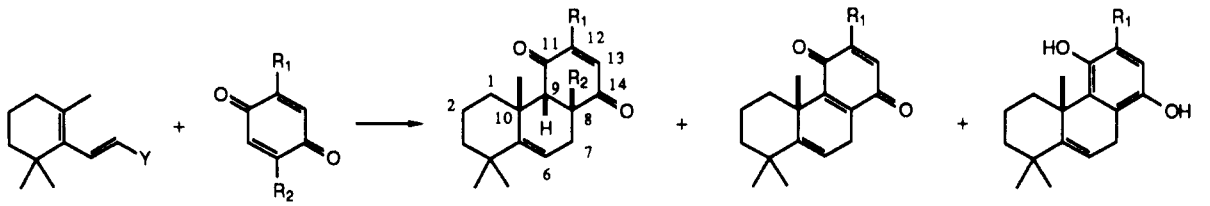
The origin of quinone **13a** and hydroquinone **14a** in the high-pressure experiments warrants some comment. Both enedione **12a** and hydroquinone **14a** are stable to air oxidation and their interconversion upon SiO_2 chromatography is unlikely since no evidence of the latter is observed when **12a** is prepared by other methods and isolated by SiO_2 chromatography (vide ante). As indicated in Scheme V, hydroquinone **14a** is quantitatively oxidized to **13a** by treatment with 1,4-benzoquinone at atmospheric pressure. Upon pressurization of a mixture of enedione **12a** and 1,4-benzoquinone, the presence of **13a** is evident. However, no quinone **13a** or hydroquinone **14a** results from pressurization of **12a** in the absence of 1,4-benzoquinone. Thus, quinone **13a** apparently results from direct, pressure promoted oxidation of enedione **12a** by 1,4-benzoquinone, which is present in the reaction mixture. Hydroquinone **14a** may be formed as an equilibrium mixture of **14a** and **13a**, which is established at high pressure in the presence of 1,4-benzoquinone.

High-pressure reactions of diene **3a** and 2-methoxy-1,4-benzoquinone, **11b**, are highly stereo- and regioselective and are also subject to Lewis acid catalysis (Scheme IV and Table I). Reaction at 7 kbar for 14 days gave exclusively adduct **12b** in 80% yield. Some loss in stereoselectivity was observed in reactions conducted at higher

(12) For other examples of hydrogenation in acidic media of the 5,6-olefin unit in podocarpane diterpenes and related compounds to afford trans AB ring fusions, see: (a) Matsumoto, T.; Usui, S.; Morimoto, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1575. (b) Tachibana, Y. *Ibid.* **1975**, *48*, 298 and ref 2b.

(13) Pelletier, S. W.; Ohtsuka, Y. *Tetrahedron* **1977**, *33*, 1021.

Scheme IV



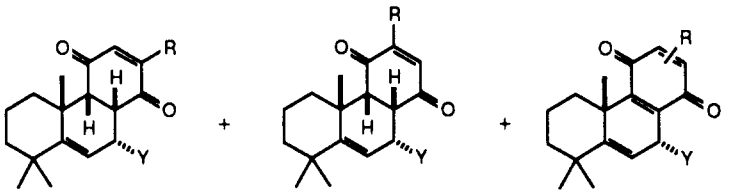
3a, Y=H

11a, R_1=R_2=H
11b, R_1=OCH_3, R_2=H
11c, R_1=OCH_3, R_2=CH_3

12a, R_1=R_2=H
12b, R_1=OCH_3, R_2=H
12c, R_1=OCH_3, R_2=CH_3

13a, R_1=H
13b, R_1=OCH_3

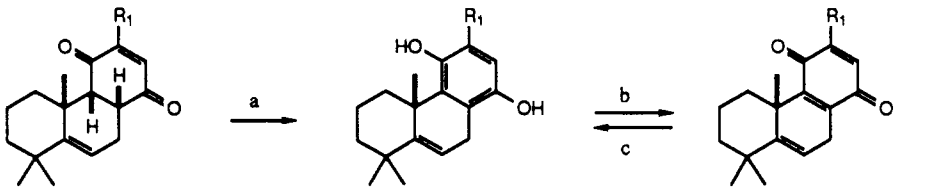
14a, R_1=H
14b, R_1=OCH_3



3b, Y=OCH_3 + **11a**, **11b** → **23**, R=H, Y=OCH_3; **26**, R=OCH_3, Y=OCH_3; **27**, R=OCH_3, Y=OCH_3; **24**, R=H, Y=OCH_3; **30**, R=OCH_3, Y=OCH_3

3l, Y=OAc + **11a**, **11b** → **25**, R=H, Y=OAc; **28**, R=OCH_3, Y=OAc; **29**, R=OCH_3, Y=OAc

Scheme V[a]



12a, **12b** → **14a**, **14b** → **13a**, **13b**

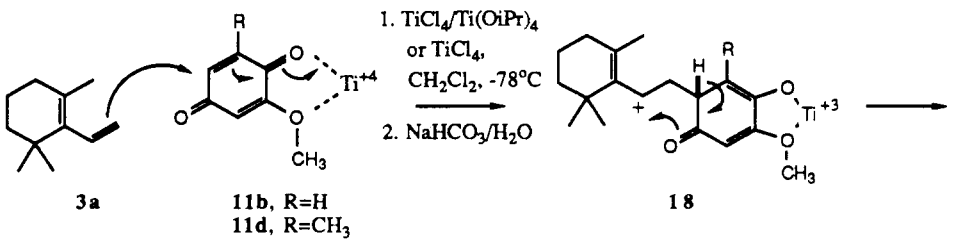
15a, R_1=H
15b, R_1=OCH_3

16a[13]

16b[11]

[a] Reagents and conditions: (a) aqueous HCl/THF, room temperature, 84% for **14a**; 93% for **14b**; (b) 1,4-benzoquinone, PhH/EtOAc, room temperature, 100% for **13a**; (c) Zn/HOAc, CH_2Cl_2, room temperature, 97% for **14a**; (d) NaO*t*-Bu/$(CH_3O)_2SO_2$, THF, room temperature, 65–78% for **15a**; KO*t*-Bu/$(CH_3O)_2SO_2$, THF, room temperature, 41% for **15b**; (e) H_2, Pd/C, HOAc, room temperature, 92% for **16a**/**b**.[12]

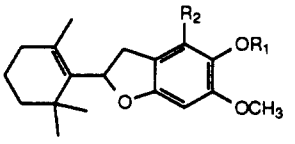
Scheme VI



3a

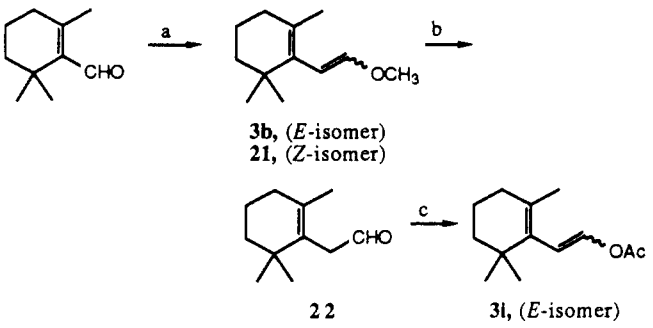
11b, R=H
11d, R=CH_3

18



19a, R_1=H, R_2=H; 54%
19b, R_1=CH_3, R_2=H
20, R_1=H, R_2=CH_3; 41%

Scheme VII[a]

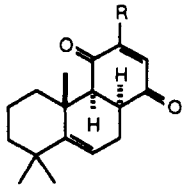


3b, (*E*-isomer)
21, (*Z*-isomer)

22 **3i**, (*E*-isomer)

[a] Reagents and conditions: (a) KO*t*-Bu/$Ph_3P^+CH_2OCH_3$ Cl^-, THF, 80–90 °C, 82%; (b) 50% aq $HClO_4/Et_2O$, room temperature, 80%; (c) (i) KO*t*-Bu, THF, room temperature; (ii) Ac_2O, THF, room temperature 80%.

pressures and longer reaction times (entries 7 and 8).[14] For example, at 12 kbar for 14 days, an 8.6:1 ratio of **12b** and an isomer, tentatively identified as exo isomer **17b**,[15] was found in 96% yield, and reaction at 12 kbar for 5 days produced a 24:1 mixture of **12b** and **17b** in 74% yield.



17a, R=H
17b, R=OCH_3

However, of greater interest is that the reaction is more stereoselective when conducted under the combined Lewis acid/high-pressure conditions (Table I, entry 9). Thus, pressurization of a CH_2Cl_2 solution of **3a**, **11b**, and zinc bromide to 12 kbar for 15 h gives exclusively **12b** in 52% yield. As with enedione **12a**, adduct **12b** underwent enolization to **14b** (Scheme V) and hydroquinone **14b** was methylated to give **15b**,[9b] which was spectrally similar to a previously reported compound.[12b]

Lewis acid catalyzed reactions of diene **3a** and quinone **11b** at atmospheric pressure follow a different path.[9b] Reaction of **3a** and **11b**, catalyzed by a 2:3 mixture of $Ti(Oi\text{-}Pr)_4$–$TiCl_4$ gave dihydrobenzofuran **19a** (Scheme VI), the structure of which was established by methylation to **19b** (72%) and by single-crystal X-ray analysis.[16] Similarly, $TiCl_4$-catalyzed reaction of **3a** and 2-methoxy-6-methyl-1,4-benzoquinone, **11d**, produced **20**. The formation of **19a** and **20** can be rationalized as shown in the scheme.

Potential Diels–Alder reactions of diene **3a** and quinone **11c** were of interest as a route to terpene systems possessing the ring system **2**. In the experiment (Scheme IV), pressurization of a CH_2Cl_2 solution of the diene, the quinone **11c**, and zinc bromide (1.1 equiv) to 12 kbar for 14 days gave a single adduct **12c** in >90% yield. Interestingly, the combination of high-pressure and Lewis acid catalysis *was required* to effect cycloaddition in this case. No reaction between **3a** and **11c** was observed in the absence of $ZnBr_2$ even upon pressurization of a CH_2Cl_2 solution to 12 kbar for 21 days.

Diels–Alder reactions of oxygenated dienes **3b** and **3i** with quinones were also examined. Enol ether **3b** was prepared (Scheme VII) via reaction of β-cyclocitral with methoxymethylenetriphenylphosphorane, which gave a 2:1 *E*/*Z* ratio of double-bond isomers **3b**/**21** in 82% yield. The isomers **3b**/**21** were separable by careful column chromatography. Enol acetate **3i** was prepared from a mixture of **3b**/**21** by hydrolysis to aldehyde **22** followed by deprotonation and trapping of the resulting enolate with Ac_2O. This sequence gave **3i** as the major component of an inseparable 2:1 *E*/*Z* mixture of isomeric enol acetates in 80% combined yield. Mixtures of **3i** and its isomer were used in the following Diels–Alder reactions, and the minor isomer did not react. The yields reported are based on the amount of trans diene **3i** used in the experiments.

Reaction of enol ether **3b** with 1,4-benzoquinone at 12 kbar for 2 days produced endo adduct **23** in 38% yield and trace amounts of the quinone **24**, which apparently arises from in situ (vide supra) oxidation of **23** (Scheme IV). Pressure promoted reaction (12 kbar, 8.5 days) of **3i** and 1,4-benzoquinone stereoselectively gave endo adduct **25** in 60% yield. Diels–Alder reactions of **3b** and **3i** with unsymmetrical quinone **11b** were stereoselective, but not regioselective, producing mixtures of endo adducts **26**:**27** and **28**:**29**, respectively (Table I). Addition of Lewis acids to these high-pressure reactions (entries 13, 14 and 18, 19) produced a significant increase in rate of product formation, and in the case of enol acetate **3i**, the regioselectivity was also increased. In reaction of enol ether **3b**, trace amounts of a quinone **30** could be observed by TLC; however, it was usually not isolated (≤2%). Of the various Lewis acids examined in these experiments, $Yb(fod)_3$ (typically 10 mol % with respect to the quinone) was superior to $Eu(fod)_3$, $ZnBr_2$, or $MgBr_2$ in reactions of enol acetate **3i**, whereas $Yb(fod)_3$ and $Eu(fod)_3$ were equally effective in reactions of enol ether **3b**. It is noteworthy that, (a) previous attempts to effect Diels–Alder reactions of **3b** and **3i** with several dienophiles met with, at best, limited success,[2b,4] and (b) the regioselectivity of the reactions of dienes **3b** and **3i** with unsymmetrical quinones is reversed.[17]

Stereochemical Assignments of the Diels–Alder Adducts. The stereochemistry of enediones **12a**/**b** is assigned as that resulting from endo addition of the diene and the quinone and is based on ^1H NMR data from which resonances from all of the hydrogens in the B and C rings can be assigned by selective decoupling experiments (Table II). In both **12a**/**b**, unusual low-field multiplets at 2.38 ppm (ddd, J = 13.5, 13.5, and 4.4 Hz for **12a** and 13, 13, 4 Hz for **12b**; J_{gem}, $J_{ax\text{-}ax}$, $J_{ax\text{-}eq}$, respectively) that are not coupled to any of the B/C ring hydrogens are attributed to the axial C_1 hydrogen.[9] The downfield shift is due to deshielding by the proximal C_{11} oxygen.[18a] Dreiding

(14) Other researchers have noted a decrease in stereoselectivity of pressure-promoted Diels–Alder reactions as the pressure used to effect the reaction is increased, see: (a) Jurczak, J.; Kozluk, T.; Tkacz, M.; Eugster, C. H. *Helv. Chim. Acta* **1983**, *66*, 218. For a possible explanation, see: (b) Jenner, G.; Papadopoulos, M.; Rimmelin, J. *J. Org. Chem.* **1983**, *48*, 748. (c) Jurczak, J.; Kawczynski, A. J.; Kozluk, T. *Ibid.* **1985**, *50*, 1106.

(15) Although not isolated, the minor adduct **17b** is assigned from ^1H NMR spectral data obtained on the mixture of **12b** and **17b**, which shows signals for **17b** at 6.08 (s, 1 H, H_{14}), 5.51 (dd, 1 H, J = 4, 4 Hz, H_7), 3.78 (s, 3 H, OCH_3), 3.1–3.2 (m, 2 H, H_8 and eq H_1), 2.97 (d, 1 H, J = 5 Hz, H_9). The stereochemistry of **17b** is suggested by the appearance of the multiplet at ~3.15, which is assigned to the equatorial H_1 proton.

(16) ORTEP plots and crystallographic data for **19a** and **36** are provided as supplementary material. The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Leusfield Road, Cambridge CB2 1EW, UK.

(17) Reactions of 1-alkoxy and 1-(acyloxy)butadienes have been reported to react with unsymmetrical dienophiles with variable regioselectivity; see: Onishchenko, A. S. *Diene Synthesis*; Israel Program for Scientific Translations: Jerusalem, 1964; pp 208–221.

Table II. Selected ^1H NMR Data for Diels–Alder Adducts and Derivatives

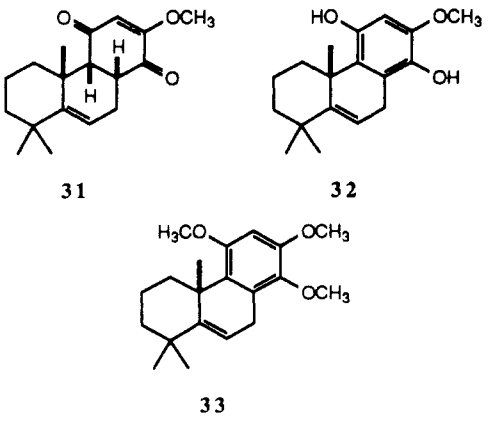
compound	chemical shift (ppm from TMS)											coupling constants[a]
	H_1(ax)	H_1(eq)	H_6	$H_7(\beta)$	$H_7(\alpha)$	H_8	H_9	H_{11}	H_{12}	H_{13}	H_{14}	
Enediones												
12a	2.38 (ddd)	–	5.33 (dd)	2.36 (ddd)	2.14 (ddd)	3.49 (ddd)	2.95 (d)	–	6.63 (d) 6.48 (d)			$H_{6-7(\beta)}$ = 3.6, $H_{6-7(\alpha)}$ = 4.1, $H_{7(\beta)-8}$ = 7.4, $H_{7(\alpha)-8}$ = 10.8, H_{8-9} = 4.9, $H_{7(\beta)-7(\alpha)}$ = 18.3, H_{12-13} = 11.0, $H_{1(ax)}$ = 13.5, 13.5, 4.4
12b	2.38 (ddd)	–	5.31 (dd)	2.44 (ddd)	2.15 (ddd)	3.47 (ddd)	2.94 (d)	–	–	5.70 (s)	–	$H_{6-7(\beta)}$ = 4.0, $H_{6-7(\alpha)}$ = 3.2, $H_{7(\beta)-8}$ = 8.0, $H_{7(\alpha)-8}$ = 11.0, H_{8-9} = 5.0, $H_{7(\beta)-7(\alpha)}$ = 18.0, $H_{1(ax)}$ = 13.0, 13.0, 4.0
12c	–	–	5.75 (dd)	2.81 (dd)	1.70 (dd)	–	2.84 (s)	–	–	5.78 (s)	–	$H_{6-7(\beta)}$ = 8.0, $H_{6-7(\beta)}$ = 2.0, $H_{7(\beta)-7(\alpha)}$ = 16.0
23	2.59 (ddd)	–	5.66 (d)	3.94 (dd)	–	3.60 (dd)	2.87 (d)	–	6.64 (AB q)		–	$H_{6-7(\beta)}$ = 4.0, $H_{7(\beta)-8}$ = 5.4, H_{8-9} = 5.2, H_{12-13} = 10.0, $H_{1(ax)}$ = 12.5, 12.5, 4.0
25	2.53 (ddd)	–	5.49 (d)	5.52 (dd)	–	3.73 (dd)	2.98 (d)	–	6.68 (AB q)		–	$H_{6-7(\beta)}$ = 4.1, $H_{7(\beta)-8}$ = 6.4, H_{8-9} = 5.5, H_{12-13} = 12.4, $H_{1(ax)}$ = 12.7, 12.7, 4.1
26	2.67 (ddd)	–	5.64 (d)	3.97 (dd)	–	3.68 (dd)	2.73 (d)	–	5.90 (s)	–	–	$H_{6-7(\beta)}$ = 3.8, $H_{7(\beta)-8}$ = 6.7, H_{8-9} = 5.4, $H_{1(ax)}$ = 12.8, 12.8, 4.0
27	2.56 (ddd)	–	5.65 (d)	3.93 (dd)	–	3.57 (dd)	2.86	–	–	5.85 (s)	–	$H_{6-7(\beta)}$ = 4.0, $H_{7(\beta)-8}$ = 5.7, H_{8-9} = 5.3, $H_{1(ax)}$ = 12.2, 12.2, 4.3
28	2.56 (ddd)	–	5.46 (d)	5.56 (dd)	–	3.76 (dd)	2.89 (d)	–	5.95 (s)	–	–	$H_{6-7(\beta)}$ = 3.6, $H_{7(\beta)-8}$ = 6.8, H_{8-9} = 5.3, $H_{1(ax)}$ = 12.8, 12.8, 4.3
29	2.42 (ddd)	–	5.41 (d)	5.48 (dd)	–	3.63 (dd)	2.90 (d)	–	–	5.79 (s)	–	$H_{6-7(\beta)}$ = 4.0, $H_{7(\beta)-8}$ = 6.3, H_{8-9} = 5.4, $H_{1(ax)}$ = 12.6, 12.6, 4.2
37	–	–	5.49 (dd)	2.61 (dd)	2.26 (dd)	–	2.78 (s)	–	–	5.79 (s)	–	$H_{6-7(\beta)}$ = 3.0, $H_{6-7(\alpha)}$ = 5.0, $H_{7(\beta)-7(\alpha)}$ = 18.2
45	2.35	–	5.29	2.38	2.00	3.45	2.88	–	–	–	–	$H_{6-7(\beta)}$ = 4.0, $H_{6-7(\alpha)}$ = 4.0, $H_{7(\beta)-8}$ = 8.0, $H_{7(\alpha)-8}$ = 11.0, H_{8-9} = 5.0, $H_{7(\beta)-7(\alpha)}$ = 18.0, $H_{1(ax)}$ = 12.0, 12.0, 4.0
Quinones												
13a	–	2.81 (ddd)	5.70 (dd)	3.23 (dd)	2.88 (dd)	–	–	–	6.63 (AB q)		–	$H_{6-7(\beta)}$ = 5.1, $H_{6-7(\alpha)}$ = 2.3, $H_{7(\beta)-7(\alpha)}$ = 24.3, H_{12-13} = 10.1, $H_{1(eq)}$ = 13.6, 3.6, 3.6
24	–	2.75 (ddd)	5.78 (d)	4.81 (d)	–	–	–	–	6.69 (AB q)			$H_{6-7(\beta)}$ = 3.5, H_{12-13} = 10.1, $H_{1(eq)}$ = 13.7, 3.8, 3.8
30	–	2.80 (ddd)	5.79 (d)	4.82 (d)	–	–	–	–	5.85 (s)		–	$H_{6-7(\beta)}$ = 3.4, $H_{1(eq)}$ = 13.2, 3.8, 3.8
Hydroquinones												
14a	–	3.34 (m)	5.81 (dd)	3.42 (dd)	3.05 (dd)	–	–	–	6.51 (AB q)		–	$H_{6-7(\beta)}$ = 5.1, $H_{6-7(\alpha)}$ = 2.5, $H_{7(\beta)-7(\alpha)}$ = 22.4, H_{12-13} = 8.3, $H_{1(gem)}$ = 13
14b	–	3.22 (ddd)	5.79 (dd)	3.33 (dd)	3.09 (dd)	–	–	–	–	6.38 (s)	–	$H_{6-7(\beta)}$ = 5.2, $H_{6-7(\alpha)}$ = 2.5, $H_{7(\beta)-7(\alpha)}$ = 21.1, $H_{1(eq)}$ = 13.7, 4.9, 4.7
15a	–	3.1 (m)	5.79 (dd)	3.46 (dd)	3.06 (dd)	–	–	–	6.73 (d) 6.64 (d)		–	$H_{6-7(\beta)}$ = 5.0, $H_{6-7(\alpha)}$ = 2.5, $H_{7(\beta)-7(\alpha)}$ = 23.0, H_{12-13} = 7.0
15b	–	3.05 (m)	5.83 (dd)	3.42 (dd)	2.98 (dd)	–	–	–	–	6.43 (s)	– –	$H_{6-7(\beta)}$ = 5.4, $H_{6-7(\alpha)}$ = 2.5, $H_{7(\beta)-7(\alpha)}$ = 22.3
Others												
34	–	–	5.7 (dd)	2.5 (ddd)	2.3 (ddd)	2.98 (ddd)	1.93 (dd)	4.48 (dd)	–	5.3 (s)	–	$H_{6-7(\beta)}$ = 4.3, $H_{6-7(\alpha)}$ = 2.9, $H_{7(\beta)-8}$ = 8.0, $H_{7(\alpha)-8}$ = 11.6, H_{8-9} = 4.5, $H_{7(\beta)-7(\alpha)}$ = 18.8, H_{9-11} = 4.3
35	2.66 (ddd)	–	5.26 (dd)	2.08 (m)		3.16 (m)	2.30 (d)	–	–	5.36 (dd)	4.91 (dd)	$H_{6-7(\beta)}$ = 3.7, $H_{6-7(\alpha)}$ = 3.7, H_{8-9} = 3.7, $H_{1(ax)}$ = 12.7, 12.7, 4.0, H_{8-14} = 5.0, H_{13-14} = 2.0, H_{8-13} = 2.0 (*W* coupling)

[a] Coupling constants are reported in hertz.

models of the possible exo cycloadducts **17a/b** suggest that the C_{11} oxygen would be too far from the axial C_1 hydrogen to have a noticeable effect on its chemical shift. In fact, the equatorial C_1 hydrogens in **17a/b** would be expected to be deshielded.[18d] Indeed, in quinone **13a** and hydroquinones **14a/b**, it is the equatorial C_1 hydrogen (ddd, J = 13.6, 3.6, and 3.6 Hz, J_{gem} and J_{ax-eq}) that appears downfield (2.81 ppm for **13a**; 3.33 ppm for **14a**). A general observation is that the equatorial H_1 resonance in quinone **13a**, in hydroquinones **14a/b**, and in their derivatives **15a/b** appear downfield (2.8–3.3 ppm) in comparison to the axial H_1 resonance (2.2–2.6 ppm) in molecules related to endo adducts **12a/b**.

Although a single isomer, the position of the OCH_3 substituent in **12b** was not apparent from spectral data, and neither **12b**, **14b**, or **15b** could be unequivocally differentiated from the other possible endo regioisomer from the cycloaddition, i.e. **31**, and its derivatives **32** and **33**. Thus, the following experiments were used to establish the position of the OCH_3 substituent. Reduction of **12b** with 1 equiv of L-Selectride in THF at −78 °C gave alcohols **34** and **35** in 45% and 25% yields, respectively (Scheme VIII). The structures of **34/35** are assigned from ^1H NMR data including selective ^1H–^1H decoupling and COSY experiments (Table II). The noteworthy data is summarized as follows. For cycloadduct **35**, irradiation of the H_6 resonance at 5.26 ppm results in collapse of a multiplet at 2.02–2.14 ppm, which is thus assigned to the C_7 methylene

(18) For examples, see: (a) Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2396. (b) Nagata, W.; Terasawa, T.; Tori, K. *J. Am. Chem. Soc.* **1964**, *86*, 3746. (c) Eugster, C. H.; Ruedi, P.; Alder, A. C. *Helv. Chim. Acta* **1984**, *67*, 1523. (d) Miyase, T.; Ruedi, P.; Eugster, C. H. *Helv. Chim. Acta* **1977**, *60*, 2770, ref 13 and references cited in the above.



31 32

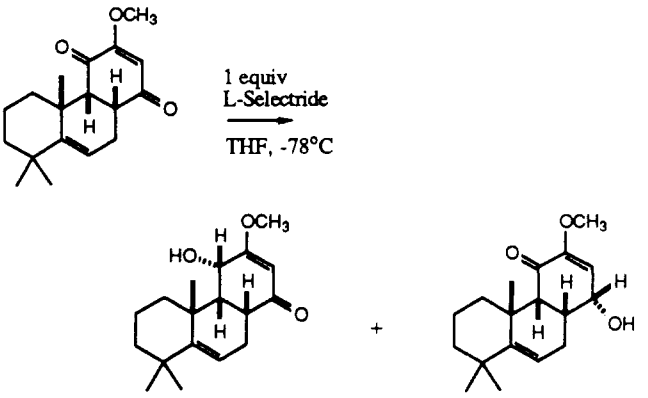
33

hydrogens. A COSY analysis establishes that the hydrogens at C_7 are also coupled to a multiplet at 3.16 ppm, which is the resonance for H_8, and H_9 is identified as a doublet at 2.30. The appearance of H_9 as a doublet confirms that the C_{11} carbonyl group is intact and the $J_{H_8-H_9}$ = 3.7 Hz suggests a cis B/C ring juncture. Further evidence comes from the position of the axial H_1 resonance at 2.66 ppm as a ddd (J_{gem} = 12.7, J_{ax-ax} = 12.7, J_{ax-eq} = 4.0 Hz), which is not coupled to any of the hydrogens in the B/C rings. On selective irradiation of H_8, multiplets at 2.30 (H_9), 4.91, and 5.36 ppm collapse to a singlet, doublet, and doublet, respectively. The signal at 5.36 is also coupled to the signal at 4.91 as verified by COSY experiments. Thus, the 5.36 ppm resonance is assigned to H_{13} and that at 4.91 ppm is attributed to the newly introduced H_{14}. The two couplings to H_{13} are the vicinal H_{14} coupling (J = 2 Hz) and a W coupling to H_8 (J = 2 Hz). Thus, the OCH_3 in structure **35** must be at the C_{12} position.

Similar analysis of the spectral data for **34** reveals the following information. The H_8 resonance appears at 2.98 ppm (ddd, J = 11.6, 8, 4.5 Hz) and is identified by observed couplings to the C_7-methylene multiplets at 2.51 ppm (ddd, J = 18.8, 8, 4.3 Hz) and 2.29 ppm (ddd, J = 18.8, 11.5, 2.9 Hz), which are in turn coupled to H_6 at 5.66 ppm (dd, J = 4.3, 2.9 Hz). The H_9 resonance can be identified at 1.93 ppm (dd, J = 4.5 and 4.3 Hz) and the H_{11} signal is at 4.48 ppm (dd, $J_{H_9-H_{11}}$ = 4.3 Hz, $J_{H_{11}-OH}$ = 3.5 Hz). The $J_{H_9-H_{11}}$ is consistent with an α-OH group at C_{11}. A singlet at 5.30 ppm is assigned to the H_{13} and indicates that the OCH_3 is also in the C_{12} position in **34**.

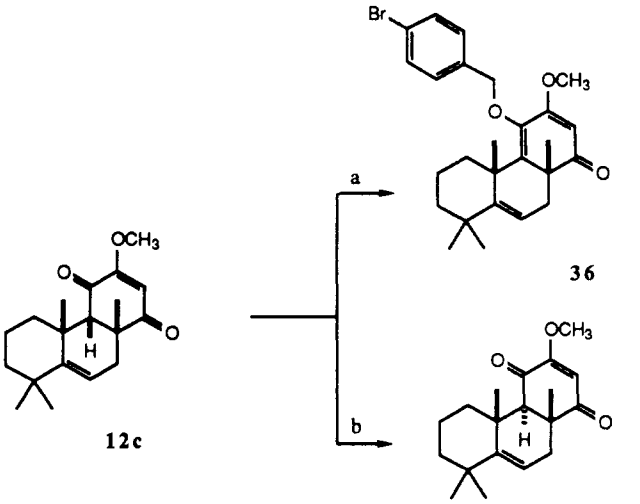
The assignment of stereochemistry in adduct **12c** was more difficult than with endo adducts **12a** or **12b** since the axial H_1 resonance is not observed in a distinct region of the ^1H NMR spectrum of **12c**, presumably due to a conformational change in the B ring to avoid 1,3-diaxial interactions between the C_8 and C_{10} angular methyl groups. Dreiding models show that this conformational change moves the C_{11} carbonyl out of proximity of the C_1 hydrogens and prevents direct spectral evidence for the stereochemical assignment of **12c** as an endo adduct. However, enedione **12c** was converted to enol ether **36**[9b] (Scheme IX), and the structure of **36** was confirmed by single-crystal X-ray analysis.[16] Thus, a cis relationship between the C_8 and C_{10} methyl groups in **12c** was established, and this stereochemistry must result from endo addition of **3a** and **11c**. The configuration of the stereocenter at C_9 was determined by differential NOE experiments on **12c** and on isomer **37**.[9b] Irradiation of the methyl resonances at 1.37 and 1.24 ppm in the ^1H NMR spectrum of **12c** resulted in approximately 25% and 16% enhancement, respectively, of the H_9 hydrogen signal at 2.84 ppm. Sequential irradiation of all of the methyl resonances in **37** failed to

Scheme VIII



34 35

Scheme IX[a]



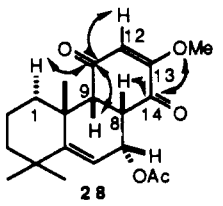
12c 36 37

[a] Reagents and conditions: (a) KO*t*-Bu/*p*-BrPhCH$_2$Br, THF, 0 °C to room temperature, 53%; (b) (i) KO*t*-Bu, THF, 0 °C; (ii) 5% aqueous HCO_2H, 79%.

indicate any significant enhancement of the H_9 resonance at 2.78 ppm. These results are consistent with a β C_9–H bond in **12c** and α C_9–H bond in **37**.

The stereochemical assignment of endo adducts **23**/**25** results from analogy to products **12a**/**b**. Thus, in the ^1H NMR spectra of **23** and **25** (Table II), the chemical shift of the axial H_1 appears at 2.59 (ddd, J = 12.5, 12.5, 4 Hz) and 2.53 ppm (ddd, J = 12.7, 12.7, 4.1 Hz), respectively, and a $J_{H_9-H_9}$ of 5–6 Hz in each suggests a cis B/C ring fusion. The endo stereochemistry in **26**–**29** is also apparent from ^1H NMR spectra as described above (see Table II).

The location of the methoxy substituent in adducts **26**/**27** and **28**/**29** was not directly discernible from their ^{13}C or ^1H NMR spectra. However, as with enediones **12a**/**b**, all of the proton resonances from the B/C ring protons and also the axial H_1 resonance were distinct in the 300 or 500 MHz spectra of **28**/**29**, and the signals were assigned from selective ^1H–^1H decoupling and COSY experiments (Table II). With this information, the structures of **28** and **29** were determined by the combination of long-range homonuclear and heteronuclear NOE studies and measurements of ^1H–^{13}C coupling constants. The results of the heteronuclear NOE experiments on **28** and **29** are summarized in Figure 1. Irradiation of the axial H_1 and H_9 results in a NOE enhancement of the carbon resonance at 197 ppm, which establishes this signal as due to the C_{11} carbonyl carbon. An additional NOE is observed


28

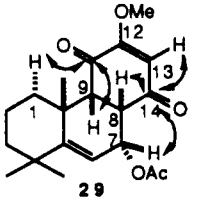

29

Figure 1. Summary of observed $^1H-^{13}C$ NOE enhancements in adducts **28** and **29**.

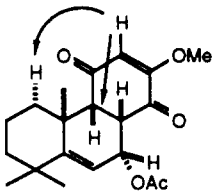


Figure 2. Summary of observed long-range $^1H-^1H$ NOE (NOESY) enhancements in **28**.

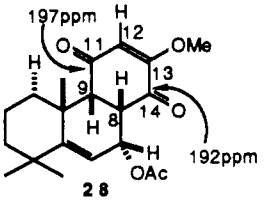
between the vinyl signal of the enol ether moiety in **28** and the C_{11} resonance at 197 ppm. An enhancement of the C_{14} carbonyl resonance at 192 ppm in **28** also results from irradiation of the overlapping H_8 multiplet and OMe singlet at 3.76 ppm. This data is indicative that structure **28** is the 13-OCH_3 isomer. Similar NOE studies on adduct **29** (Figure 1) support the structure shown. Additional supportive evidence comes from long-range $^1H-^1H$ NOESY experiments on **28** in which enhancements are observed between the ring C enol ether proton and the H_9 and axial H_1 signals (Figure 2). Similar long-range $^1H-^1H$ NOE effects are not observed in **29**.

Finally, measurement of the magnitude[19] and sign[20] of the $^{13}C-^1H$ coupling constants to the ^{13}C carbonyl resonances at 197 and 192 ppm in both **28** and **29** corroborate the structural assignments. Typically, two-bond coupling constants, $^2J_{C-H}$, range from −5 to ±2 Hz and are smaller than three-bond coupling constants, $^3J_{C-H}$, which generally range from +3 to +13 Hz. A negative coupling constant is indicative of a $^2J_{C-H}$. The magnitude of the coupling constants in **28**/**29** were determined by observing the collapse of the carbonyl multiplets in the fully coupled 125-MHz ^{13}C spectra upon selective ^1H decoupling. The relative signs of the coupling constants were determined, when possible, via a selective population inversion technique.[20] The data for **28** and **29** is summarized in Chart I, and the noteworthy features of the data are as follows. In **28**, larger C–H coupling constants between the 192 ppm carbonyl and the ring C vinyl proton and between the 197 ppm carbonyl and the H_8 proton than between the same hydrogens and the 197 and 192 ppm resonances, respectively, indicate $^3J_{C-H}$ couplings. A negative coupling constant between H_9 and the 197 ppm carbonyl signal implies a $^2J_{C-H}$. The C_{11} carbonyl is assigned to the 197 ppm resonance and the C_{14} carbonyl is assigned to the 192 ppm resonance; **28** is thus the 13-methoxy isomer.

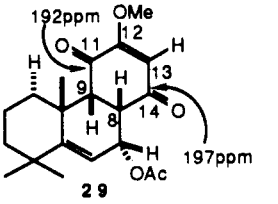
In **29**, larger J_{C-H} between the 192 ppm ^{13}C signal and the ring C vinyl proton and between the 192 ppm signal and the H_8 proton than between the 197 ppm signal and the same hydrogen resonances imply a $^3J_{C-H}$ and suggests that it is the C_{11} carbonyl which resonates at 192 ppm. Therefore, **29** is identified as C_{12} methoxy isomer. Spectral comparison of **26**/**27** with **28**/**29** allowed the structural assignments of the former.

(19) Wehrli, F. W.; Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*; Heyden and Son, Inc.: Philadelphia, 1980; pp 53–56.
(20) Sanders, J. K. M.; Hunter, B. K. *Modern NMR Spectroscopy: A Guide for Chemists*; Oxford University Press: New York, 1987; pp 77–9, 143–4, 186–8, and 293–4.

Chart I. Selected $^{13}C-^1H$ Coupling Constants for Compounds 28 and 29

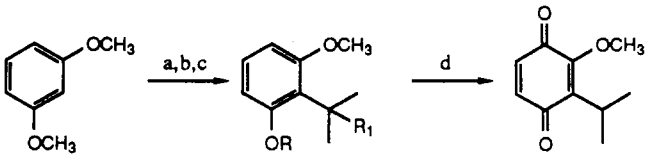

28

$J_{C_{11}-H_8}$ = +9.1 Hz $J_{C_{14}-H_9}$ = 7.2 Hz
$J_{C_{11}-H_9}$ = −7.0 Hz $J_{C_{14}-H_9}$ = 2.0 Hz
$J_{C_{11}-H_{12}}$ = +2.0 Hz $J_{C_{14}-H_{12}}$ = +7.2 Hz


29

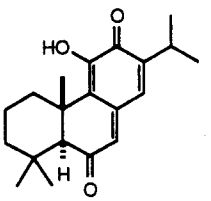
$J_{C_{11}-H_8}$ = +9.0 Hz $J_{C_{14}-H_8}$ = +7.0 Hz
$J_{C_{11}-H_9}$ = +5.0 Hz $J_{C_{14}-H_9}$ = 2.0 Hz
$J_{C_{11}-H_{13}}$ = +7.5 Hz $J_{C_{14}-H_{13}}$ = +2.0 Hz

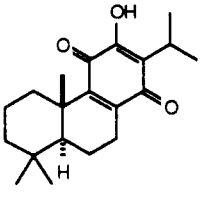
Scheme X[a]


40 41, R=CH_3, R_1=OH 42, R=CH_3, R_1=H 43, R=R_1=H 44

[a] Reagents and conditions: (a) (i) *t*-BuLi/TMEDA, Et_2O, −78 °C, (ii) $(CH_3)_2CO$, Et_2O, −78 °C, 68%; (b) 50 psi of H_2, Pd/C, H_2SO_4/EtOAc, room temperature, 85%; (c) BBr_3, CH_2Cl_2, −78 °C to room temperature, 89%; (d) O_2/Co(salen), DMF, room temperature, 44%.

Synthesis of (±)-Taxodione and (±)-Royleanone. Application of the strategy described herein to the preparation of the antitumor abietane diterpenes (±)-taxodione (**38**)[21] and (±)-royleanone (**39**)[21,22] required access to 2-

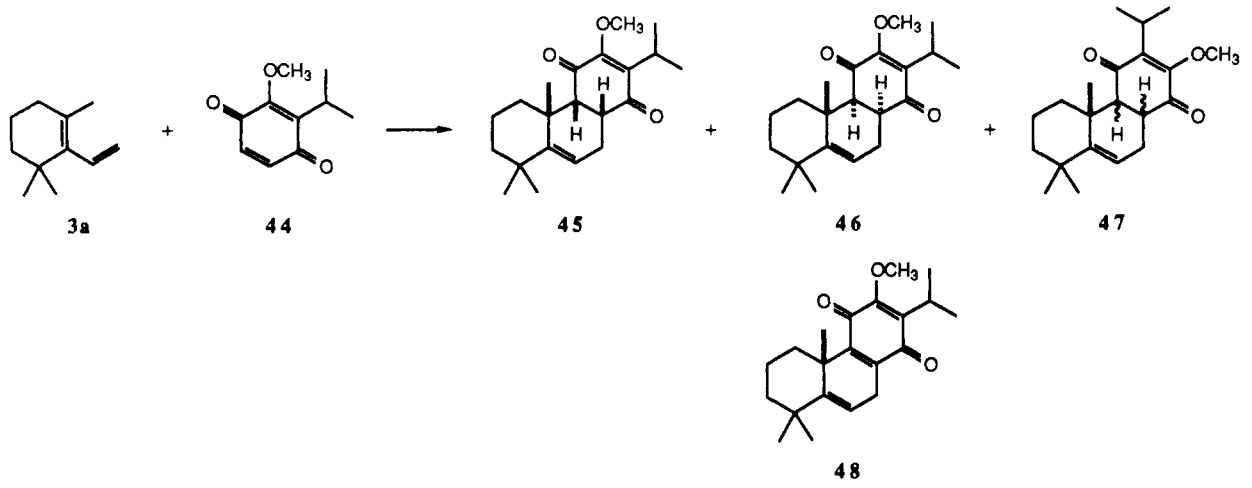

38


39

methoxy-3-isopropyl-1,4-benzoquinone, **44**, which was prepared in a straightforward manner from resorcinol dimethyl ether, **40** (Scheme X). Metalation of **40** and treatment with acetone gave alcohol **41**,[23] which upon

(21) (a) Kupchan, S. M.; Karim, A.; Marcks, C. *J. Org. Chem.* **1969**, *34*, 3912. For a summary of previous synthetic approaches to (±)-taxodione, see: (b) Haslinger, E.; Michl, G. *Tetrahedron Lett.* **1988**, 5751. See also: (c) Edstrom, E. D.; Livinghouse, T. *J. Org. Chem.* **1987**, *52*, 951. (d) Matsumoto, T.; Tachibana, Y.; Uchida, J.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2766. (e) Mori, K.; Matsui, M. *Tetrahedron* **1970**, *26*, 3467. (f) Torii, S.; Umeyama, K.; Hamada, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2503. (g) Watt, D. S.; Snitman, D. L.; Haltiwanger, R. C.; Himmelsbach, R. J. *Synth. Commun.* **1978**, *8*, 187. (h) Banerjee, A.; Carrasco, M. C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 25 and ref 12a and 18a.
(22) For reported syntheses of (±)-royleanone, see: Matsumoto, T.; Harada, S. *Chem. Lett.* **1976**, *1311*, and ref 21b.

Scheme XI

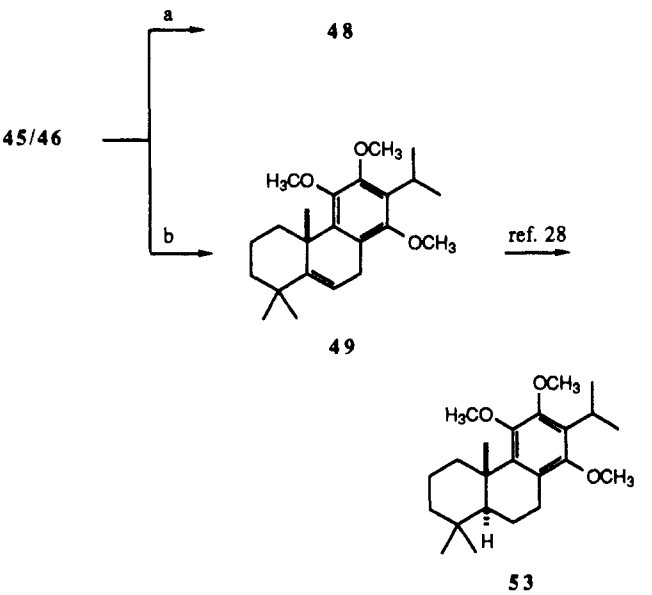


hydrogenolysis produced 2-isopropyl-1,3-dimethoxybenzene, **42**. Monodemethylation of **42** to phenol **43** was effected with boron tribromide and oxidation of phenol **43** with Fremy's salt,[24] O_2/Co(salen),[25] or $Tl(NO_3)_3$[26] gave quinone **44** in 44–52% yield. In some instances, some of the starting phenol **43** contaminated the product quinone **44**, and purification was troublesome; however, mixtures of **43**/**44** could be employed in the subsequent cycloaddition reactions.

Pressure-promoted Diels–Alder reaction of diene **3a** and quinone **44** at 12 kbar/5 days gave an inseparable mixture of isomeric enediones **45**/**46** and a third enedione **47** in a 4.5:2.1:1 ratio, respectively, and in 61% combined yield (Scheme XI and Table I). The minor product was not separated and was tentatively identified as the regioisomeric 4 + 2 cycloadduct **47**. Reactions of **3a** and **44** at lower pressure required longer reaction times and were less selective; at 6 kbar/14 days a 1.4:1.4:1 ratio of **45**:**46**:**47**, respectively, was obtained. Addition of $ZnBr_2$ to these high-pressure reactions produced a slight increase in reaction rate, higher yields, and a significant increase in selectivity. Thus, reaction of **3a** and **44** at 11–12 kbar for 30–120 h in the presence of ≤1 equiv of $ZnBr_2$ afforded an ~4–5:1 mixture of **45**:**46** in 55–74% yields; trace amounts of quinone **48** were also observed. A systematic study of the effect of various Lewis acids on reaction of **3a** and **44** was not conducted. However, it was observed that higher yields and stereoselectivity were obtained with ≤1 equiv of $ZnBr_2$ and relatively short (1–5 days) reaction times; reaction times of >5 days or ≥1 equiv of $ZnBr_2$ gave approximately 1.2–3:1 ratios of **45**:**46** and more of the quinone **48**. Data from additional experiments appear in Table I. It should be noted that since the C-8 and C-9 carbons in **45** and **46** will be converted to sp^2-hybridized carbons in the synthesis of **38** or **39**, the relative stereochemistry at these two centers is not synthetically important.

Enediones **45** and **46** result from endo and exo addition, respectively, of the diene and quinone and were identified by spectral comparison of the ^1H NMR spectra of the mixture to those of **12a**/**b** (Table II) and chemical transformations (Scheme XII). A cis B/C ring juncture in both is evident from $J_{H_8-H_9}$ = ~5 Hz in each and the appearance of the C_1-H axial hydrogen at 2.35 ppm (J_{gem} = 13, J_{ax-ax} = 13, J_{ax-eq} = 4.5 Hz) in **45** is consistent with the endo stereochemistry. In isomer **46**, the equatorial C_1-H is deshielded and resonates at 3.1 ppm (m). Treatment of a 2.8:1 mixture of **45**:**46** with aqueous HCl in THF followed by oxidation of the resulting hydroquinone with silver carbonate on Celite gave a single quinone **48** in 92% overall yield. In addition, reaction of a 3.4:1 mixture of **45**:**46** with KO*t*-Bu/CH_3I gave **49** in 91% yield as a single isomer. Adducts must therefore be stereoisomers and not regioisomers. The lower stereoselectivity of Diels–Alder reactions of **44**, as compared to those of **11a–c**, may be due to more steric congestion generated by the *i*-Pr group in the endo transition state leading to **45**.

Scheme XII[a]

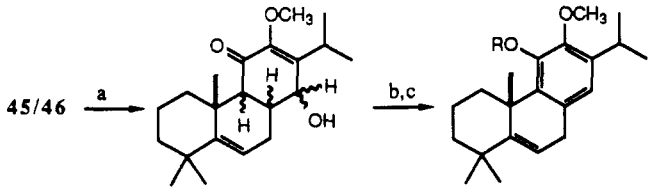


[a] Reagents and conditions: (a) (i) aqueous HCl/THF, room temperature, (ii) Ag_2CO_3/Celite, CH_2Cl_2, room temperature, 92%; (b) KO*t*-Bu/CH_3I, THF, room temperature; 91%.

Conversion of **45**/**46** into taxodione and related diterpenes required removal of the oxygen functionality at C-14. This was accomplished (Scheme XIII) by selective reduction of the C-14 carbonyl group in the mixture of enediones **45**:**46** with 1 equiv of L-Selectride at −78 °C. The resulting mixture of alcohols **50** was not separated or

(23) Boltze, K. H.; Dell, H. D.; Jansen, H. *Justus Liebigs. Ann. Chem.* **1967**, *709*, 63.
(24) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229.
(25) (a) Fullerton, T. J.; Ahern, S. P. *Tetrahedron Lett.* **1976**, 139 and references cited. For the preparation of Co(salen), see: (b) Bailes, R. H.; Calvin, M. *J. Am. Chem. Soc.* **1947**, *69*, 1886.
(26) McKillop, A.; Swann, B. P.; Taylor, E. C. *Tetrahedron* **1970**, *26*, 4031.
(27) Thiel, F.; Lindig, C.; Repke, K. *Z. Chem.* **1980**, *20*, 372.

Scheme XIII[a]



50 51, R=H 52, R=CH_3

[a] Reagents and conditions: (a) 1 equiv of L-selectride, THF, −78 °C, 88%; (b) PPh_3/CBr_4, CH_3CN, 50 °C, 75%; (c) KH/CH_3I, THF, room temperature, 66%.

purified. Rather, direct treatment of the crude reaction mixture with CBr_4/PPh_3[28] effected dehydration and enolization and produced a single isolable phenol **51** in 64% overall yield from **45/46**. Methylation of phenol **51** with KH/CH_3I gave **52** in 66% yield, which has been used previously[21d] in a synthesis of (±)-taxodione, **38**. In addition, compound **15b** has been reported as an intermediate in a synthesis of royleanone.[12b] Formal syntheses of **38** and **39** are therefore complete. Finally, **49** has been hydrogenated to **53**[28] and compounds **45–53** should be useful intermediates in syntheses of a variety of naturally occurring diterpenes.[29]

Summary and Conclusions

The research described above establishes that Diels–Alder reactions of 1,3,3-trimethyl-2-vinylcyclohexanes with various 1,4-benzoquinones provides an efficient and highly convergent route to a variety of tricyclic diterpene systems. The method should also be applicable to higher terpenes which contain the 4,4,10-trimethyl- and 4,4,8,10-tetramethylperhydrophenanthrene ring structures. Several features of this approach are noteworthy. The Diels–Alder reactions are highly stereo- and regioselective, which is particularly remarkable in the preparation of **12c** in which the two quaternary centers at C-8 and C-10 are formed in a single step and with the relative configuration found in most naturally occurring terpenes which incorporate the 4,4,8,10-tetramethylperhydrophenanthrene moiety. The cycloaddition provides products with oxygen functionality (as C=O groups) at C-11 and C-14, which is also found in many natural products.[1,29,30] In the cycloadducts from **3a** and unsymmetrical quinones, all of the carbons in the B/C rings should be chemically distinguishable, and rapid and selective manipulation of these adducts into a variety of natural products which possess varied and diverse oxidation patterns in the B/C rings should be possible. In addition, the research demonstrates that the combination of high pressure and Lewis acid catalysis can be used to effect particularly difficult Diels–Alder reactions even in systems in which an entirely different reaction manifold is accessed by Lewis acids alone. Finally, these high-pressure/Lewis acid promoted Diels–Alder reactions are more stereoselective than the high-pressure reactions conducted in the absence of Lewis acids. Further studies on these observations are in progress.

Experimental Section

All experiments were carried out in oven-dried or flame-dried (under vacuum) glassware and were magnetically stirred. Reactions involving air-sensitive material were carried out under a positive pressure of dry nitrogen. High-pressure reactions were conducted in a Leco Tem-Pres high-pressure reactor (Leco Corp., Bellefonte, PA).

All compounds were prepared as racemic mixtures. NMR spectra were recorded in $CDCl_3$, unless indicated otherwise, on a Varian FT-80A, operating at 80 MHz, a Varian XL-300, operating at 300 MHz for proton and 75.1 MHz for carbon, or a Bruker AM-500 spectrometer, operating at 500 MHz for proton and 125 MHz for carbon-13. The chemical shifts (δ) are indicated in ppm downfield from tetramethylsilane used as an internal standard. Samples for NOE experiments were prepared by degassing of the solution by sonication under an atmosphere of argon immediately before the experiments. Exact masses (HRMS) were obtained on a VG Analytical Model ZAB instrument. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Dichloromethane was distilled from calcium hydride. Ethyl ether and THF were distilled from sodium benzophenone ketyl. Titanium(IV) chloride, tin(IV) chloride, boron trifluoride etherate, and *tert*-butyl alcohol were distilled from calcium hydride. Zinc bromide was fused under vacuum and transferred in a glovebag under dry nitrogen. Ethyl acetate was purchased from Fischer (Optima grade) and was distilled from anhydrous potassium carbonate. Hexanes were fractionally distilled, and the fraction between 65 and 70 °C was used. All other reagents were used as received. The drying agent employed was anhydrous sodium sulfate. PCTLC refers to preparative centrifugal thin-layer chromatography and was done on Chromatotron Model 7924T (Harrison Research, Palo Alto, CA) on silica gel (art. no. 7749, Merck). Analytical and preparative thin-layer chromatography were done on precoated silica gel plates (art. no. 5715, Merck) with a 254-nm fluorescent indicator and were visualized under a UV lamp and/or by staining with a *p*-anisaldehyde/H_2SO_4 or phosphomolybdic acid solutions.

Lewis Acid Catalyzed Diels–Alder Reaction of 3a with 1,4-Benzoquinone (11a): 4aβ,4b,5,6,7,8,10,10aβ-Octahydro-4aβ,8,8-trimethyl-1,4-phenanthrenedione (12a). To a solution of 1,4-benzoquinone (**11a**) in dichloromethane (1 g, 9.26 mmol in 8 mL) at −40 °C was added tin(IV) chloride (330 μL, 2.8 mmol), and the mixture was stirred for 1 h. A solution of **3a**[2b] in dichloromethane (500 μL, 2.8 mmol in 5 mL) was added dropwise over 15 min. After being stirred for 3 h at −40 °C, the reaction mixture was quenched with pH 7 buffer and poured into dichloromethane, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL), and the combined organic layers were washed with water and dried, and the solvent was evaporated in vacuo. Purification by PCTLC with 1:4 ethyl acetate/hexanes as eluent yielded **12a** (501 mg, 69%) as a pale yellow oil. Crystallization from hexanes at −20 °C gave pale yellow crystals: mp 92–93 °C; R_f (1:4 EtOAc/hex) 0.35; ^{1}H NMR (300 MHz, ppm) 1.72–1.91 (m, 1 H), 1.48–1.68 (m, 3 H), 1.25 (s, 3 H), 1.10–1.16 (m, 1 H), 1.10 (s, 3 H), 1.09 (s, 3 H), other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 201.61, 199.12, 149.89, 142.05, 136.26, 114.53, 59.54, 45.09, 39.96, 35.56, 35.21, 34.01, 31.56, 30.80, 29.84, 26.84, 18.22; HRMS *m/e* 258.1618 (calcd for $C_{17}H_{22}O_2$ 258.1618). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.04; H, 8.58. Found: C, 78.96; H, 9.00.

High-Pressure Diels–Alder Reaction of 3a with 1,4-Benzoquinone (11a). Preparation of high-pressure reaction tubes: A tightly fitting glass rod, about 3 cm long, was inserted into a heat-shrinkable Teflon tube so that about half the rod is outside the tube. The portion of the rod outside the tube was heated over a burner for a few minutes and then allowed to cool. The seal of the tube was tested by introducing a few drops of dichloromethane.

To a high-pressure reaction tube was added 1,4-benzoquinone (38 mg, 0.35 mmol) followed by **3a** (110 mg, 0.73 mmol) and dichloromethane (1.2 mL). Anhydrous zinc bromide (69 mg, 0.30 mmol) was then added, and the top end was sealed with brass

(28) Marletti, F.; Delle Monache, F.; Marini-Bettolo, G. B.; De Araujo, M. D. C. M.; Caralcanti, M. D. S. B.; D'Albuquerque, I. L.; DeLima, O. G. *Gazz. Chim. Ital.* **1976**, *106*, 119.

(29) For example, 14-hydroxytaxodione,[30] the coleons, and related diterpenes should be readily prepared from either **49** or **53**. For a leading reference of the structures of the various coleons and related molecules, see: ref 1, 18c, and Thomson, R. H. *Naturally Occurring Quinones*; Chapman and Hall: New York, 1987; Vol. III, and references cited therein.

(30) (a) Ruedi, P.; Eugster, C. H. *Helv. Chim. Acta* **1981**, *64*, 2219. (b) Ruedi, P.; Eugster, C. H.; Miyase, T.; Yoshizaki, F.; Bieri, J. H. *Ibid.* **1981**, *64*, 2227. (c) Ruedi, P.; Eugster, C. H.; Uchida, M. *Ibid.* **1981**, *64*, 2251.

clamps. The tube was pressurized for 1 h at 12 kbar. The reaction mixture was filtered through silica gel with dichloromethane as the eluent, and the residue obtained on evaporation of solvent was purified by column chromatography with 1:9 ethyl acetate in hexanes to yield **12a** (60 mg, 67%), as previously identified, and **13a** (7.4 mg, 8%). Recrystallization of **13a** from pentanes at −20 °C gave bright yellow crystals: mp 81–82 °C; R_f of **13a** (1:4 EtOAc/hex) 0.57; ^{1}H NMR (500 MHz, ppm) 1.88 (m, 2 H), 0.85–1.56 (m, 3 H), 1.49 (s, 3 H), 1.22 (s, 3 H), 1.14 (s, 3 H), other data appears in Table II; ^{13}C NMR (125 MHz, ppm) 187.47, 187.36, 148.40, 148.11, 139.69, 138.62, 134.29, 115.08, 40.46, 39.41, 36.62, 36.49, 33.10, 30.67, 26.07, 24.67, 18.83; HRMS m/e 256.1467 (calcd for $C_{17}H_{20}O_2$ 256.1462).

In the absence of zinc bromide, the above Diels–Alder reaction did not proceed to completion after 1 h at 12 kbar, and 15.6 mg (17%) of **12a** and 7 mg (8%) of **13a** were isolated.

4b,5,6,7,8,10-Hexahydro-4bβ,8,8-trimethyl-1,4-phenanthrenediol (14a). Concentrated aqueous hydrochloric acid (30 μL) was added to a soltuion of **12a** in THF (150 mg, 0.58 mmol, in 2 mL), and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous sodium bicarbonate, and the resulting solution was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried, and the solvent was removed in vacuo. Purification by PCTLC with 3:7 ethyl acetate in hexanes yielded **14a** (126.4 mg, 84%), which crystallized from ethyl acetate/hexanes as colorless cyrstals: mp 174–176 °C (dec); R_f (1:4 EtOAc/hex) 0.14; ^{1}H NMR (acetone-d_6, 300 MHz, ppm) 7.62 (s, 1 H, exchanges with CD_3OD), 7.49 (s, 1 H, exchanges with CD_3OD), 1.55 (s, 3 H), 1.25 (s, 3 H), 1.17 (s, 3 H), other data appears in Table II; ^{13}C NMR (acetone-d_6, 75.1 MHz, ppm) 148.06, 147 32, 146.09, 133.08, 121.42, 115.35, 114.11, 111.50, 40.65, 39.06, 36.05, 33.27, 30.50, 25.60, 25.14, 24.81, 18.96; HRMS m/e 258.1608 (calcd for $C_{17}H_{22}O_2$ 258.1618).

Reduction of 13a to 14a. To a stirred solution of **13a** in dichloromethane (21 mg, 0.082 mmol in 1 mL) was added 0.5 mL of glacial acetic acid followed by zinc dust (10 mg, 0.15 mmol). The yellow solution turned colorless instantaneously. Saturated aqueous bicarbonate was added after 5 min, and the mixture was poured into ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic layers were washed with saturated ammonium chloride and water and dried. The pale yellow solid obtained on evaporation of solvent was purified by PCTLC with 3:7 ethyl acetate in hexanes as eluent to yield **14a** (14.5 mg) as a colorless solid and **13a** (6 mg); 96% yield based on recovered **13a**.

Oxidation of 14a with 1,4-Benzoquinone. A solution of **14a** and 1,4-benzoquinone in benzene/ethyl acetate was stirred at room temperature for 1 h. After this time, TLC showed no remaining **14a**, and the ^{1}H NMR spectrum of the crude product was identical with that of **13a**.

Control Experiments. i. A solution of **14a** in 3:7 ethyl acetate in hexanes was stirred open to the atmosphere and checked by TLC for the formation of **13a**. Solvent was periodically replaced as demanded by evaporation. After 48 h, formation of some **13a** was detected, although the major part of **14a** still remained.

ii. A solution of **12a** in dichloromethane was stirred open to the atmosphere for 6 h. No formation of **13a** was apparent by TLC.

iii. To the solution in ii above were added silica gel and 1,4-benzoquinone. After 9 h, some **13a** was observed, but a major portion of **12a** remained as indicated by TLC.

iv. A solution of **12a** in dichloromethane was pressurized to 12 kbar for 24 h. Analysis of the reaction mixture by TLC and by ^{1}H NMR showed no formation of **14a**.

v. A solution of **12a** and 1,4-benzoquinone in dichloromethane was pressurized to 12 kbar for 24 h. Analysis of the reaction mixture by TLC showed the formation of **13a**, although a major portion of **12a** remained.

5,8-Dimethoxy-1,2,3,4,4a,9-hexahydro-1,1,4aβ-trimethylphenanthrene (15a). Method A. A flame-dried flask was charged with a 50% suspension of NaH in mineral oil (400 mg, 8.33 mmol), and the oil was washed away with hexanes. THF (5 mL) was added followed by dimethyl sulfate (1.1 mL, 11.6 mmol) and *tert*-butyl alcohol (10 μL, 0.11 mmol). A solution of **12a** in THF (200 mg, 0.775 mmol in 200 μL) was then added dropwise, and the mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ether (3 × 10 mL), and the combined ether extracts were washed with water and dried. The oil obtained after evaporation of the ether was purified by PCTLC using 1:19 ethyl acetate in hexanes as eluent to yield **15a** as a colorless solid (144.1 mg, 65%). Recrystallization from methanol yielded colorless needles: mp 103–104 °C; R_f (1:19 EtOAc/hex) 0.35; ^{1}H NMR (300 MHz, ppm) 3.78 (s, 3 H), 3.77 (s, 3 H), 1.85 (m, 1 H), 1.3–1.6 (m, 4 H), 1.51 (s, 3 H), 1.25 (s, 3 H), 1.18 (s, 3 H), other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 152.02, 150.47, 148.21, 136.25, 123.90, 115.96, 110.14, 106.96, 55.68, 55.62, 40.80, 39.81, 36.81, 36.69, 33.64, 31.06, 26.58, 25.35, 19.55; HRMS m/e 286.1933 (calcd for $C_{19}H_{26}O_2$ 286.1931). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.54; H, 9.33.

Method B. A flame-dried flask was charged with a 50% suspension of NaH in mineral oil (96 mg, 2.0 mmol), and the oil was washed away with hexanes. THF (1 mL) was added followed by dimethyl sulfate (300 μL, 3.2 mmol) and *tert*-butyl alcohol (20 μL, 0.21 mmol). A solution of **14a** in THF (50 mg, 0.19 mmol in 200 μL) was added dropwise, and the mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ether (3 × 10 mL), and the combined ether extracts were washed with water and dried. The oil obtained after evaporation of ether was purified by PCTLC to yield **15a** (43.2 mg, 78%).

5,8-Dimethoxy-1,2,3,4,4a,9,10,10a-octahydro-1,1,4aβ-trimethylphenanthrene (16a/16b). A bottle was charged with 10% palladium on charcoal (~10 mg) followed by a solution of **15a** in acetic acid (144.1 mg, 0.50 mmol in 20 mL). The bottle was pressurized to 50 psi of hydrogen at room temperature in a Parr hydrogenator for 12 h. The reaction mixture was filtered through Celite, the acid was neutralized with saturated aqueous sodium bicarbonate, and the aqueous solution was then extracted with ether (3 × 20 mL). The combined ether extracts were washed with additional bicarbonate solution, water, and brine and dried. The residue remaining after the evaporation of ether was purified by PCTLC using 1:19 ethyl acetate in hexanes as eluent to yield **16a** (134 mg, 92%) as colorless needles from ether: mp 133–134 °C; R_f (1:19 ethyl acetate in hexanes) 0.35; ^{1}H NMR[13] (500 MHz, ppm) 6.64 (AB q, 2 H, J = 8.8 Hz), 3.76 (s, 3 H) 3.75 (s, 3 H), 3.10 (ddd, 1 H, J = 13.1, 3.1, 3.1 Hz), 2.85 (dd, 1 H, J = 17.5, 5.2 Hz), 2.52 (m, 2 H), 1.85 (dd, 1 H, J = 12.9, 6.6 Hz), 1.72 (dd AB q, 2 H, J = 13.5, 3.3, 3.3 Hz), 1.52–1.42 (m, 2 H), 1.31 (s, 3 H), 1.31–1.14 (m, 2 H), 0.95 (s, 3 H); ^{13}C NMR (75.1 MHz, ppm) 152.68, 151.55, 139.20, 127.33, 109.43, 106.75, 55.63, 55.47, 52.64, 41.50, 39.69, 36.60, 33.76, 27.07, 22.14, 19.86, 19.49, 18.32; IR (ν_{max}) 3000, 2950, 1600, 1465, 1440, 1385, 1365, 1350, 1250, 1080 cm^{-1}; UV (hexane) λ (log ϵ_{max}) 287 (3.55), 230 (3.77), 220 (3.90); EIMS m/e (relative intensity) 288 (M^+, 99), 273 (9), 217 (14), 203 (47), 191 (67), 177 (100); HRMS m/e 288.2088 (calcd for $C_{19}H_{28}O_2$ 288.2091).

High-Pressure Diels–Alder Reaction of 3a and 11b: 3-Methoxy-4aβ,4b,5,6,7,8,10,10aβ-octahydro-4bβ,8,8-trimethyl-1,4-phenanthrenedione (12b). A high-pressure reaction tube was charged with 2-methoxy-1,4-benzoquinone, **11b** (40 mg, 0.29 mmol), followed by diene **3a** (125 μL, 0.7 mmol) and dichloromethane (1 mL). Anhydrous zinc bromide (65.3 mg, 0.29 mmol) was added, and the tube was then sealed on the top with brass clamps and pressurized to 11 kbar for 15 h. The reaction mixture was filtered through silica gel with dichloromethane as eluent. The residue obtained upon evaporation of solvent was purified by PCTLC with 30% ethyl acetate in hexanes as eluent. Recrystallization from ethyl acetate–hexanes gave **12b** (43 mg, 52%) as colorless needles: mp 121–122.5 °C; R_f (3:7 EtOAc/hex) 0.22; ^{1}H NMR (300 MHz, ppm) 3.77, (s, 3 H), 1.24 (s, 3 H), 1.08 (s, 3 H), 1.06 (s, 3 H), 1.0–1.9 (m, 4 H), other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 200.85, 193.95, 163.75, 149.79, 114.70, 107.44, 59.62, 56.48, 45.02, 39.90, 35.50, 35.18, 34.15, 31.54, 30.96, 30.09, 27.66, 18.29; HRMS m/e 288.1722 (calcd for $C_{18}H_{24}O_3$ 288.1724). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.28; H, 8.37.

4b,5,6,7,8,10-Hexahydro-3-methoxy-4b,8,8-trimethyl-1,4-phenanthrenediol (14b). To a solution of **12b** (23 mg, 0.08 mmol) in THF (1.5 mL) was added 10 μL of concentrated aqueous HCl, and the mixture was allowed to stir under nitrogen at room

temperature for 2 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with ether (2 × 10 mL). The combined organic layers were dried and evaporated, and the residue obtained was purified by PCTLC with 3:7 ethyl acetate/hexanes to yield **14b** (21.4 mg, 93%) as a pale yellow oil; R_f (3:7 ethyl acetate/hexanes) 0.32 (Note: the product **14b** oxidizes to **13b** on silica gel as shown by 2D TLC); ^{1}H NMR (300 MHz, ppm) 5.72 (s, 1 H, exchanges with D_2O), 4.40 (s, 1 H, exchanges with D_2O), 3.83 (s, 3 H), 1.89 (m, 1 H), 1.65–1.0 (m, 4 H), 1.55 (s, 3 H), 1.26 (s, 3 H), 1.18 (s, 3 H), other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 148.85, 145.09, 144.63, 137.33, 133.77, 114.96, 112.50, 97.19, 56.29, 40.97, 39.81, 36.74, 36.37, 33.64, 30.80, 25.90, 24.54, 19.29; HRMS *m/e* 288.1728 (calcd for $C_{18}H_{24}O_3$ 288.1724).

1,2,3,4,4a,9-Hexahydro-5,6,8-trimethoxy-1,1,4a-trimethylphenanthrene (15b). The oil was washed away from a mineral oil suspension of potassium hydride (34 mg of 35% suspension, 0.29 mmol) with hexanes, and the remaining solid was suspended in THF (800 μL). Dimethyl sulfate (142 μL, 1.49 mmol) was added followed by a solution of **12b** (21.4 mg, 0.074 mmol) in THF (200 μL) and then *tert*-butyl alcohol (7 μL, 0.074 mmol). The reaction mixture was allowed to stir at room temperature for 2.5 h. A solution of 1 N aqueous NaOH was added, and the mixture was stirred for an additional 3 h. The mixture was poured into ether, the aqueous layer was separated and extracted with ether (3 × 20 mL), and the combined organic layers were washed with water and brine and dried. The product was purified by PCTLC to yield a colorless oil (9.5 mg, 41%): R_f (1:9 EtOAc/hex) 0.44; ^{1}H NMR[12b] (300 MHz, ppm) 3.86 (s, 3 H, 3.80 (s, 3 H), 3.79 (s, 3 H), 1.8–2.0 (m, 1 H), 1.48 (s, 3 H), 1.3–1.7 (m, 1 H), 1.24 (s, 3 H), 1.17 (s, 3 H), other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 151.84, 151.77, 148.06, 141.79, 140.74, 116.90, 115.38, 95.20, 60.41, 56.23, 55.63, 40.41, 40.36, 37.47, 36.57, 33.63, 31.32, 27.94, 24.62, 19.58; HRMS *m/e* 316.2028 (calcd for $C_{20}H_{28}O_3$ 316.2037).

Lewis Acid Catalyzed Reaction of 3a and 2-Methoxybenzoquinone: 2,3-Dihydro-6-methoxy-2-(2,6,6-trimethyl-1-cyclohexenyl)-5-benzofuranol (19a). Titanium(IV) isopropoxide (28 μL, 0.094 mmol) was added to a solution of 2-methoxy-1,4-benzoquinone in dichloromethane (40 mg, 0.29 mmol, in 1.5 mL), and the mixture was cooled to −20 °C. Titanium(IV) chloride (16 μL, 0.146 mmol) was then added, and the reaction mixture was stirred for 1 h. Then, **3a** (150 μL, 0.7 mmol) was added, and the reaction mixture was stirred at −20 °C for 3 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane (3 × 10 mL), and the combined organic layers were washed with water and dried. The residue remaining after evaporation of solvent in vacuo was purified by PCTLC using 1:4 ethyl acetate in hexanes as eluent to yield **19a** (45.3 mg, 54%). Recrystallization from ether/hexanes gave colorless crystals: mp 124–125 °C; R_f (1:4 EtOAc/hex) 0.32; ^{1}H NMR (300 MHz, ppm) 6.74 (s, 1 H), 6.41 (s, 1 H), 5.25 (s, 1 H), 5.23 (dd, 1 H, J = 11.9, 10 Hz), 3.83 (s, 3 H), 3.2 (dd, 1 H, J = 16, 10 Hz), 3.1 (dd, 1 H, J = 16, 11.9 Hz), 1.59 (s, 3 H), 1.14 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (75.1 MHz, ppm) 152.72, 146.11, 139.37, 137.29, 133.52, 117.98, 110.38, 94.07, 82.03, 56.07, 39.53, 37.69, 34.36, 33.90, 28.76, 27.51, 20.42, 19.30; HRMS *m/e* 288.1717 (calcd for $C_{18}H_{24}O_3$ 288.1724).

2,3-Dihydro-5,6-dimethoxy-2-(2,6,6-trimethyl-1-cyclohexenyl)benzofuran (19b). A flame-dried flask was charged with a suspension of KH in mineral oil (35%, 100 mg, 0.876 mmol), and the oil was washed away with hexanes (3 × 1 mL). THF was added (2 mL) followed by dimethyl sulfate (140 μL, 1.47 mmol), a solution of **19a** in THF (42 mg, 0.146 mmol in 50 μL), and *tert*-butyl alcohol (27 μL, 0.292 mmol). The reaction mixture was stirred at room temperature for 1.5 h, aqueous 1 N NaOH was added, and stirring was continued for an additional 3 h. The mixture was then poured into ether, and the aqueous layer was separated and extracted with ether. The combined ether extracts were washed with water and brine, dried, and concentrated. The product was then purified by chromatography on silica gel with 1:4 ethyl acetate in hexanes to yield **19b** (31.5 mg, 72%) as a colorless oil: R_f (1:4 EtOAc/hex) 0.37; ^{1}H HMR (300 MHz, ppm) 6.75 (s, 1 H), 6.46 (s, 1 H), 5.26 (dd, 1 H, J = 11.3, 10.1 Hz), 3.83 (s, 6 H), 3.18 (d of AB quartet, 2 H, J ≈ 15.0, 11.3, 10.1 Hz), 2.0 (m, 2 H), 1.58 (s, 3 H), 1.15 (s, 3 H), 1.00 (s, 3 H), 1.0–1.8 (m, 4 H); ^{13}C NMR (75.1 MHz, ppm) 153.68, 149.41, 143.16, 137.29, 133.59, 116.91, 109.09, 94.99, 82.28, 56.92, 55.98, 39.56, 37.85, 34.39, 33.90, 28.80, 27.56, 20.45, 19.30; HRMS *m/e* 302.1883 (calcd for $C_{19}H_{26}O_3$ 302.1881).

2-Methoxy-6-methyl-1,4-benzoquinone (11d). To a solution of 2-methoxy-6-methylphenol[31] in dry DMF (1.53 g, 11.09 mmol, in 5 mL) was added Co(salen)[25] (0.125 g, 0.39 mmol), and the reaction mixture was stirred under a positive pressure of oxygen, attained using a mercury ballast. The red suspension turned black in ~1 h, and stirring was continued for 35 h. The black reaction mixture was poured into a bilayer of water (250 mL), and a 1:1 solution of ether in hexanes (250 mL). This mixture was stirred gently, and the organic layer was periodically decanted off and replaced with more of the 1:1 ether/hexanes solution. The above process was repeated until the organic layer was no longer yellow. The combined organic layers were dried, and the solvent was removed under reduced pressure to yield pure **11d** as a yellow solid, which could be recrystallized from hexanes to yield yellow needles (1.55 g, 92%): R_f (3:7 EtOAc/hex) 0.23; ^{1}H NMR (80 MHz, ppm) 6.53 (m, 1 H), 5.86 (d, 1 H, J = 2 Hz), 3.81 (s, 3 H), 2.06 (d, 3 H, J = 2 Hz).

Lewis Acid Catalyzed Reaction of 3a to 11d: 2,3-Dihydro-6-methoxy-4-methyl-2-(2,6,6-trimethyl-1-cyclohexenyl)-5-benzofuranol (20). A solution of **11d** in dichloromethane (44 mg, 0.29 mmol, in 1.5 mL) was cooled to −78 °C, titanium(IV) chloride (32 μL, 0.29 mmol) was added, and the mixture was stirred for 1 h. Then, diene **3a** (150 μL, 0.7 mmol) was added, and the solution was stirred for 40 min. The reaction was quenched with saturated aqueous ammonium chloride and extracted with dichloromethane (3 × 10 mL), and the combined organic layers were washed with water and dried. The residue obtained on evaporation of solvent in vacuo was purified by PCTLC to yield **20** as an oil (36.2 mg, 41%): R_f (1:4 EtOAc/hex) 0.44; ^{1}H NMR (300 MHz, ppm) 6.30 (s, 1 H), 5.25 (s, 1 H, exchanges with D_2O), 5.23 (dd, 1 H, J = 11.3, 10 Hz), 3.82 (s, 3 H), 3.20 (dd, 1 H, J = 15, 10 Hz), 3.04 (dd, 1 H, J = 15, 11.3 Hz), 2.16, (s, 3 H), 1.59 (s, 3 H), 1.14 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR (75.1 MHz, ppm) 151.69, 145.91, 137.58, 137.45, 133.47, 119.88, 118.02, 91.58, 81.73, 56.21, 39.64, 36.95, 34.45, 33.96, 28.85, 27.62, 20.50, 19.37, 12.70; HRMS *m/e* 302.1883 (calcd for $C_{19}H_{26}O_3$ 302.1881).

3-Methoxy-4aβ,4b,5,6,7,8,10,10a-octahydro-4bβ,8,8,10aβ-tetramethyl-1,4-phenanthrenedione (12c). A high-pressure reaction vessel was charged with 2-methoxy-5-methyl-1,4-benzoquinone, **11c** (44 mg, 0.29 mmol), **3a** (125 μL, 0.7 mmol), and dichloromethane (1 mL). Anhydrous zinc bromide (71 mg, 0.32 mmol) was added, and the tube was sealed with brass clamps and pressurized for 14 days at 12 kbar. The reaction mixture was filtered through silica gel with dichloromethane as eluent. Evaporation of the solvent and purification of the residue by PCTLC using 3:7 ethyl acetate in hexanes as eluent gave **12c** (81 mg; 92%) as a colorless solid. Recrystallization from ethyl acetate/hexanes afforded colorless needles: mp 204–205 °C; R_f (3:7 EtOAc/hex) 0.27; ^{1}H NMR (300 MHz, ppm) 3.78 (s, 3 H), 1.37 (s, 3 H), 1.24 (s, 3 H), 1.11 (s, 3 H), 1.1–1.8 (m, 6 H), 1.04 (s, 3 H), other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 201.19, 197.35, 162.73, 148.26, 120.04, 110.09, 68.18, 56.41, 48.90, 40.46, 40.06, 37.32, 36.38, 33.13, 31.75, 30.21, 29.92, 29.75, 18.82 ppm; HRMS *m/e* 302.1885 (calcd for $C_{19}H_{26}O_3$ 302.1881). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.55; H, 8.97.

1-(β-Methoxyvinyl)-2,6,6-trimethylcyclohexene (3b/21). To a flame-dried flask under a stream of nitrogen was added KH (35% in oil, 6.412 g, 55.9 mmol), which was washed with distilled hexanes (5 × 3 mL) and suspended in dry THF (50 mL). Dry *t*-BuOH (5.3 mL, 55.9 mmol) was added dropwise followed by (methoxymethyl)triphenylphosphonium chloride (11.5 g, 33.5 mmol) to give a dark red solution. After 20 min, a solution of β-cyclocitral (3.412 g, 22.36 mmol) in dry THF (50 mL) was added dropwise. When the addition was complete, the reaction mixture was refluxed at 80–90 °C (oil bath temperature) for ~6 h. The reaction mixture was poured into ether, and the ether solution was washed with saturated sodium bicarbonate solution and dried over sodium sulfate. The ether solution was filtered and concentrated (with addition of small amounts of ethyl acetate to keep the triphenylphosphine oxide in solution) to give a dark red liquid,

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which was chromatographed on a short silica gel column with hexane to remove base-line impurities. A second chromatography (1% EtOAc/hex) gave a 1:2 cis:trans mixture of 1-(β-methoxyvinyl)-2,6,6-trimethylcyclohexenes **3b/21**[2b,4] (3.32 g, 82.2%) as a clear oil. Isomers **3b** and **21** were separable by careful column chromatography.

(2,6,6-Trimethylcyclohexen-1-yl)ethanal (22).[4] To a solution of enol ethers **3b/21** (1.3051 g, 7.24 mmol) in ether (10 mL) was added dropwise a 50% aqueous perchloric acid solution (10 mL) with constant stirring. After the addition was complete, the reaction mixture was allowed to stir for 3–5 h. The reaction mixture was poured into a separatory funnel, and to it were added small amounts of solid sodium bicarbonate until the acid was neutralized. The ether extract was separated, dried over sodium sulfate, and concentrated to a light yellow oil. Flash chromatography on silica gel with 1–2% EtOAc/hexanes as eluent gave **22** as a clear oil (0.95 g, 78.9%).

1-(β-Acetoxyvinyl)-2,6,6-trimethylcyclohexene (3i).[2b] A mineral oil suspension of KH (35%, 0.15 g, 1.32 mmol) was washed five times with distilled hexanes and suspended in dry THF (10 mL). Dry *t*-BuOH (0.124 mL, 1.32 mmol) was added dropwise followed by a dry THF (15 mL) solution of (2,6,6-trimethylcyclohexene-1-yl)ethanal, **22** (0.22 g, 1.32 mmol). The reaction mixture was stirred for 25 min, and a solution of acetic anhydride (1.24 mL, 13.2 mmol) in dry THF (10 mL) was then added dropwise. After 1 h, the reaction mixture was poured into ether and washed with saturated aqueous saturated sodium bicarbonate. The ether layer was dried over sodium sulfate and concentrated to a yellow oil. Flash column chromatography using 5% ethyl acetate/hexane as eluent gave a 2:1 mixture of **3i** and its *Z* isomer (0.221 g, 80%) as a clear oil.

Diels–Alder Reaction of 3b with 1,4-Benzoquinone: 10α-Methoxy-4aβ,4b,5,6,7,8,10,10a-octahydro-4bβ,8,8-trimethyl-1,4-phenanthrenedione (23) and 10α-Methoxy-4b,5,6,7,8,10-hexahydro-4bβ,8,8-trimethyl-1,4-phenanthrenedione (24). A solution of enol ether **3b** (155 mg, 0.86 mmol) and 1,4-benzoquinone **11a** (71 mg, 0.65 mmol) in dichloromethane (3 mL) was pressurized to 12 kbar for 2 days. Concentration of the solution and flash chromatography of the residue with 1:3 ethyl acetate/hexanes as eluent afforded enedione **23** (71 mg, 38%) and quinone **24** (~1 mg, 1%). Recrystallization of **23** from EtOAc/hexanes gave colorless crystals: mp 114–115 °C; R_f (1:3 EtOAc/hex) 0.41; ^{1}H NMR (300 MHz, ppm) 3.17 (s, 3 H), 1.4–1.9 (m, 5 H), 1.19 (s, 3 H), 1.17 (s, 3 H), 1.13 (s, 3 H), other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 200.0, 198.2, 154.5, 144.3, 139.1, 115.4, 74.2, 57.3, 57.1, 50.2, 39.5, 35.7, 35.5, 33.4, 31.5, 31.0, 29.5, 18.1; HRMS *m/e* 288.1733 (calcd for $C_{18}H_{24}O_3$ 288.1726). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 75.01; H, 8.47.

Spectral data for **24**: R_f (1:4 EtOAc/hex) 0.38; ^{1}H NMR (500 MHz, ppm) 3.37 (s, 3 H), 2.4–1.0 (m, 5 H), 1.38 (s, 3 H), 1.21 (s, 3 H), 1.17 (s, 3 H), other data appears in Table II.

Diels–Alder Reaction of 3i with 1,4-Benzoquinone: 10α-Acetoxy-4aβ,4b,5,6,7,8,10,10a-octahydro-4bβ,8,8-trimethyl-1,4-phenanthrenedione (25). A mixture of enol acetate **3i** (57 mg, 0.27 mmol) and 1,4-benzoquinone (13 mg, 0.12 mmol) in CH_2Cl_2 (1.2 mL) was maintained at 12 kbar for 8.5 days. Flash chromatography (1:3 EtOAc/hexanes) on silica gel of the residue obtained on concentration of the reaction mixture produced **25** (23 mg, 60%), which recrystallized from EtOAc/hexanes to give colorless crystals: mp 148–149 °C; R_f (1:4 EtOAc/hex) 0.22; ^{1}H NMR (300 MHz, ppm) 1.87 (s, 3 H), 1.45–1.85 (m, 5 H), 1.23 (s, 3 H), 1.13 (s, 6 H), other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 198.1, 198.0, 169.4, 156.3, 144.1, 138.7, 115.1, 67.1, 57.0, 48.3, 39.4, 35.6, 35.5, 33.4, 31.3, 30.9, 29.4, 21.0, 18.0; HRMS *m/e* 316.1674 (calcd for $C_{19}H_{24}O_4$ 316.1673). Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 71.87; H, 7.59.

Diels–Alder Reactions of Enol Ether 3b with 2-Methoxy-1,4-benzoquinone (11b): 2,10α-Dimethoxy-4aβ,4b,5,6,7,8,10,10a-octahydro-4bβ,8,8-trimethyl-1,4-phenanthrenedione (26) and 3,10α-Dimethoxy-4aβ,4b,5,6,7,8,10,10a-octahydro-4bβ,8,8-trimethyl-1,4-phenanthrenedione (27). Pressurization of a CH_2Cl_2 solution (1.2 mL) of enol ether **3b** (51.4 mg, 0.29 mmol), quinone **11b** (57.5 mg, 0.42 mmol), and Yb(fod)$_3$ (31.6 mg, 0.030 mmol) to 12 kbar for 18 h gave, after flash chromatography on silica gel with 3:7 EtOAc/hexanes as eluent, adducts **26** (24.6 mg, 27%), mp 165–166 °C (EtOAc/hex), and **27** (11 mg, 12%), mp 132–134 °C, both as colorless crystals. Spectral data for **26**: R_f (3:7 EtOAc/hexanes) 0.19; ^{1}H NMR (300 MHz, ppm) 3.74 (s, 3 H), 3.19 (s, 3 H), 1.35–1.85 (m, 5 H), 1.17 (s, 3 H), 1.16 (s, 3 H), 1.13 (s, 3 H), other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 197.5, 195.0, 161.8, 155.2, 115.9, 115.5, 74.9, 58.2, 56.7, 56.5, 49.2, 39.8, 36.2, 35.8, 34.0, 31.8, 31.5, 30.3, 18.5; HRMS *m/e* 318.1830 (calcd for $C_{19}H_{26}O_4$ 318.1830). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.63; H, 7.99.

Spectral data for **27**: R_f (3:7 EtOAc/hexanes) 0.13; ^{1}H NMR (300 MHz, ppm) 3.75 (s, 3 H), 3.17 (s, 3 H), 1.3–1.8 (m, 5 H), 1.20 (s, 3 H), 1.17 (s, 3 H), 1.13 (s, 3 H), other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 198.7, 193.0, 166.6, 154.2, 115.6, 110.7, 73.7, 57.4, 57.3, 56.4, 50.6, 39.6, 35.8, 35.5, 33.6, 31.6, 30.9, 29.7, 18.1; HRMS *m/e* 318.1838 (calcd for $C_{19}H_{26}O_4$ 318.1830). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.83; H, 8.32.

Spectral data for **30**: R_f (3.7 EtOAc/hex) 0.26; ^{1}H NMR (300 MHz, ppm) 3.81 (s, 3 H), 3.41 (s, 3 H), 1.89 (m, 1 H), 1.7–1.3 (m, 4 H), 1.48 (s, 3 H), 1.26 (s, 3 H), 1.23 (s, 3 H), other data appears in Table II; HRMS *m/e* 316.1677 (calcd for $C_{19}H_{24}O_4$ 316.1673).

Diels–Alder Reaction of Enol Acetate 3i with 2-Methoxy-1,4-benzoquinone (11b): 10α-Acetoxy-2-methoxy-4aβ,4b,5,6,7,8,10,10a-octahydro-4bβ,8,8-trimethyl-1,4-phenanthrenedione (28) and 10α-Acetoxy-3-methoxy-4aβ,4b,5,6,7,8,10,10a-octahydro-4bβ,8,8-trimethyl-1,4-phenanthrenedione (29). A 2:1 *E/Z* mixture of enol acetates **3i** (33.2 mg of *E*-**3i**, 0.16 mmol), quinone **11b** (33.1 mg, 0.24 mmol), and Yb(fod)$_3$(16 mg, 0.015 mmol) in CH_2Cl_2 (1–2 mL) was pressurized to 12 kbar for 4.5 days. Flash chromatography on silica gel with 3:7 and then 1:1 EtOAc/hexanes gave enediones **28** (6 mg, 11%), mp 190–191 °C (EtOAc/hex), and **29** (35 mg, 66%), mp 162–163 °C (EtOAc/hex), both as colorless crystals. Spectral data for **28**: R_f (35% EtOAc/hexanes) 0.24; ^{1}H NMR (300 MHz, ppm) 3.76 (overlapping s and dd, 3 H/1 H, J = 6.8, 5.3 Hz), 1.9 (s, 3 H), 1.40–1.85 (m, 5 H), 1.22 (s, 3 H), 1.12 (s, 6 H), other spectral data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 196.8, 192.8, 169.6, 161.3, 156.5, 115.5, 114.8, 67.3, 56.3, 56.2, 47.3, 39.3, 35.8, 35.5, 33.7, 31.2, 30.9, 29.7, 20.9, 18.1; HRMS *m/e* 346.1786 (calcd for $C_{20}H_{26}O_5$ 346.1779). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.07; H, 7.35.

Spectral data for **29**: R_f (35% EtOAc/hex) 0.15; ^{1}H NMR (300 MHz, ppm) 3.71 (s, 3 H), 1.78 (s, 3 H), 1.3–1.75 (m, 5 H), 1.16 (s, 3 H), 1.06 (s, 6 H), other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 196.6, 192.8, 169.3, 166.3, 156.1, 115.1, 110.3, 66.7, 57.1, 56.6, 48.6, 39.3, 35.5, 35.4, 33.5, 31.3, 30.9, 29.6, 21.0, 18.0; HRMS *m/e* 346.1779 (calcd for $C_{20}H_{26}O_5$ 346.1779). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.58; H, 7.45.

1α-Hydroxy-3-methoxy-4aβ,4b,5,6,7,8,10,10aβ-octahydro-4bβ,8,8-trimethylphenanthren-4(1*H*)-one (35) and 4α-Hydroxy-3-methoxy-4aβ,4b,5,6,7,8,10,10aβ-octahydro-4bβ,8,8-trimethylphenanthren-1(4*H*)-one (34). A 1 M solution of L-Selectride in THF (125 μL, 0.125 mmol) was added to a stirred solution of **12b** (34.2 mg, 0.119 mmol) in dry THF (0.5 mL) at −78 °C. The pale yellow solution turned orange almost instantly. After 5 min, saturated aqueous ammonium chloride was added to the mixture which was then warmed to room temperature. The mixture was extracted with ether (2 × 10 mL), and the combined ether extracts were washed with water and brine and dried. The mixture obtained on evaporation of solvent was separated by preparative TLC with 3:7 EtOAc/hexanes and subsequently with 1:1 EtOAc/hexanes. The compounds were washed from the silica gel with ethyl acetate to yield **35** (8.6 mg, 25%) and **34** (15.3 mg, 44.5%): mp for **34** 162–163 °C (EtOAc/hex); R_f (3:7 EtOAc/hex) for **35** 0.07; for **34** 0.11. Spectral data for **35**: ^{1}H NMR (300 MHz, ppm) 3.77 (d, 1 H, J = 5 Hz, exchanges with D_2O), 3.59 (s, 3 H), 1.0–1.9 (m, 5 H), 1.25 (s, 3 H), 1.08 (s, 3 H), 1.07 (s, 3 H), other spectral data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 194.33, 150.89, 150.34, 114.88, 111.36, 69.65, 58.15, 55.11, 39.91, 38.17, 36.41, 35.14, 34.35, 31.46, 30.99, 30.94, 22.43, 18.57; HRMS *m/e* 290.1888 (calcd for $C_{18}H_{26}O_3$ 290.1882).

Spectral data for **34**: ^{1}H NMR (300 MHz, ppm) 3.76 (s, 3 H), 3.21 (d, 1 H, J = 3.5 Hz, exchanges with D_2O), 2.05–1.80 (m, 2 H), 1.70–1.20 (m, 4 H), 1.32 (s, 3 H), 1.15 (s, 3 H), 1.12 (s, 3 H),

other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 202.66, 174.73, 152.29, 119.21, 99.70, 67.13, 56.06, 46.88, 40.75, 39.17, 36.16, 35.85, 34.22, 32.58, 30.97, 30.29, 28.16, 18.02; HRMS *m/e* 290.1888 (calcd for $C_{18}H_{26}O_3$ 290.1882).

4-[(4-Bromobenzyl)oxy]-5,6,7,8,10,10a-hexahydro-3-methoxy-4bβ,8,8,10aβ-tetramethyl-1(4b*H*)-phenanthrenone (36). A suspension of KH in mineral oil (35%, 42 mg, 0.37 mmol) was placed in a flask flame-dried under vacuum, and the oil was washed away with hexanes (3 × 1 mL). A solution of *p*-bromobenzyl bromide (57 mg, 0.228 mmol) in THF (1.5 mL) was added, and the mixture was cooled to 0 °C. To this mixture were added *tert*-butyl alcohol (7 μL, 0.078 mmol), and a solution of **12c** in THF (23 mg, 0.076 mmol in 1.5 mL). The reaction mixture changed in color from pale blue to dark blue to green. After 1 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for 12 h. The resulting reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ether (3 × 20 mL), and the combined extracts were dried. The solvent was evaporated under reduced pressure, and the residue was purified by PCTLC with 3:7 EtOAc/hexanes to yield **36** (19 mg, 53%) as a colorless oil, which crystallized from hexanes as colorless prisms: mp 109–111 °C; R_f (3:7 EtOAc/hex) 0.38; ^1H NMR (300 MHz, ppm) 7.54 (d, 2 H, *J* = 8.2 Hz), 7.32 (d, 2 H, *J* = 8.2 Hz), 5.69 (dd, 1 H, *J* = 6.4, 1.8 Hz), 5.54 (s, 1 H), 4.93 (d, 1 H, *J* = 11.5 Hz), 4.65 (d, 1 H, *J* = 11.5 Hz), 3.81 (s, 3 H), 2.81 (m, 1 H), 2.53 (dd, 1 H, *J* = 17.4, 6.4 Hz), 2.06 (dd, 1 H, *J* = 17.4, 1.8 Hz), 1.64 (s, 3 H), 1.41 (s, 3 H), 1.21 (s, 3 H), 1.16 (s, 3 H), 1.0–1.9 (m, 5 H); ^{13}C NMR (75.1 MHz, ppm) 203.55, 168.71, 151.36, 147.02, 139.83, 136.67, 131.56, 131.43, 129.01, 121.66, 116.37, 99.03, 72.99, 56.13, 48.47, 43.23, 40.73, 38.85, 37.46, 33.31, 32.77, 29.29, 28.16, 27.66, 19.62; HRMS *m/e* 471.1532 (calcd for $C_{26}H_{31}{}^{79}BrO_3$ (M^+ + 1) 471.1536).

3-Methoxy-4aλ,4b,5,6,7,8,10,10a-octahydro-4bβ,8,8,10aβ-tetramethyl-1,4-phenanthrenedione (37). A flask flame-dried under a stream of dry nitrogen was charged with a suspension of KH in mineral oil (35%; 44 mg, 0.38 mmol). The oil was washed away with hexanes (3 × 1 mL) under nitrogen, and THF (700 μL) was added. The suspension was cooled to 0 °C, and *t*-BuOH (14 μL, 0.48 mmol) was added followed by the dropwise addition of a solution of **12c** in THF (23 mg, 0.076 mmol, in 800 μL). The resulting orange suspension was stirred at 0 °C for 40 min, and the reaction was quenched by the addition of 5% aqueous formic acid. The aqueous layer was extracted with ether (3 × 20 mL), and the combined organic layers were washed with saturated aqueous sodium bicarbonate and brine and dried. The residue obtained on evaporation of the solvent was purified by PCTLC with 3:7 ethyl acetate/hexanes to yield **37** (18.2 mg, 79%) as a colorless solid: mp 149.5–151 °C (EtOAc/hex); R_f (3:7 EtOAc/hexanes) 0.32; ^1H NMR (300 MHz, ppm) 3.78 (s, 3 H), 2.65–2.55 (m, 1 H), 1.85 (m, 1 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 1.16 (s, 3 H), 1.08 (s, 3 H), 0.8–1.5 (m, 4 H), other data appears in Table II; ^{13}C NMR (75.1 MHz, ppm) 203.97, 193.92, 162.55, 148.55, 115.21, 107.95, 62.79, 56.35, 48.00, 41.35, 40.30, 38.31, 36.40, 35.12, 33.10, 29.64, 25.41, 22.32, 18.16; HRMS *m/e* 302.1880 (calcd for $C_{19}H_{26}O_3$ 302.1881). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.81; H, 8.62.

2-(2,6-Dimethoxyphenyl)-2-propanol (41).[23] A solution of 1,3-dimethoxybenzene (10 mL, 76.4 mmol) and tetramethylethylenediamine (13 mL, 86 mmol) in 250 mL of ether was cooled to −78 °C under nitrogen, and a solution of *t*-BuLi (1.7 M in hexanes, 52 mL; 87 mmol) was added dropwise. The solution turned pale yellow, and a yellow precipitate appeared. The suspension was stirred for 5 h, and acetone (7 mL, 95 mmol) was then added at −78 °C. The precipitate dissolved almost instantaneously. The pale yellow solution was allowed to stir for 15 min and was quenched with saturated aqueous ammonium chloride. The ether layer was separated and washed repeatedly with aqueous ammonium chloride until the aqueous layer was neutral. After drying, the ether solution was concentrated in vacuo. The product was separated from the starting material by chromatography on silica gel with 1:9 EtOAc/hexanes as eluent to yield **41** as a pale yellow oil (9.21 g, 61.4%): R_f (1:9 EtOAc/hex) 0.08; ^1H NMR (300 MHz, ppm) 7.15 (dd, 1 H, *J* = 9, 8 Hz), 6.61 (d, 2 H, *J* = 8 Hz), 5.79 (br s, 1 H), 3.83 (s, 6 H), 1.66 (s, 6 H); ^{13}C NMR (75.1 MHz, ppm) 157.59, 127.45, 124.09, 105.81, 73.94, 55.87, 30.87.

1,3-Dimethoxy-2-(1-methylethyl)benzene (42). A mixture of **41** (9.21 g, 47 mmol), 5% palladium on charcoal (900 mg), and concentrated sulfuric acid (25 drops) in ethyl acetate (150 mL) was shaken in a Parr hydrogenator for 10 h at 50 psi of hydrogen. After that time, the reaction mixture was filtered through Celite, and the solvent was evaporated. The residue was dissolved in ether and washed with saturated sodium bicarbonate. The ether layer was then dried and concentrated to yield **42** (7.2 g, 85%). The pale yellow oil was pure by NMR and was used without further purification: R_f (1:9 EtOAc/hex) 0.48; ^1H NMR (300 MHz, ppm) 7.04 (dd, 1 H, *J* = 9, 8 Hz), 6.49 (d, 2 H, *J* = 8 Hz), 3.73 (s, 6 H), 3.64 (septet, 1 H, *J* = 7 Hz), 1.29 (d, 6 H, *J* = 7 Hz); ^{13}C NMR (75.1 MHz, ppm) 154.44, 126.38, 124.11, 104.27, 55.29, 23.88, 20.48.

3-Methoxy-2-(1-methylethyl)phenol (43). To a solution of **42** in dichloromethane (7.2 g, 40 mmol, in 100 mL) at −78 °C was added a 1 M solution of BBr_3 (30 mL, 30 mmol) in dichloromethane. The solution was stirred at −78 °C for 5 h, warmed to room temperature, and stirred for an additional 8 h. The reaction mixture was cooled to 0 °C and quenched with water. The organic layer was separated, dried, and concentrated. The residue was purified by PCTLC with 1:19 ethyl acetate in hexanes as eluent to yield **43** (5.91 g, 89%), along with a small amount of the didemethylated compound (2-isopropylresorcinol): R_f (1:9 EtOAc/hex) 0.20 for **43**: 0.08 for 2-isopropylresorcinol. This material was used without further purification. Spectral data for **43**: ^1H NMR (80 MHz, ppm) 6.94 (dd, 1 H, *J* = 8, 8 Hz), 6.35 (dd, 2 H, *J* = 8, 8 Hz), 5.23 (br s, 1 H), 3.80 (s, 3 H), 3.50 (septet, 1 H, *J* = 7 Hz), 1.26 (d, 6 H, *J* = 7 Hz).

2-Methoxy-3-isopropyl-1,4-benzoquinone (44). A solution of **43** (0.945 g, 5.7 mmol) and Co(salen)[25] (1.85 g, 5.7 mmol) in dry DMF (20 mL) was stirred under a positive pressure of oxygen maintained using a mercury ballast. The red suspension turned black in about 1 h, and the stirring was continued for 3 days. The black reaction mixture was poured into a bilayer of water (250 mL) and a 1:1 solution of ether in hexanes (250 mL), which was stirred gently. The organic layer was periodically decanted off and replaced with additional 1:1 ether–hexanes solution. The above process was repeated until the organic layer was no longer yellow. The combined organic layers were dried, and the solvent was removed under reduced pressure. The resulting brown residue was purified by PCTLC using 3:97 ethyl acetate in hexanes to afford **44** as a yellow oil (455.8 mg, 44%). This was used as such in further reactions. A sample for analysis was obtained by bulb-to-bulb distillation, 40 °C/2 mm: R_f (1:9 EtOAc/hex) 0.22; ^1H NMR (300 MHz, ppm) 6.63 (q, 2 H, *J* = 9 Hz), 4.00 (s, 3 H) 3.26 (septet, 1 H, *J* = 7 Hz), 1.23 (d, 6 H, *J* = 7 Hz); ^{13}C NMR (75.1 MHz, ppm) 188.05, 183.89, 155.93, 137.97, 136.92, 134.32, 60.96, 24.61, 20.37; HRMS *m/e* 180.0796 (calcd for $C_{10}H_{12}O_3$ 180.0786). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.57; H, 7.04.

Diels–Alder Reaction of 3a with 44: 3-Methoxy-2-(1-methylethyl)-4aβ,4b,5,6,7,8,10,10aβ-octahydro-4bβ,8,8-trimethyl-1,4-phenanthrenedione (45) and 3-Methoxy-2-(1-methylethyl)-4aα,4b,5,6,7,8,10,10aα-octahydro-4bβ,8,8-trimethyl-1,4-phenanthrenedione (46). To a high-pressure reaction tube was added a solution of **44** (60.4 mg, 0.34 mmol) in dichloromethane (1 mL) followed by **3a** (125 μL, 0.7 mmol). Anhydrous zinc bromide (48.9 mg, 0.22 mmol) was added, and the top end of the tube was sealed with brass clamps. The tube was then pressurized to 11–12 kbar for 5 days. The reaction mixture was filtered through silica gel with dichloromethane as eluent. The residue obtained on evaporation of solvent was purified by PCTLC using 3:97 ethyl acetate in hexanes to yield a 4.4:1 mixture of **45** and **46** as a pale yellow oil (82 mg, 73%): R_f of **45** and **46** (1:9 EtOAc/hex) 0.30; spectral data for **45** (as identified from that of the mixture); ^1H NMR (500 MHz, ppm) 5.29 (t, 1 H, *J* = 4 Hz), 3.84 (s, 3 H), 3.45 (ddd, 1 H, *J* = 11, 8, 5), 3.12 (septet, 1 H, *J* = 7 Hz), 2.88 (d, 1 H, *J* = 5 Hz), 2.38 (ddd, 1 H, *J* = 18, 8, 4 Hz), 2.35 (ddd, 1 H, *J* = 12, 12, 4 Hz), 2.00 (ddd, 1 H, *J* = 18, 11, 4 Hz), 1.82 (ddq, 1 H), 1.23 (s, 3 H), 1.16 (d, 3 H, *J* = 7 Hz), 1.12 (d, 3 H, *J* = 7 Hz), 1.10 (s, 3 H), 1.09 (s, 3 H); EIMS *m/e* (relative intensity) 330 (M^+), 315.

Spectral data for **46** (only the signals that are clearly distinguishable as that of the minor compound, **46**, in a spectrum of the mixture of **45**/**46** are reported): ^1H NMR (500 MHz, ppm)

5.54 (t, 1 H, J = 4 Hz), 3.90 (s, 3 H), 3.26 (septet, 1 H, J = 7 Hz), 3.1 (m), 2.16 (ddd, 1 H, J = 19, 9.5, 4 Hz).

After 30 h at 12 kbar, a mixture of diene **3a** (125 μL, 0.7 mmol), quinone **44** (54.1 mg, 0.30 mmol), and $ZnBr_2$ (42.2 mg, 0.187 mmol) gave a 3.8:1 mixture of **45/46** (66 mg, 67%). In the absence of $ZnBr_2$, the diene **3a** and quinone **44** gave a 4.5:2.2:1 ratio of **45/46** and a third compound, **47**, in 61% combined yield. Spectral data for **47**: R_f (1:9 EtOAc/hex) 0.26; ^{1}H NMR (300 MHz, ppm) 5.52 (t, 1 H, J = 4 Hz), 3.93 (s, 3 H), 3.25 (septet, 1 H, J = 7 Hz), 3.05–3.15 (m, 2 H), 2.92 (d, 1 H, J = 8 Hz), 2.1–2.4 (m), 1.06–1.6 (m), 1.18 (d, 6 H, J = 7 Hz), 1.08 (s, 3 H), 1.07 (s, 3 H), 0.96 (s, 3 H).

4b,5,6,7,8,10-Hexahydro-3-methoxy-2-(1-methylethyl)-4bβ,8,8-trimethyl-1,4-phenanthrenedione (48). To a solution of **45/46** (2.8:1) in THF (60 mg, 0.18 mmol, in 2 mL) was added 10 drops of concentrated aqueous hydrochloric acid, and the mixture was stirred under nitrogen for 26 h. The solvent was then evaporated under reduced pressure, the residue was dissolved in dichloromethane (3 mL), and silver carbonate on Celite (250 mg, 0.46 mmol) was added. The yellow mixture turned gray immediately. After being stirred at room temperature for 5 min, the mixture was filtered through Celite, and the residue remaining on evaporation of solvent was purified by PCTLC with 1:49 ethyl acetate in hexanes as eluent to yield **48** (55 mg, 92%) as a yellow oil. The oil was crystallized from methanol to give bright yellow crystals: mp 78.5–79 °C; R_f (1:9 EtOAc/hex) 0.52; ^{1}H NMR (300 MHz, ppm) 5.31 (dd, 1 H, J = 5, 2 Hz), 3.87 (s, 3 H), 3.19 (dd, 1 H, J = 24, 5 Hz), 3.17 (septet, 1 H, J = 7 Hz), 2.84 (dd, 1 H, J = 24, 2 Hz), 2.76 (ddd, 1 H, J = 12, 4, 4 Hz), 1.49 (s, 3 H), 1.20 (d, 3 H, J = 7 Hz), 1.17 (d, 3 H, J = 7 Hz), 1.13 (s, 3 H); ^{13}C NMR (75.1 MHz, ppm) 187.75, 183.81, 156.90, 148.51, 146.35, 13[a].94, 135.23, 115.67, 60.66, 40.47, 39.20, 36.52, 36.39, 33.06, 30.74, 26.12, 24.85, 24.39, 20.63, 20.44, 18.77; HRMS m/e 328.2042 (calcd for $C_{21}H_{28}O_3$ 328.2039).

1,2,3,4,4a,9-Hexahydro-7-(1-methylethyl)-5,6,8-trimethoxy-1,1,4aβ-trimethylphenanthrene (49). The oil was washed away from a suspension of potassium hydride in mineral oil (98 mg of a 35% suspension, 0.85 mmol) with hexanes (3 × 1 mL) under nitrogen, and THF (5 mL) was added. This suspension was cooled to 0 °C and iodomethane (250 μL, 4.00 mmol), *tert*-butyl alcohol (28 μL, 0.3 mmol), and a solution of **45/46** (3.4:1) in THF (62.5 mg, 0.19 mmol, in 5 mL) were added in that order. The reaction mixture turned green instantaneously and was allowed to warm to room temperature over 11 h. The now colorless reaction mixture was cooled to 0 °C, quenced with saturated aqueous ammonium chloride, and poured into dichloromethane. The aqueous layer was extracted with dichloromethane (3 × 10 mL), and the combined organic layers were washed with water and brine and dried. After concentration of the solution the crude product was purified by PCTLC with 3:97 ethyl acetate in hexanes as eluent to yield **49** as a colorless oil (61.8 mg, 91%): R_f (1:9 EtOAc/hex) 0.60; ^{1}H NMR[28] (300 MHz, ppm) 5.86 (dd, 1 H, J = 5.7, 2.3 Hz), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 3.53 (dd, 1 H, J = 21.9, 5.7 Hz), 3.38 (septet, 1 H, J = 7.1 Hz), 3.11 (dd, 1 H, J = 21.9, 2.1 Hz), 3.05 (ddd, 1 H, J = 13, 4.6, 4.6 Hz), 1.47 (s, 3 H), 1.36 (d, 3 H, J = 7 Hz), 1.33 (d, 3 H, J = 7 Hz), 1.26 (s, 3 H), 1.25 (s, 3 H); ^{13}C NMR (75.1 MHz, ppm) 151.91, 149.86, 149.01, 148.65, 138.45, 132.26, 123.10, 117.03, 60.93, 59.78, 59.42, 40.28, 37.64, 36.50, 33.47, 31.42, 29.71, 27.71, 25.80, 25.00, 22.22, 22.16, 19.45; HRMS m/e 358.2500 (calcd for $C_{23}H_{34}O_3$ 358.2506).

4b,5,6,7,8,10-Hexahydro-3-methoxy-2-(1-methylethyl)-4bβ,8,8-trimethyl-4-phenanthrenol (51). A flame-dried flask was charged with a solution of **45/46** (~4:1) in dry THF (41 mg, 0.124 mmol, in 1 mL) and cooled to −78 °C. A solution of L-Selectride in THF (125 μL, 1 M, 0.125 mmol) was added. The pale yellow solution turned bright orange instantaneously. After being stirred for 5 min, the reaction mixture was diluted with saturated aqueous ammonium chloride and warmed to room temperature. The resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were then washed with water and brine and dried. The residue obtained on evaporation of solvent (36 mg, 0.11 mmol, 88%) was identified as a mixture (~2:1) of alcohols **50** and was used without further purification in the next step: R_f (1:9 EtOAc/hex) 0.16. Selected spectral information of the mixture: ^{1}H NMR (300 MHz, ppm) 5.68 (dd, 1 H, J = 6, 2 Hz), 5.30 (t, 1 H, J = 5 Hz), 4.84 (t, 2 H, J = 7 Hz), 3.96 (s, 3 H, minor isomer), 3.58 (s, 3 H, major isomer) 3.17 (d, 1 H, J = 7 Hz), 3.06 (m, 1 H), 2.99 (septet, 1 H, J = 7 Hz), 2.76 (d), 2.67 (ddd, 1 H, J = 12, 12, 4 Hz), 2.25 (d, 1 H, J = 4 Hz), 2.10 (m, 2 H), 1.25 (s, 3 H), 1.23 (d, 3 H, J = 7 Hz), 1.22 (d, 3 H, J = 7 Hz), 1.08, (s, 6 H); IR (ν_{max}) 3600, 1690.

To a solution of the above residue in acetonitrile (2 mL) was added triphenylphosphine (62.5 mg, 0.238 mmol) and tetrabromomethane (358 mg, 1.08 mmol). The solution was heated to 50 °C for 3 h. The solvent was then evaporated from the pale brown reaction mixture on a rotary evaporator, and the resulting residue was filtered through silica gel with 1:4 ethyl acetate in hexanes as eluent. The eluate was concentrated, and the remaining brown oil was purified by PCTLC with 1:49 ethyl acetate in hexanes to yield **51** (25.3 mg, 73%) as a pale brown oil: R_f (1:9 EtOAc/hex) 0.41; ^{1}H NMR (300 MHz, ppm) 6.50 (s, 1 H), 6.14 (s, 1 H), 5.82 (dd, 1 H, J = 4 Hz), 3.76, (s, 3 H), 3.33 (dd, 2 H, J = 4 Hz), 3.19 (septet, 1 H, J = 7 Hz), 3.15–3.25 (m, 1 H), 1.51 (s, 3 H), 1.24 (s, 3 H), 1.23 (d, 3 H, J = 7 Hz), 1.20 (d, 3 H, J = 7 Hz), 1.16 (s, 3 H); ^{13}C NMR (75.1 MHz, ppm) 149.17, 146.44, 142.96, 137.92, 130.67, 130.40, 116.83, 116.02, 61.85, 40.84, 39.76, 36.70, 36.64, 33.48, 30.97, 30.92, 26.42, 25.67, 23.88, 23.65, 19.26; HRMS m/e 314.2234 (calcd for $C_{21}H_{30}O_2$ 314.2244).

5,6-Dimethoxy-1,2,3,4,4a,9-hexahydro-7-(1-methylethyl)-1,1,4aβ-trimethylphenanthrene (52). A flame-dried flask was charged with a suspension of potassium hydride in mineral oil (35%, 36 mg, 0.322 mmol), and the oil was washed away with dry hexanes (3 × 1 mL) under nitrogen. THF was added (500 μL), and the suspension was cooled to 0 °C. Iodomethane (50 μL, 0.81 mmol) was added followed by a solution of **51** in THF (25.3 mg, 0.081 mmol in 500 μL). The gray suspension was stirred at 0 °C for 2 h and then at room temperature for 10 h. The resulting white suspension was cooled to 0 °C, diluted with saturated aqueous ammonium chloride, and extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with water and dried, and residue obtained after evaporation of solvent was purified by PCTLC with 3:97 ethyl acetate in hexanes to yield **52** (17.4 mg, 66%) as a colorless oil: R_f (1:9 EtOAc/hex) 0.64; ^{1}H NMR[21d] (300 MHz, ppm) 6.67 (s, 1 H), 5.86 (dd, 1 H, J = 4 Hz), 3.86 (s, 3 H), 3.77 (s, 3 H), 3.32 (d, 2 H, J = 4 Hz), 3.25 (septet, 1 H, J = 7 Hz), 3.05 (ddd, 1 H, J = 14, 4, 4 Hz), 1.46 (s, 3 H), 1.24 (s, 3 H), 1.22 (d, 3 H, J = 7 Hz), 1.18 (d, 3 H, J = 7 Hz), 1.17 (s, 3 H); ^{13}C NMR (75.1 MHz, ppm) 151.90, 149.62, 149.24, 140.03, 137.53, 129.86, 119.85, 117.50, 60.12, 59.76, 40.29, 40.24, 37.58, 36.57, 33.47, 31.41, 30.97, 27.43, 26.54, 23.77, 23.33, 19.42; HRMS m/e 324.2408 (calcd for $C_{22}H_{32}O_2$ 328.2402).

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Registry No. **3a**, 5293-90-3; **3b**, 86558-55-6; **3i**, 58937-20-5; (*Z*)-**3i**, 63193-51-1; **11a**, 106-51-4; **11b**, 2880-58-2; **11c**, 614-13-1; **11d**, 611-68-7; (±)-**12a**, 106573-10-8; (±)-**12b**, 123151-54-2; (±)-**12c**, 123151-53-1; (±)-**13a**, 106549-27-3; (±)-**13b**, 123151-55-3; (±)-**14a**, 106573-11-9; (±)-**14b**, 123151-56-4; (±)-**15a**, 106549-28-4; (±)-**15b**, 55824-01-6; (±)-**16a**, 106623-26-1; (±)-**16b**, 106623-27-2; (±)-**17b**, 123151-57-5; (±)-**19a**, 123151-30-4; (±)-**19b**, 123151-29-1; (±)-**20**, 123151-31-5; **21**, 86558-54-5; **22**, 472-66-2; (±)-**23**, 123151-32-6; (±)-**24**, 123151-33-7; (±)-**25**, 123151-34-8; (±)-**26**, 123151-35-9; (±)-**27**, 123151-36-0; (±)-**28**, 123151-37-1; (±)-**29**, 123151-38-2; (±)-**30**, 123151-39-3; (±)-**34**, 123151-40-6; (±)-**35**, 123151-41-7; (±)-**36**, 123151-42-8; (±)-**37**, 123151-43-9; (±)-**38**, 34160-74-2; (±)-**39**, 37866-99-2; **40**, 151-10-0; **41**, 16929-70-7; **42**, 123151-44-0;

43, 123151-45-1; 44, 123151-46-2; (±)-45, 123151-47-3; (±)-46, 123151-48-4; 47, 123151-49-5; (±)-48, 123151-50-8; (±)-49, 123237-56-9; (±)-50 (isomer 1), 123151-51-9; (±)-50 (isomer 2), 123151-58-6; (±)-51, 123151-52-0; (±)-52, 34160-77-5; (±)-53, 60268-93-1; β-cyclocitral, 432-25-7; 2-isopropylresorcinol, 62858-83-7; 2-methoxy-6-methylphenol, 2896-67-5.

Supplementary Material Available: IR, UV, and mass spectral data for **12–15, 19, 20, 23, 25–30, 34–37, 44, 48, 49, 51, 52**; crystallographic data, ORTEP plots, tables of atomic coordinates, bond lengths, bond angles, and torsional angles for **19a** and **36** (36 pages). Ordering information is given on any current masthead page.

Novel Rearranged Spongian Diterpenes from the Palauan Sponge *Dendrilla* sp.: Reassessment of the Structures of Dendrillolide A and Dendrillolide B

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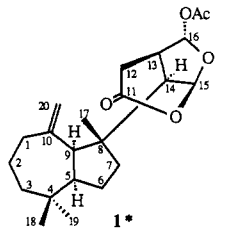
A reinvestigation of the Palauan sponge *Dendrilla* sp. has led to the isolation of four novel rearranged spongian diterpenes in addition to five of the diterpene metabolites previously reported from this sponge. Dehydroambliol A (**9**), 1-bromo-8-ketoambliol A acetate (**10**), norrisolide (**11**), dendrillolide A (**4**), and dendrillolide C (**3**) were reisolated and identified by comparison of spectral data with that of authentic samples. In addition, the novel diterpenes dendrillolide D (**5**), dendrillolide E (**6**), 12-desacetoxypolyrhaphin A (**7**), and 12-desacetoxyshahamin C (**8**) were isolated as minor constituents of this sponge. The structures of the four novel metabolites were determined by interpretation of spectral data. The structure of dendrillolide A (**4**) has been reassigned to that previously proposed for dendrillolide B by interpretation of new spectral data, particularly the two-dimensional heteronuclear NMR shift correlation experiments. The structure of dendrillolide B, which was not reisolated, remains undetermined.

We have previously reported[1] a chemical investigation of the Palauan sponge *Dendrilla* sp., in which the structures of three rearranged spongian diterpenes, dendrillolides A–C (**1–3**), were elucidated by interpretation of spectral data and by application of a biosynthetic hypothesis. Subsequent studies of the rearranged spongian diterpenes from the dorid nudibranch *Chromodoris macfarlandi*[2] revealed that the structure reported for dendrillolide A (**1**) was incorrect and that the structure assigned to dendrillolide B (**2**) was also suspect. This error



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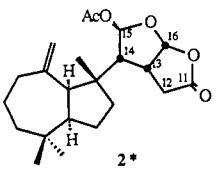
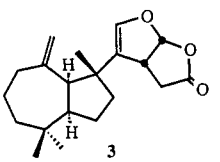


2*

* Asterisk denotes incorrect structures

was confirmed when a different compound, aplyviolene,[3] was determined by X-ray analysis to have the same structure as that proposed for dendrillolide A. We therefore recollected the purple dendroceratid sponge *Dendrilla* sp. from exactly the same location at Kaibaku Island in Iwayama Bay, Palau, in order to determine revised structures for dendrillolides A and B. In this paper we report that the correct structure of dendrillolide A (**4**) is that previously assigned to dendrillolide B and that the structure of dendrillolide B is unknown. In addition, four new diterpenes, dendrillolide D (**5**), dendrillolide E (**6**), 12-desacetoxypolyrhaphin A (**7**), and 12-desacetoxyshahamin C (**8**) are reported.



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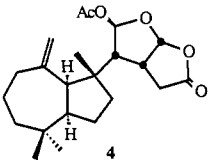

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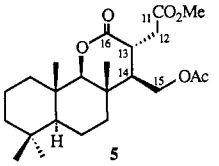

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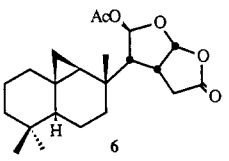

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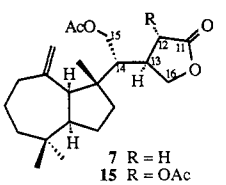

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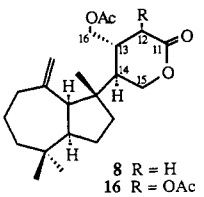
15 R = OAc



8 R = H
16 R = OAc

The dichloromethane extract of the lyophilized sponge was separated by flash chromatography on silica to yield four fractions that were determined by ^{1}H NMR spectroscopy to possess diterpene metabolites. Pure compounds were isolated from three of these fractions by HPLC on Partisil while the fourth fraction required additional isolation steps involving Sephadex LH-20 and silica flash chromatography in addition to HPLC on

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