π-Facial Selectivity in Nucleophilic Additions to 4,4-Disubstituted Dienones: Experimental Support for Electrostatic Control

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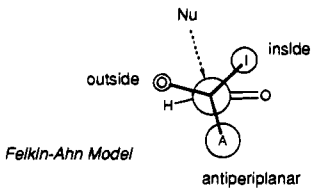
Abstract: The 4,4-disubstituted cyclohexadienones **5**−**10** and **32** were prepared by hypervalent iodine oxidation of the corresponding phenols. Our study of the facial selectivity in nucleophilic carbonyl additions provided experimental evidence for dominant dipolar control in these substrates. Hyperconjugative orbital stabilization in the transition state and orbital distortion effects appeared to be of secondary importance. Dienones **5**−**10** showed predominant attack of methyl Grignard reagents *anti* to the oxygen substituent at C(4) from the α-face of the dienone. In contrast, fluorinated substrate **32** demonstrated inverse selectivity, in accordance with an inversion of the molecular dipole moment $\mu_\perp$. The structure of all addition products was unequivocally established on the basis of NMR, X-ray, and chemical correlations. Dipole moments were calculated with the AM1 MO method and compared to the experimentally observed facial selectivities. In a series of structurally closely related dienones, an excellent linear correlation of the logarithm of the facial selectivities vs the calculated dipole moments was observed. Facial selectivities were strongly dependent on the nature of the nucleophile. Hydride ions and alkynyl groups added essentially nonselectively, whereas sp^2- and sp^3-hybridized C-nucleophiles led to α/β ratios of 32:1 to 1:5.

Introduction

Since the conception of the Cram rule for the prediction of the facial selectivity of nucleophilic attack to a carbonyl group,[1] numerous alternative models have been formulated as a consequence of a growing appreciation of steric and stereoelectronic effects in organic chemistry.[2−5] It is indeed difficult to overemphasize this problem, since the desymmetrization of the two faces of a planar carbonyl group is a fundamental paradigm of stereoselective synthesis. The influence of steric and conformational factors in kinetically controlled reactions is appropriately reflected by the Felkin−Ahn model,[2e,g] where



the transition state assumes a staggered arrangement with respect to the attacking nucleophile and the largest substituent is placed in an antiperiplanar position. Medium- and small-sized substituents at the α-carbon are at inside and outside positions, respectively. Donor ligands can modify this array via chelation to the reagent.

The spatial orientation of polar substituents with respect to the incoming nucleophile and the electronic control of face selection in carbonyl additions has been considerably more

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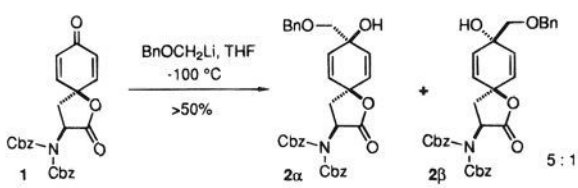
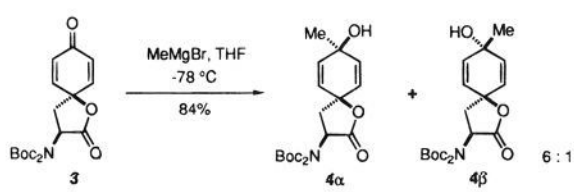
controversial.[5] Cornforth published an extension of the Cram rule for electronegative α-substituents in 1959.[2b] On the basis of STO-3G *ab initio* calculations, Ahn and Eisenstein proposed that the newly forming σ-orbital in the transition state would delocalize into an appropriate σ*-orbital of a carbon-substituent bond.[2e] This hypothesis places electron-withdrawing groups with energetically low σ*-orbitals preferentially into the antiperiplanar positions of the Felkin−Ahn model. In spite of substantial support of this concept in the literature,[6] many alternative theoretical and computational models have been proposed. Cieplak argued that the transition state of nucleophilic attack of carbonyl groups is stabilized by hyperconjugative delocalization of the newly forming σ*-orbitals into the σ-orbitals of antiperiplanar bonds.[2k] This provides predictions for stereoselectivity that are often just the reverse of the Ahn−Eisenstein model, even though the attempt was made to unify the two concepts.[5c] In an alternative approach, Klein and Burgess and Liotta pointed out the importance of desymmetrization of frontier orbitals by substituents.[2f,i] The differential change in the orbital coefficients on the two sides of the carbonyl plane causes an orbital distortion that directly induces facial selectivity. High-level *ab initio* calculations by Frenking have recently validated this concept for cyclohexanones.[4f,7] In spite of this strong attention to frontier orbitals and hyperconjugative stabilization of the transition state,[3] it seems clear that electrostatic effects should not be neglected, and Paddon-Row and Houk have reported MO calculations that indicate that electrostatic interactions may well outweigh Ahn−Eisenstein electronic effects.[4] Additional theories have been discussed, and there is an increasing number of molecular mechanics, semiempirical, and *ab initio* algorithms that are being applied toward the elusive goal of a general prediction of facial selectivities in carbonyl additions.[2g,l,3r,s,4,5b,7] This bewildering array of theoretical models with sometimes controversial status adds, unfortunately, a highly empirical flavor to the analysis of experimental data.

In the course of our recent total synthesis of the antitumor antibiotic aranorosin,[8] we observed an intriguing selectivity in the 1,2-addition of organometallic reagents to 4,4-disubstituted dienones. Treatment of spirolactone **1** with ((benzyloxy)methyl)lithium provided the bis-allylic alcohols **2**α,β in a 5:1 ratio in >50% yield (eq 1).



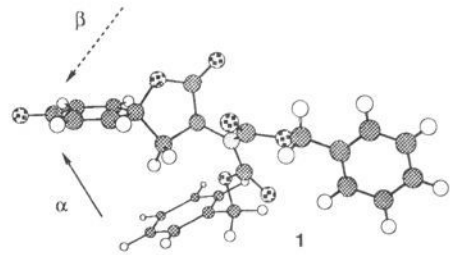
(1)

Similarly, addition of a methyl Grignard reagent to **3** resulted in a 6:1 ratio of alcohols **4**α,β (eq 2).



(2)

Molecular mechanics minimization of the geometry of dienones **1** and **3** revealed little steric bias for a face-selective addition of organometallics.[9] In fact, the observed attack mainly

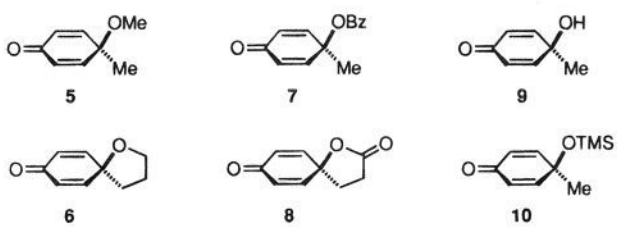


from the α-face of the planar dienone seems to be sterically slightly more cumbersome *syn* to the C(4) methylene and C(3) amino groups vs the O(1) lactone oxygen.

Due to the planar geometry, the relative distance of the *para* substituents of the dienone from the reaction center (approximately 4 Å), and the absence of charged, strongly haptophilic groups, steric and torsional effects as well as ligand-assisted nucleophilic addition were likely to be of minor significance in the reactions of **1** and **3**. Therefore, 4,4-disubstituted dienones appeared ideally suited for the critical analysis of the various theoretical models for stereoelectronic control in carbonyl additions.

Results and Discussion

A. Experimental Results. The remote functionalization at the amino function of dienones **1** and **3** could possibly attenuate the impact of any electronic effects responsible for facial selectivity. We hoped that an investigation of nucleophilic addition to model dienones **5**−**10** would remove this bias and



create the structurally consistent experimental data set that is necessary for the discussion of general mechanistic models in organic chemistry.

Phenol oxidation with hypervalent iodine reagents provided a versatile entry to cyclohexadienones.[10] Treatment of *p*-cresol (**11**) with $PhI(OAc)_2$[11] in MeOH afforded the desired **5** in 46% yield (Scheme 1). Alternatively, oxidation in a *tert*-butyl alcohol/water mixture provided the 4-hydroxy dienone **9** in 61% yield. *O*-Silylation and -benzoylation with hexamethyldisilazane and benzoic acid/DCC coupling, respectively, resulted in 94 and 88% of **10** and **7**. The spirocyclic dienones **6** and **8** were obtained by oxidative cyclization of (hydroxyphenyl)propanol **12** and the corresponding carboxylic acid **13** (Scheme 2). These efficient pathways to cyclohexadienones considerably facilitated

(6) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier, Amsterdam, 1984; pp 177−237.

(7) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1146.

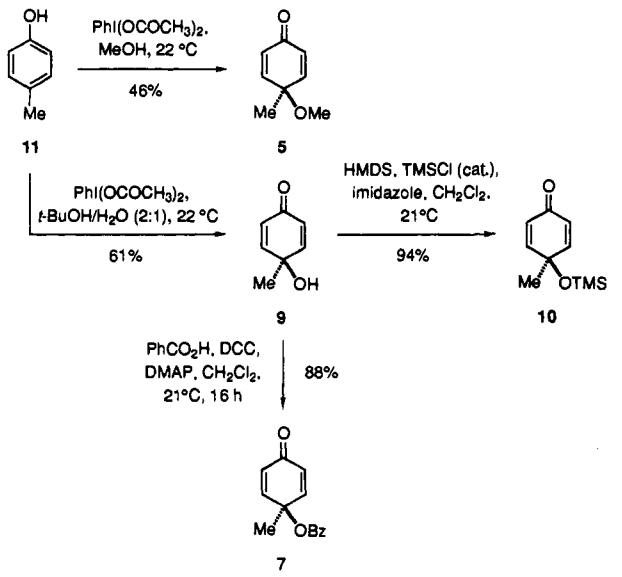
(8) (a) Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195. (b) Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649.

(9) The MM2 and AMBER parametrizations of MacroModel 3.5 were used. The calculated planar dienone geometry of **1** is supported by X-ray structural data of related cyclohexa-1,4-dienes with essentially planar geometries; the exact conformation of the ring in the solid state is controlled by crystal packing requirements: (a) Cheetham, A. K.; Grossel, M. C.; Newsam, J. M. *J. Am. Chem. Soc.* **1981**, *103*, 5363. (b) Jefford, C. W.; Bernardinelli, G.; McGoran, E. C. *Helv. Chim. Acta* **1984**, *67*, 1952. (c) Perry, N. B.; Blunt, J. W.; McCombs, J. D.; Munro, M. H. G. *J. Org. Chem.* **1986**, *51*, 5476. (d) Albertsson, J.; Oskarsson, A.; Svensson, C. *Acta Crystallogr., Sect. B* **1978**, *34*, 3027.

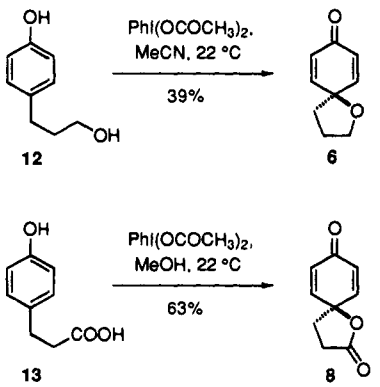
(10) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677. (c) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477.

(11) Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244.

Scheme 1



Scheme 2



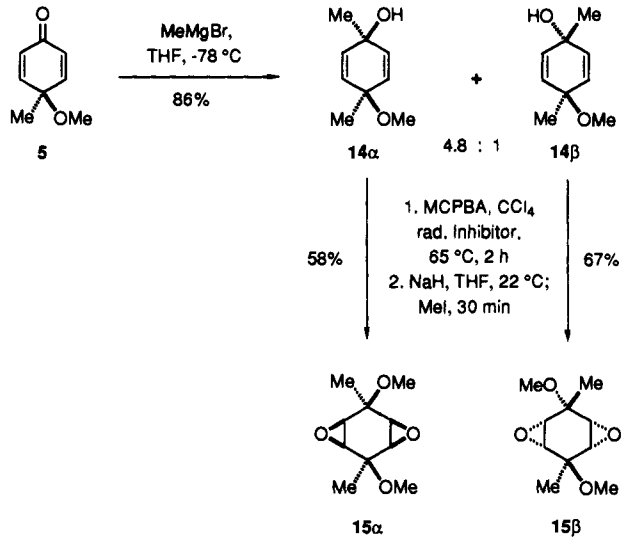
the subsequent determination of the facial selectivity of nucleophilic carbonyl additions. Due to the relative stability of the resulting methylated bis-allylic alcohols, we chose the addition of methylmagnesium bromide in THF at −78 °C as a standard reaction. Under these conditions, dienone **5** was rapidly converted in high yield into a 4.8:1 mixture of two diastereomers that were separated by chromatography on silica gel (Scheme 3).

In order to achieve an unambiguous structural assignment of the two diastereomers of **14**, each was subjected to a hydroxyl-directed[12] epoxidation in the presence of Kishi's[13] radical inhibitor. Subsequently, *O*-methylation with sodium hydride and methyl iodide provided methyl ethers **15**α,β in 58 and 67% overall yield, respectively. The C_{2v}-symmetric major isomer **15**α showed characteristically simple NMR spectra with three singlets in ^{1}H and four signals in ^{13}C. The less symmetric (C_s) minor isomer **15**β displayed the expected combination of four singlets and two multiplets in ^{1}H NMR and eight signals in ^{13}C NMR. These symmetry considerations established an unequivocal preference for α-face attack on dienone **5** leading to C,C-bond formation *anti* to the 4-methoxy substituent, in agreement with our earlier results obtained with spirocyclic dienones **1** and **3**.

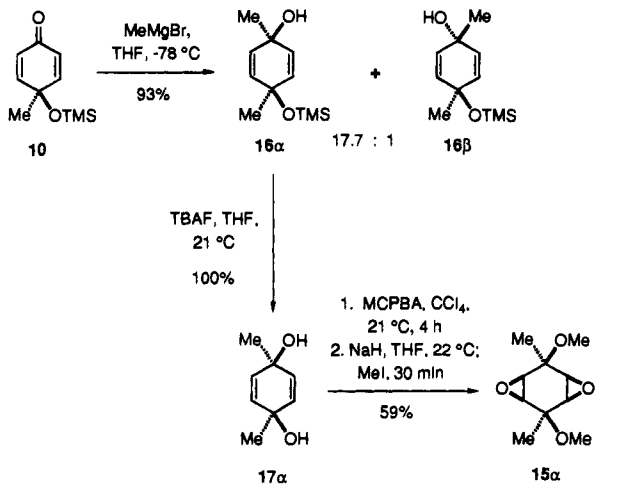
If complexation of the Grignard reagent to the oxygen substituent at the 4-position of dienone **5** had any influence on

(12) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958.
(13) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. Chem. Soc., Chem. Commun.* **1972**, 64.

Scheme 3



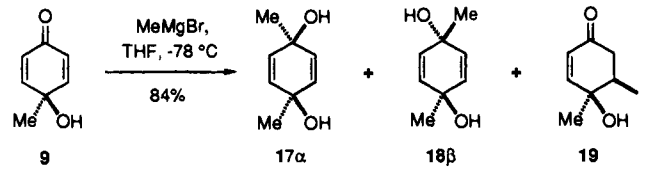
Scheme 4



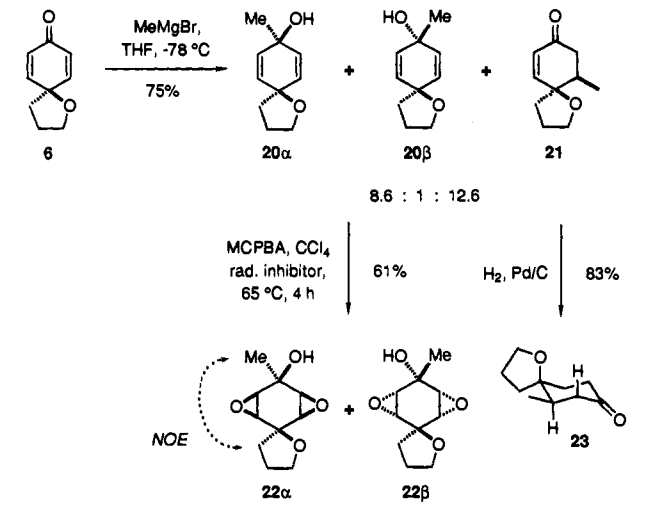
the stereochemical course of the nucleophilic addition to the remote carbonyl group, then such an effect would be expected to be more pronounced in alcohol **9** and significantly less effective in silyl ether **10**.[14] Treatment of **10** with methylmagnesium bromide in THF led, however, to a considerable increase in the facial selectivity, and a 17.7:1 ratio of **16**α,β was isolated in 93% yield (Scheme 4). After separation, the major isomer was deprotected to give diol **17**α. The tentative structural assignment of **16**α was validated by subsequent diepoxidation and *O*-methylation of **17**α to give the C_{2v}-symmetric **15**α. In contrast, treatment of alcohol **9** with an excess of Grignard reagent resulted in a reduced α/β selectivity of 7.9:1, as determined by integration of a mixture of **17**α and **18**β in ^{13}C NMR (Scheme 5). As expected,[14,15] alkoxide-directed conjugate addition provided enone **19** as the predominant reaction product (58%) in this process. The combined yield for 1,2-addition to the carbonyl group amounted to 26%, and the major isomer was spectroscopically identical to diol **17**α prepared by desilylation of **16**α. Additionally, the spectroscopic data for **17**α and **18**β were identical to literature values.[16]

(14) γ-Hydroxy enones such as **9** have been used by Liotta and Maryanoff and others in the study of ligand-assisted nucleophilic addition reactions: Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702 and references cited therein.
(15) Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synlett* **1992**, 127.

Scheme 5



Scheme 6



Somewhat surprisingly, conjugate addition was also the major reaction product for the spirocyclic ether **6** in the presence of methylmagnesium bromide (Scheme 6). Enone **21** was isolated in 42% yield in addition to an inseparable 8.6:1 mixture of **20**α,β. This mixture was epoxidized with MCPBA, and on the basis of the NOE effect between methylene and methyl groups in **22**α, the major isomer of the 1,2-addition pathway was identified as the α-addition product.

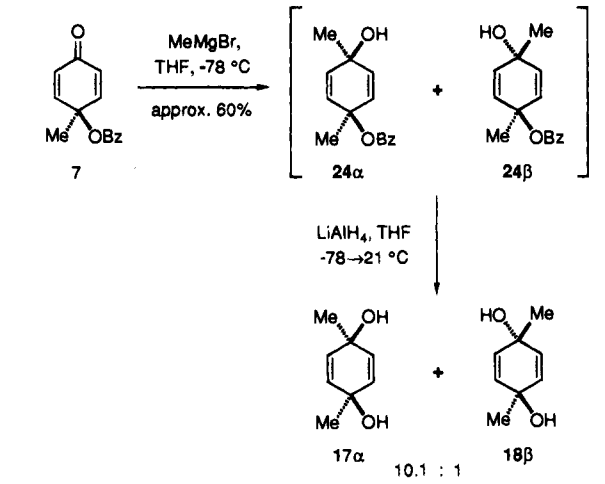
Due to the conformational flexibility of **21**, spectroscopic analysis did not allow for an unambiguous assignment of the relative stereochemistry at the methine carbon. The stereochemistry of the conjugate addition product **21** was determined as shown in Scheme 6 by conversion to the saturated derivative **23** and analysis of the vicinal coupling constant of the axial α-proton (J = 12.2 Hz).[17] The haptophilic effect of the tetrahydrofuran ring oxygen in **6** is therefore comparable to that of the alkoxide ligand in the Grignard addition to **9** and far superior to that of the methyl ether in **5**. This chelation skews the nucleophilic attack of the Grignard reagent toward conjugate addition from the β-face of the enone.

Treatment of 4-benzoyl dienone **7** with methylmagnesium bromide led to approximately 60% of a >8:1 mixture of allylic alcohols **24**α,β, as determined by integration of the crude ^{1}H NMR (Scheme 7). Due to the instability of these addition products, the crude mixture was directly subjected to an excess of $LiAlH_4$ in THF to give the previously characterized diols **17**α and **18**β in a 10.1:1 ratio.

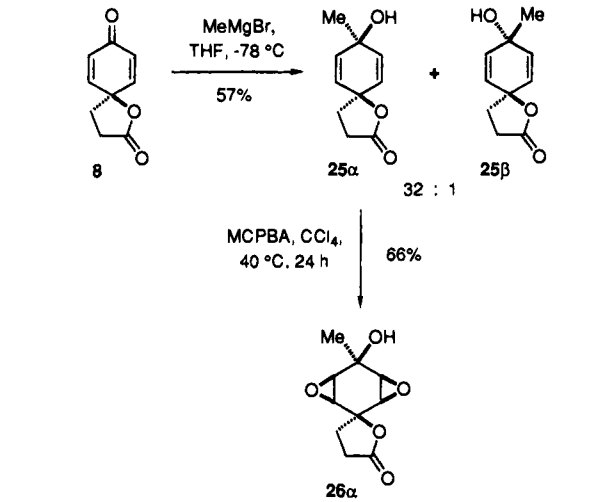
The spirocyclic analog of benzoate **7**, lactone **8**, provided the highest α-face selectivity observed thus far in this study. Allylic alcohols **25**α,β were detected in a ratio of 32:1 by NMR analysis of the crude reaction mixture after the Grignard reaction (Scheme 8). The major isomer decomposed more rapidly during further purification and chromatography, and a 23:1 ratio of **25**α,β was isolated in 57% yield. Epoxidation was performed

(16) Fischer, A.; Henderson, G. N. *Tetrahedron Lett.* **1980**, *21*, 701.
(17) See also: Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.

Scheme 7



Scheme 8



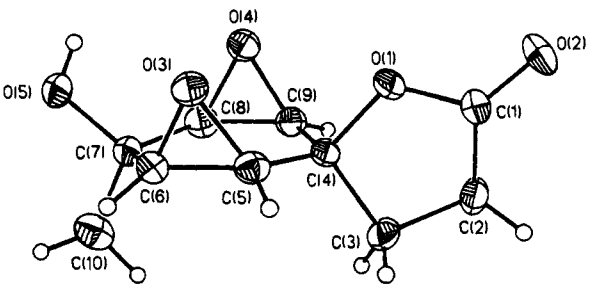


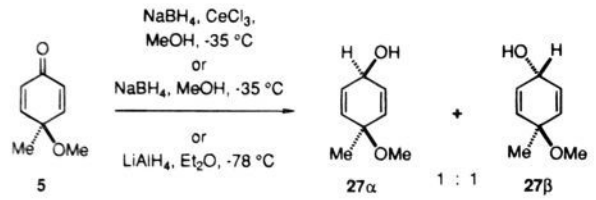
Figure 1.

on the mixture of diastereomers, and the major compound **26**α was crystallized and its structure unambiguously established by X-ray analysis (Figure 1).

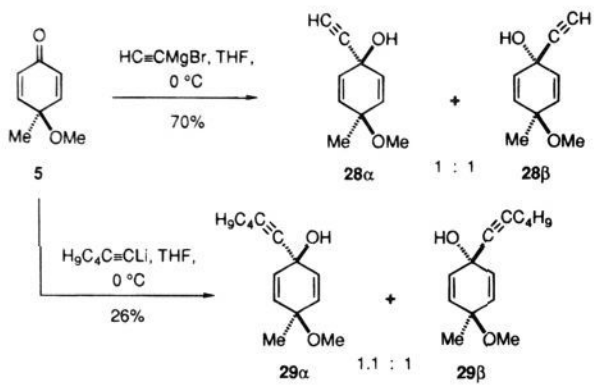
In order to expand the scope of our investigation of the facial selectivity in nucleophilic addition to cyclohexadienones, we also studied the course of reaction with hydride reagents, organolithium compounds, and sp^2- as well as sp-hybridized C-nucleophiles. In contrast to the addition of alkyl Grignard reagents, reduction of **5** with various hydride sources did not occur selectively and 1:1 mixtures of secondary alcohols **27**α,β were isolated (Scheme 9). Similarly, ethynylmagnesium bromide as well as hexynyllithium reacted without stereocontrol (Scheme 10).

Phenylmagnesium bromide, an example of an sp^2-hybridized carbon nucleophile added to dienone **5** predominantly from the α-face and in lower selectivity than the methyl Grignard reagent

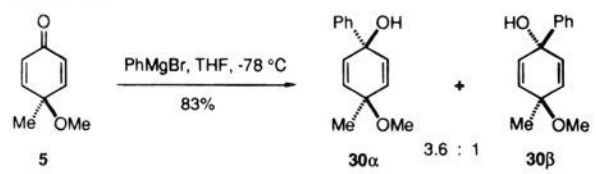
Scheme 9



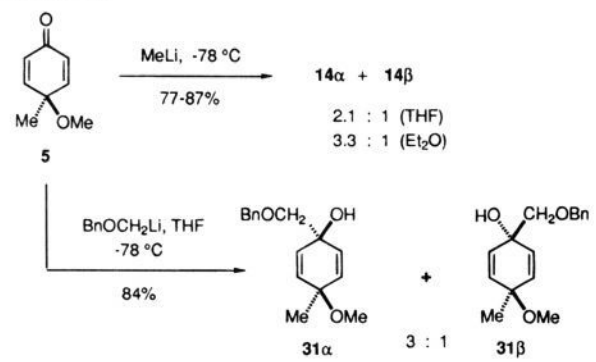
Scheme 10



Scheme 11



Scheme 12



(Scheme 11). A slight drop in stereoselectivity versus this standard was also observed when alkyllithium reagents were employed (Scheme 12). In contrast, a change in solvent from THF to the less polar Et_2O led to an improved α/β ratio.

These results, especially the lack of selective addition observed with reducing agents and sp-hybridized carbon nucleophiles, clearly illustrate the high sensitivity of the stereoselectivity of the 1,2-addition process toward the solvent medium, the electronic structure, and accordingly, the state of aggregation of the nucleophile. However, all variations of reaction parameters only led to an erosion of α-diastereoselectivity, and in no case were we able to observe a change in the facial selectivity toward an excess of β-attack. The results of this first phase of our experimental studies on 4,4-disubstituted dienones are summarized in Table 1.

Theoretical Model and Experimental Proof of Principle. We had initiated this study on the basis of the experimentally observed selectivity of aranorosin intermediate **1** to undergo

Table 1. Facial Selectivity in Nucleophilic Additions to Dienones

entry	dienone	nucleophile	product (% yield)	α/β selectivity
1	**1**	$BnOCH_2Li$	**2** (>50)	5:1
2	**3**	MeMgBr	**4** (84)	6:1
3	**5**	MeMgBr	**14** (86)	4.8:1
4	**5**	$NaBH_4$ or $LiAlH_4$	**27** (100)	1:1
5	**5**	HC≡CMgBr	**28** (70)	1:1
6	**5**	$H_9C_4C{\equiv}CLi$	**29** (26)	1.1:1
7	**5**	PhMgBr	**30** (83)	3.6:1
8	**5**	MeLi/THF	**14** (87)	2.1:1
9	**5**	MeLi/Et_2O	**14** (77)	3.3:1
10	**5**	$BnOCH_2Li$	**31** (84)	3:1
11	**6**	MeMgBr	**20** (75)	8.6:1
12	**7**	MeMgBr	**24** (>61)	10.1:1
13	**8**	MeMgBr	**25** (79)	32:1
14	**9**	MeMgBr	**17/18** (81)	7.9:1
15	**10**	MeMgBr	**16** (93)	17.7:1

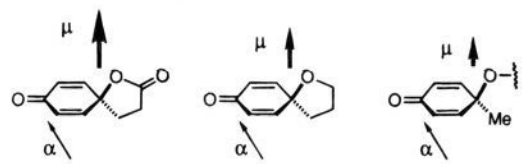
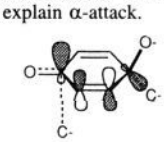


Figure 2. Qualitative order of dipole moments of dienones. The experimentally observed α-selectivity decreases from left to right.

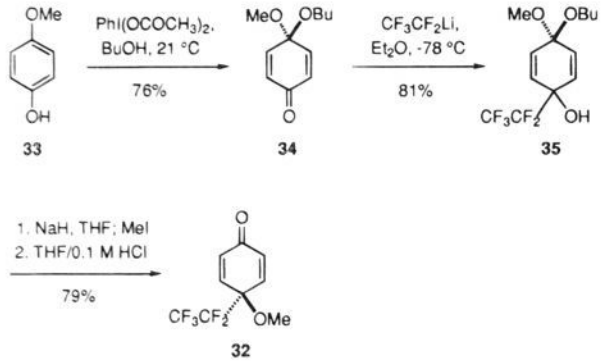
nucleophilic attack of an α-alkoxy organolithium reagent preferentially from the α-face of the dienone opposite the 4-alkoxy substituent. The data outlined in Table 1 confirmed that this represented indeed a general trend for 4,4-disubstituted cyclohexadienones. We were intrigued by the great variation of selectivity as a function of seemingly subtle changes at the 4-position, e.g. methyl ether **5** compared to spiroether **6** or benzoate **7** compared to spirolactone **8**. Whereas the Ahn–Eisenstein argumentation[2g] of transition state stabilization by $\sigma \rightarrow \sigma^*$ interaction of the newly forming σ-bond with the σ^* of the electronegative substituent accounted for the general increase in selectivity from 4-alkoxy to 4-acyloxy dienones, this theory did not easily lend itself to an explanation of the significant differences between monocyclic and spirocyclic systems or the high selectivity of the 4-silyloxy dienone **10**. Similar problems arose in the consideration of a "vinylogous Cieplak effect", e.g. the stabilization of the transition state by hyperconjugation of the newly forming σ^*-bond by the σ-orbital of the 4-alkyl substituent *via* a $\sigma-\pi^*-\sigma^*$ interaction.[18] Application of the principle of frontier orbital distortion as described by Burgess and Liotta[2i,3c] would lead to an (experimentally incorrect) prediction for β-selectivity. Therefore, we considered more closely the possibility of an electrostatic control mechanism in these dienone additions. Qualitatively, there appeared to be a reasonable correlation of the observed α-selectivity with the expected dipole moment of dienones **5**–**10** (Figure 2).

It is clear, however, that caution must be exercised in the qualitative use of a ground state parameter such as the molecular dipole moment in the explanation of kinetic selectivity. We argued that an appropriate test of the role of electrostatic control in the observed facial selectivity was the design of a substrate with an inverted dipole moment opposite the carbon–oxygen bond. In pentafluoroethyl dienone **32**, for example, electrostatic

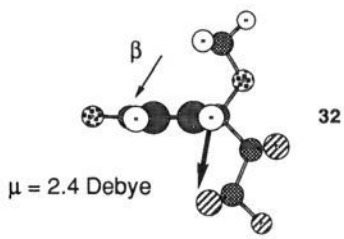
(18) The proposed hypothetical "vinylogous Cieplak" effect would be equivalent to an allylic inversion of the "normal Cieplak" effect and could thus in principle serve to explain α-attack.



Scheme 13



control should now lead to preferential β-face attack, whereas hyperconjugative transition state stabilization would still induce α-selectivity.

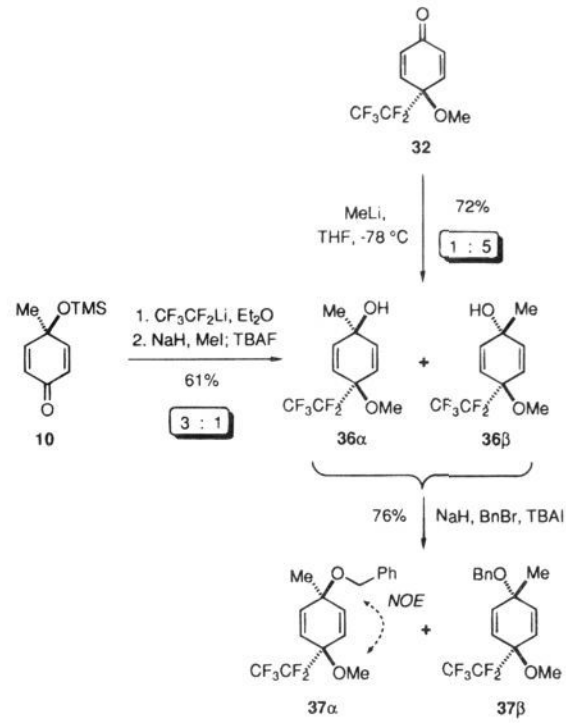


The synthesis of dienone **32** is shown in Scheme 13. Oxidation of *p*-methoxyphenol **33** in butanol provided mixed acetal **34** in 76% yield. Addition of (pentafluoroethyl)lithium[19] in ether resulted in 81% of the fluorinated alcohol **35** which was *O*-methylated and hydrolyzed to give the desired **32**.

Treatment of dienone **32** with methyllithium in THF led to a 1:5 mixture of diastereomeric alcohols **36** in 72% yield (Scheme 14). Indeed, as predicted by the electrostatic effect, the β-face addition product **36**β was isolated as the major product. The two isomers were correlated chemically to a 3:1 mixture of addition products of (pentafluoroethyl)lithium to dienone **10**, which was previously shown to undergo preferential α-attack. Additionally, the α-isomer was identified spectroscopically by a long-range NOE effect upon *O*-benzylation of **36** (Scheme 14).

The unique β-selectivity observed with the 4-fluoroalkyl-substituted dienone **32** represents clearly a significant support for dipolar control in these kinetically controlled nucleophilic additions. The importance of electric fields imposed by ionic groups or salts on the substrate reactivity is evident in enzymes and can also be used for specific rate acceleration in organic transformations.[20] However, our experimentally uniform studies with structurally closely related dienone substrates allowed us to address an additional intriguing question: Can the dipole moment be used for a *quantitative* prediction of facial selectivities? The electrostatic field of the substrate exercises a torque on any approaching reagent dipole and vice versa. The torque on the dipole is zero only when it is aligned with the electric field, and its potential energy is directly proportional to the dipole moment.[21] Accordingly, the dipole moment and possibly also the electrostatic potential at the site of attack should correlate linearly with the energy of activation of the addition

Scheme 14



process and the logarithm of the facial selectivity. This correlation would be analogous to a Hammett free-energy relationship.[22] However, in a series of 4,4-disubstituted dienones, only substrates with functional groups that are positioned in close vicinity to the dienone chromophore could be expected to lend themselves to a good quantitative correlation of facial selectivities with overall dipole moments. Our dienones **5**, **6**, and **8** fulfill this requirement, whereas **3**, **7**, and **10** appear too remotely functionalized and also sterically too hindered at the β-face. The introduction of functional groups that are in greater spatial separation from the center of reaction should have a diminishing electrostatic directing effect on the carbonyl addition but still contribute evenly to a change in the overall dipole moment.

We calculated the dipole moments of dienones **5**, **6**, and **8** with the semiempirical AM1 parameter set[23] on the SPARTAN[24] computational interface.[25] Optimized starting geometries were obtained from the MM2 and Sybyl force fields implemented in SPARTAN. The vector components of the calculated dipole moments orthogonal to the plane of the dienones ($\mu_\perp$) were correlated to the natural logarithm of the observed facial selectivities and linearly extrapolated. Upon the basis of this extrapolation and the calculated dipole moment of dienone **32**, the experimentally observed selectivity for nucleophilic attack of the fluorinated substrate **32** was indeed very closely matched

(19) (a) Gassman, P. G.; O'Reilly, N. J. *Tetrahedron Lett.* **1985**, *26*, 5241. (b) Gassman, P. G.; O'Reilly, N. J. *J. Org. Chem.* **1987**, *52*, 2481.

(20) (a) Warshel, A. *Acc. Chem. Res.* **1981**, *14*, 284. (b) Smith, P. J.; Kim, E. I.; Wilcox, C. S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1648.

(21) Weidner, R. T.; Sells, R. L. In *Elementary Classical Physics*; Allyn and Bacon: Boston, MA, 1965; Volume 2, pp 631–650.

(22) For correlations of log k_{ax}/k_{eq} vs Hammett constants σ_I in cycloketone additions, see refs 3e,n.

(23) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. AM1 has been shown to reproduce dipole moments of organic molecules with good accuracy: Stewart, J. J. P. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: Weinheim, Germany, 1991; pp 45–81.

(24) Hehre, W. J.; et al. SPARTAN, Version 3.1.2, Wavefunction, Inc., Irvine, CA.

(25) The dipole moment orthogonal to the dienone plane ($\mu_\perp$) of the *anti*-conformer of **5** was used; $\mu_\perp$ of the energetically more stable *syn*-conformer of **5** (methyl ether centered over the dienone ring) was zero. It is assumed that a Curtin–Hammett situation exists and the *anti*-isomer reacts faster due to electrostatic enhancement of the rate of addition of the polar nucleophile.

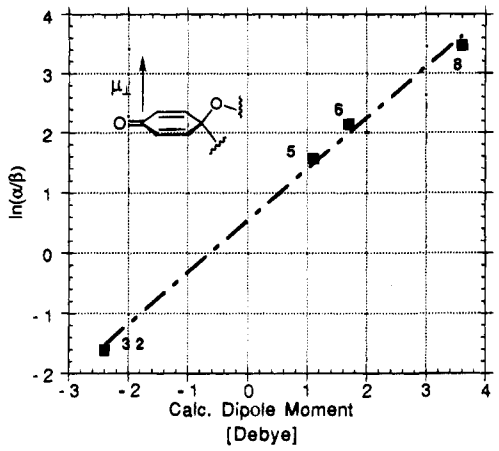


Figure 3. Least squares linear regression correlation of calculated dipole moments of dienones **5**, **6**, **8**, and **32** vs the logarithm of the experimentally observed facial selectivities in the nucleophilic carbonyl addition. The values of the components of the dipole moments orthogonal to the dienone plane ($\mu_\perp$) are given in debye [D]. Correlation coefficient $R = 0.998$.

(Figure 3).[26] The considerably more computer time intensive *ab initio* calculations of dienones **5**, **6**, **8**, and **32** with the 6-31G* and 6-31G** basis sets gave dipole moments $\mu_\perp$ within 10% of the AM1 values and identical graphical displays. To the best of our knowledge, this is the first example of a quantitative correlation between dipole moments and kinetic selectivities. The excellent linearity stresses the importance of electrostatic control in polar addition reactions to sterically unhindered carbonyl groups, even though the limited data set does not yet allow an unambigous generalization of this concept.[27] Further work with dienones and related substrates for nucleophilic additions will clarify if the present results reflect only a fortuitous cancellation of errors or indeed provide us with some insight into the early interactions in the transition states for polar addition reactions.

It is interesting to note that Figure 3 predicts an intrinsic selectivity for dienone additions even with $\mu_\perp$ equal zero. Quite possibly, this could be interpreted as a hyperconjugative effect of the C(4)–oxygen bond independent of electrostatic control. Also, we expect that both the ordinate intercept and the slope of the plot are a function of the heteroatom at C(4) and the nucleophile and could be useful for a classification of substituents and reagents. We plan to test this hypothesis in our future studies.

Conclusion

Our investigation of the facial selectivity of nucleophilic attack of 4,4-disubstituted dienones provides experimental evidence for dominant dipolar control in these carbonyl addition reactions. Hyperconjugative orbital stabilization in the Felkin–Ahn–Cieplak sense and orbital distortion effects appear to be of secondary importance. The excellent linear correlation of calculated dipole moments vs the logarithm of the facial selectivity supports the notion that, in the absence of steric hindrance, the kinetic selectivity of irreversible C,C-bond formation is strongly influenced by dipole–dipole interactions between reagent and substrate. Due to the distance equivalency of the substituents to the reaction center and the absence of steric and torsional effects, 4,4-disubstituted dienones can serve as powerful test cases for the study of stereoelectronic and electrostatic models.

(26) AM1 (SPARTAN) electrostatic potentials of dienones **1**, **3**, **5**–**10**, and **32**, correlated qualitatively but not quantitatively with the observed facial selectivites.

(27) Our correlation of ground state dipole moments with selectivities does not challenge the general validity of specific transition state analyses by semiempirical or *ab initio* methods. In fact, the magnitude of the dipole moment and the minimization of dipolar interactions can easily be reflected in the calculated $\Delta H_f°$: Jones, D. K.; Liotta, D. C.; Choi, W.-B.; Volante, R. P.; Reider, P. J.; Shinkai, I.; Churchill, H. R. O.; Lynch, J. E. *J. Org. Chem.* **1994**, *59*, 3749.

Experimental Section

General Methods. IR spectra were recorded on a IBM IR/32 spectrophotometer. NMR spectra were recorded on Bruker AM-500 or AM-300 spectrometers in $CDCl_3$ unless otherwise noted. Mass spectra were obtained on a VG-70-70 HF. Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl, P_2O_5, or CaH_2. All reactions were performed in oven-dried glassware under an argon or nitrogen atmosphere. Analytical TLC used Merck silica gel 60 F-254 plates, and flash chromatography was used to separate and purify the crude reaction mixtures.

4-Methoxy-4-methyl-2,5-cyclohexadienone (5). To a solution of 5.0 g (46.3 mmol) of *p*-cresol (**11**) in 100 mL of dry CH_3OH was added at 0 °C 16.7 g (50.9 mmol) of (diacetoxyiodo)benzene. The reaction mixture was stirred for 30 min at 21 °C, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution (2 × 40 mL) and brine, and dried ($MgSO_4$). Filtration and evaporation gave a dark brown residue which was chromatographed on silica gel (hexane/EtOAc, 2:1) to give 4.2 g of a deep yellow solid. The crude product was dissolved in 100 mL of hexanes, cooled to −78 °C, and filtered to give 2.94 g (46%) of **5** as a white solid: R_f (EtOAc/hexanes, 1:1) = 0.6; mp 53–54 °C; IR (neat) 2973, 1705, 1673, 1628, 1607, 1466, 1455, 1395, 1302, 1248, 1088, 1042, 868, 733, 696 cm^{-1}; ^1H NMR δ 6.74 (d, 2 H, J = 10.2 Hz), 6.27 (d, 2 H, J = 10.2 Hz), 3.16 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR δ 185.2, 151.8, 130.5, 72.7, 53.3, 26.3; MS (EI) *m/e* (relative intensity) 138 (M^+, 50), 123 (100), 110 (40), 107 (40), 95 (35), 77 (40), 67 (15), 63 (8), 51 (15), 43 (11), 39 (12); HRMS (EI) *m/e* calcd for $C_8H_{10}O_2$ 138.0681, found 138.0698.

1-Oxaspiro[4.5]deca-6,9-diene-8-one (6). To a solution of 100 g (0.6 mmol) of 3-(4-hydroxyphenyl)propanol (**12**) in 5 mL of EtOAc at 21 °C was added 240 mg (0.72 mmol) of (diacetoxyiodo)benzene. The reaction mixture was stirred for 30 min, diluted with EtOAc, and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give a dark brown residue which was chromatographed on silica gel (hexane/EtOAc, 1:1) to give 38 mg (39%) of **6** as a colorless liquid: R_f (EtOAc/hexanes, 1:1) = 0.5; IR 2977, 1669, 1630, 1397, 1250, 1084, 1036, 963, 924, 855 cm^{-1}; ^1H NMR δ 6.74 (d, 2 H, J = 10.0 Hz), 6.03 (d, 2 H, J = 10.0 Hz), 3.98 (t, 2 H, J = 6.4 Hz), 2.1–2.0 (m, 2 H), 2.0–1.9 (m, 2 H); ^{13}C NMR δ 185.4, 149.8, 126.9, 69.1, 36.7, 26.7; MS (EI) *m/e* (relative intensity) 150 (M^+, 8), 135 (1), 122 (4), 74 (20), 59 (30), 45 (30), 40 (100); HRMS (EI) *m/e* calcd for $C_9H_{10}O_2$ 150.0680, found 150.0678.

4-(Benzoyloxy)-4-methyl-2,5-cyclohexadienone (7). To a solution of 120 mg (0.98 mmol) of alcohol **9** in 2.5 mL of CH_2Cl_2 were added successively at 21 °C 180 mg (1.47 mmol) of benzoic acid, 303 mg (1.47 mmol) of DCC, and 1.2 mg (0.01 mmol) of DMAP. The resulting suspension was stirred for 16 h at 21 °C, diluted with EtOAc, and washed with H_2O and brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give a colorless residue which was chromatographed on silica gel (EtOAc/hexane, 2:1) to give 196 mg (88%) of **7** as a white solid: R_f (EtOAc/hexanes, 1:1) = 0.6; mp 84–85 °C; IR (neat) 2930, 1715, 1673, 1632, 1574, 1557, 1538, 1532, 1505, 1453, 1393, 1277, 1177, 1103, 1053, 1026, 860, 712, 666 cm^{-1}; ^1H NMR δ 7.99 (d, 2 H, J = 7.4 Hz), 7.58–7.50 (m, 1 H), 7.45–7.38 (m, 2 H), 6.97 (dd, 2 H, J = 12.0, 3.1 Hz), 6.27 (dd, 2 H, J = 12.0, 3.0 Hz), 1.68 (s, 3 H); ^{13}C NMR δ 185.0, 165.0, 149.3, 133.4, 129.7, 129.5, 128.5, 128.2, 74.6, 26.4; MS (CI) *m/e* (relative intensity) 229 ([M + 1]$^+$, 100), 123 (20), 105 (95).

1-Oxaspiro[4.5]deca-6,9-diene-2,8-dione (8). To a solution of 1.0 g (6.02 mmol) of 3-(4-hydroxyphenyl)propionic acid (**13**) in 15 mL of dry CH_3OH was added at 21 °C 2.2 g (6.62 mmol) of (diacetoxyiodo)-benzene. The reaction mixture was stirred for 30 min, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution and brine, and dried ($MgSO_4$). Filtration and evaporation gave a dark brown

residue which was chromatographed on silica gel (hexane/EtOAc, 1:1) to give 622 mg (63%) of **8** as a white solid: R_f (EtOAc/hexanes, 1:1) = 0.4; mp 110 °C; IR (neat) 2973, 2872, 1692, 1667, 1628, 1395, 1248, 1084, 1036, 963, 922, 855 cm^{-1}; ^1H NMR δ 6.85 (d, 2 H, J = 10.1 Hz), 6.28 (d, 2 H, J = 10.1 Hz), 2.78 (t, 2 H, J = 8.3 Hz), 2.37 (t, 2 H, J = 8.3 Hz); ^{13}C NMR δ 184.1, 175.2, 145.6, 129.3, 78.4, 32.4, 28.0; MS (EI) *m/e* (relative intensity) 164 (M^+, 80), 136 (25), 122 (40), 110 (20), 91 (53), 82 (30), 68 (10), 65 (20), 63 (20), 55 (100), 52 (20), 50 (12), 43 (13); HRMS (EI) calcd for $C_9H_8O_3$ 164.0478, found 164.0478.

4-Hydroxy-4-methyl-2,5-cyclohexadienone (9). To a solution of 200 g (1.85 mmol) of *p*-cresol (**11**) in 10 mL of *t*-BuOH and 5 mL of H_2O was added at 0 °C 670 g (2.0 mmol) of (diacetoxyiodo)benzene. The reaction mixture was stirred for 30 min at 21 °C and partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The organic layer was washed with brine and dried (Na_2SO_4). Filtration and evaporation gave a dark brown residue which was chromatographed on silica gel (hexane/EtOAc, 1:2) to give 134 mg (61%) of **9** as a viscous oil: R_f (EtOAc/hexanes, 2:1) = 0.3; IR (neat) 3393, 2980, 1669, 1651, 1622, 1397, 1092, 1065, 860 cm^{-1}; ^1H NMR δ 6.83 (dd, 2 H, J = 8.4, 1.6 Hz), 5.98 (dd, 2 H, J = 8.4, 1.8 Hz), 3.95 (s, 1 H), 1.39 (s, 3 H); ^{13}C NMR δ 186.0, 153.1, 126.6, 66.9, 26.7; MS (EI) *m/e* (relative intensity) 124 (M^+, 35), 109 (100), 96 (35), 81 (55), 77 (14), 69 (10), 55 (20), 51 (10), 43 (20); HRMS (EI) calcd for $C_7H_8O_2$ 124.0524, found 124.0530.

4-Methyl-4-((trimethylsilyl)oxy)-2,5-cyclohexadienone (10). To a solution of 108 mg (0.87 mmol) of alcohol **9** in 5 mL of CH_2Cl_2 were added successively at 21 °C 178 mg (2.61 mmol) of imidazole, 210 mg (1.3 mmol) of hexamethyldisilazane, and 10 mg (0.09 mmol) of TMSCl. The resulting suspension was stirred for 6 h, diluted with hexanes, and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give a colorless residue which was chromatographed on silica gel (hexane/EtOAc, 4:1) to give 159 mg (94%) of **10** as a white solid: R_f (EtOAc/hexanes, 1:1) = 0.8; mp 66–67 °C; IR (neat) 2980, 1663, 1626, 1601, 1391, 1302, 1252, 1183, 1130, 1086, 938, 841, 762 cm^{-1}; ^1H NMR δ 6.88 (d, 2 H, J = 10.1, Hz), 6.13 (d, 2 H, J = 10.1 Hz), 1.43 (s, 3 H), 0.09 (s, 9 H); ^{13}C NMR δ 185.6, 153.6, 126.9, 69.7, 29.7, 2.1; MS (EI) *m/e* (relative intensity) 180 (1), 149 (2.5), 124 ([M − C_3H_8Si]$^+$, 40), 109 (100), 96 (60), 81 (70), 77 (20), 68 (20), 53 (30), 43 (40); HRMS (EI) calcd for $C_7H_8O_2$ (M − C_3H_8Si) 124.0524, found 124.0508.

***syn*-4-Methoxy-1,4-dimethyl-2,5-cyclohexadienol (14α) and *anti*-4-Methoxy-1,4-dimethyl-2,5-cyclohexadienol (14β).** A solution of **5** (100 mg, 0.73 mmol) in 8 mL of dry THF was treated for 10 min at −78 °C with 3 mL (4.5 mmol) of CH_3MgBr (1.5 M solution in THF/toluene, 1:3). After 30 min, the reaction mixture was quenched with a 5% aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a colorless oil. Chromatography on silica gel (EtOAc/hexanes, 1:3) yielded 78 mg (70%) of **14α** as a colorless liquid and 18 mg (16%) of **14β** as a white solid. **14α**: R_f (EtOAc/hexanes, 1:1) = 0.35; IR (neat) 3395, 3023, 2975, 2930, 1399, 1366, 1136, 1071, 941, 783 cm^{-1}; ^1H NMR δ 6.00 (dd, 2 H, J = 8.3, 2.0 Hz), 5.62 (dd, 2 H, J = 8.3, 1.9 Hz), 3.12 (s, 3 H), 1.63 (s, 1 H), 1.31 (s, 3 H), 1.25 (s, 3 H); ^{13}C NMR δ 135.5, 131.2, 71.0, 65.8, 52.1, 28.8, 28.2; MS (EI) *m/e* (relative intensity) 154 (M^+, 0.3), 153 (0.2), 149 (0.2), 139 ([M − CH_3]$^+$, 100), 123 (90), 107 (50), 91 (20), 79 (10); HRMS (EI) calcd for $C_8H_{11}O_2$ (M − CH_3) 139.0759, found 139.0743. **14β**: R_f (EtOAc/hexanes, 1:1) = 0.4; mp 79 °C; IR (neat) 3413, 2975, 2930, 2355, 1456, 1366, 1136, 1069, 783, 687 cm^{-1}; ^1H NMR δ 6.00 (dd, 2 H, J = 12.9, 2.7 Hz), 5.57 (dd, 2 H, J = 12.9, 2.7 Hz), 3.02 (s, 3 H), 1.74 (s, 1 H), 1.33 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR δ 136.3, 131.1, 71.0, 65.7, 51.6, 28.1, 28.0; MS (EI) *m/e* (relative intensity) 154 (M^+, 2), 139 ([M − CH_3]$^+$, 100), 123 (25), 107 (20); HRMS (EI) calcd for $C_8H_{11}O_2$ (M − CH_3) 139.0759, found 139.0748.

(1*SR*,2*SR*,3*RS*,4*SR*,5*SR*,6*RS*)-2,3:5,6-Diepoxy-1,4-dimethoxy-1,4-dimethylcyclohexane (15α) from 14α. A solution of alcohol **14α** (52 mg, 0.34 mmol) in 3 mL of CCl_4 was treated with 296 mg (1.69 mmol) of MCPBA and 24 mg (0.07 mmol) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide. The resulting slurry was heated to 65 °C for 2 h. The solvent was removed under reduced pressure, and CH_2Cl_2 was added to dissolve the solid residue. Chromatography on SiO_2 (EtOAc/hexanes, 1:1) gave 42 mg (67%) of a diepoxy alcohol as a white solid: ^1H NMR δ 3.62 (s, 3 H), 3.26 (d, 2 H, J = 4.2 Hz), 3.09 (d, 2 H, J = 4.2 Hz), 2.86 (s, 1 H), 1.37 (s, 3 H), 1.29 (s, 3 H). A solution of crude diepoxide (36 mg, 0.19 mmol) in 2 mL of THF was treated at 0 °C with 76 mg (1.9 mmol) of NaH (60% emulsion in mineral oil) and 270 mg (1.9 mmol) of MeI. The reaction mixture was stirred for 30 min at 21 °C and partitioned between EtOAc and brine. The organic layer was dried (Na_2SO_4) and chromatographed on silica gel (EtOAc/hexanes, 1:4) to give 34 mg (87%) of **15α** as a white solid: R_f (EtOAc/hexanes, 1:1) = 0.7; mp 78 °C; IR (neat) 2977, 1455, 1215, 1161, 1103, 1049, 826 cm^{-1}; ^1H NMR δ 3.64 (s, 6 H), 3.12 (s, 4 H), 1.31 (s, 6 H); ^{13}C NMR δ 71.3, 56.3, 53.4, 22.3; MS (EI) *m/e* (relative intensity) 200 (M^+, 0.5), 185 ([M − CH_3]$^+$, 4), 169 (0.3), 162 (0.3), 153 (3), 141 (25), 125 (20), 109 (40), 95 (30), 89 (50), 83 (20), 72 (25), 67 (10), 59 (60), 53 (30); HRMS (EI) calcd for $C_9H_{13}O_4$ (M − CH_3) 185.0814, found 185.0807.

(1*SR*,2*SR*,3*RS*,4*SR*,5*SR*,6*RS*)-2,3:5,6-Diepoxy-1,4-dimethoxy-1,4-dimethylcyclohexane (15α) from 16α. A solution of 32 mg (0.15 mmol) of **16α** in THF (5 mL) was treated at 21 °C with 0.2 mL (0.2 mmol) of 1.0 M TBAF in THF. After 20 min, the reaction mixture was partitioned between EtOAc and brine. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give 20 mg (100%) of *syn*-1,4-dimethyl-2,5-cyclohexadien-1,4-diol (**17α**) as a white solid: R_f (EtOAc/hexanes, 1:1) = 0.3; ^1H NMR δ 5.76 (s, 4 H), 2.95 (bs, 2 H), 1.27 (s, 6 H); ^{13}C NMR δ 132.7, 65.4, 28.4; MS (EI) 125 ([M − CH_3], 100), 110 (35), 97 (15), 79 (20). The crude diol was dissolved in 10 mL of CCl_4 and treated at 21 °C with 132 mg (0.75 mmol) of MCPBA for 4 h. The solvent was removed under reduced pressure, and the solid residue was chromatographed on SiO_2 (EtOAc/hexanes, 10:1) to give 19 mg (71%) of *syn*-(2*SR*,3*RS*,5*SR*,6*RS*)-2,3:5,6-diepoxy-1,4-dimethyl-1,4-cyclohexanediol as a white solid: R_f (EtOAc) = 0.1; mp 138–140 °C; ^1H NMR (D_2O) δ 3.32 (s, 4 H), 1.38 (s, 6 H). A solution of 15 mg (0.09 mmol) of the diepoxy diol in 2 mL of THF was treated at 21 °C with 36 mg (0.9 mmol) of NaH (60% emulsion in mineral oil) and 128 mg (0.9 mmol) of MeI. The reaction mixture was stirred for 2 h and partitioned between EtOAc and brine. The organic layer was dried (Na_2SO_4) and chromatographed on SiO_2 (EtOAc/hexanes, 1:4) to give 15 mg (83%) of **15α** as a white solid. R_f, mp, IR, and ^1H NMR data were identical to those of the sample prepared from **14α**.

(1*SR*,2*RS*,3*SR*,4*RS*,5*RS*,6*SR*)-2,3:5,6-Diepoxy-1,4-dimethoxy-1,4-dimethylcyclohexane (15β). A solution of alcohol **14β** (15 mg, 0.1 mmol) in 1 mL of CCl_4 was treated with 85 mg (0.49 mmol) of mCPBA and 6.9 mg (0.02 mmol) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide. The resulting slurry was heated to 65 °C for 2 h, the solvent was removed under reduced pressure, and CH_2Cl_2 was added to dissolve the residue. Chromatography on SiO_2 (EtOAc/hexanes, 1:1) gave 13 mg (71%) of a diepoxy alcohol as a white solid: ^1H NMR δ 3.41 (s, 3 H), 3.22 (d, 2 H, J = 3.5 Hz), 3.17 (d, 2 H, J = 3.5 Hz), 2.86 (bs, 1 H), 1.54 (s, 3 H), 1.46 (s, 3 H). A solution of crude diepoxide (11 mg, 0.06 mmol) in 1 mL of THF was treated at 0 °C with 23 mg (0.58 mmol) of NaH (60% emulsion in mineral oil) and 82 mg (0.58 mmol) of MeI. The reaction mixture was stirred for 30 min at 21 °C and partitioned between EtOAc and brine. The organic layer was dried (Na_2SO_4) and chromatographed on SiO_2 (EtOAc/hexanes, 1:4) to give 21 mg (94%) of **15β** as a white solid: R_f (EtOAc/hexanes, 1:1) = 0.7; mp 38 °C; IR (neat) 2977, 1119, 1091, 1049, 833, 668 cm^{-1}; ^1H NMR δ 3.59 (s, 3 H), 3.42 (s, 3 H), 3.18 (d, 2 H, J = 3.8 Hz), 3.09 (d, 2 H, J = 3.8 Hz), 1.58 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR δ 71.3, 70.0, 57.6, 56.5, 52.5, 51.8, 21.7, 20.8; MS (EI) *m/e* (relative intensity) 200 (M^+, 0.5), 185 ([M − CH_3]$^+$, 4), 169 (0.3), 162 (0.3), 153 (4), 141 (25), 125 (20), 109 (40), 95 (30), 89 (50), 83 (20), 72 (25), 67 (10), 59 (60), 53 (30); HRMS (EI) calcd for $C_9H_{13}O_4$ (M − CH_3) 185.0814, found 185.0828.

***syn*-1,4-Dimethyl-4-((trimethylsilyl)oxy)-2,5-cyclohexadienol (16α) and *anti*-1,4-Dimethyl-4-((trimethylsilyl)oxy)-2,5-cyclohexadienol (16β).** To a solution of **10** (102 mg, 0.52 mmol) in dry THF (10 mL) was added dropwise at −78 °C 3.5 mL (5.2 mmol) of CH_3MgBr (1.5 M solution in THF/toluene, 3:1). After 30 min, the reaction mixture was quenched with 5% aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a colorless oil. Chromatographic separation on SiO_2 (EtOAc/hexanes, 1:1) gave 97 mg (88%) of **16α**

and 5.5 mg (5%) of **16β** as white solids. **16α**: R_f (EtOAc/hexanes, 1:1) = 0.6; mp 32−34 °C; IR (neat) 3386, 3029, 2971, 2926, 1402, 1364, 1250, 1138, 1092, 1015, 939, 912, 864, 841, 776 cm^{-1}; ^{1}H NMR δ 5.84 (d, 2 H, J = 10.3 Hz), 5.76 (d, 2 H, J = 10.3 Hz), 1.35 (s, 3 H), 1.31 (s, 3 H), 0.07 (s, 9 H); ^{13}C NMR δ 133.7, 131.4, 68.4, 65.7, 31.4, 28.8, 2.5; MS (EI) *m/e* (relative intensity) 197 ([M − CH_3]$^+$, 80), 181 (100), 163 (15), 149 (20), 122 (20), 105 (60), 91 (10), 75 (45), 43 (10); HRMS (EI) calcd for $C_{10}H_{17}O_2Si$ (M − CH_3) 197.0998, found 197.0992. **16β**: R_f (EtOAc/hexanes, 1:1) = 0.5; mp 53−54 °C; IR (neat) 3584, 3386, 3027, 2971, 1455, 1402, 1362, 1250, 1138, 1092, 1013, 939, 864, 841, 776 cm^{-1}; ^{1}H NMR δ 5.78 (dd, 2 H, J = 9.3, 2.1 Hz), 5.71 (dd, 2 H, J = 9.3, 2.0 Hz), 1.87 (s, 1 H), 1.24 (s, 3 H), 1.22 (s, 3 H), 0.07 (s, 9 H); ^{13}C NMR δ 134.9, 131.8, 68.2, 65.7, 31.8, 27.4, 2.3; MS (EI) *m/e* (relative intensity) 197 ([M − CH_3]$^+$, 100), 181 (80), 163 (10), 149 (10), 122 (10), 105 (30), 91 (10), 75 (25); HRMS (EI) calcd for $C_{10}H_{17}O_2Si$ (M − CH_3) 197.0998, found 197.1002.

***syn*-1,4-Dimethyl-2,5-cyclohexadien-1,4-diol (17α), *anti*-1,4-Dimethyl-2,5-cyclohexadien-1,4-diol (18β), and (4*RS*,5*RS*)-4,5-Dimethyl-4-hydroxy-2-cyclohexenone (19).** To a solution of **9** (127 mg, 1.02 mmol) in 10 mL of dry THF was added dropwise during 10 min at −78 °C 0.7 mL (10.2 mmol) of CH_3MgBr (1.5 M solution in THF/toluene, 3:1). After 30 min, the reaction mixture was quenched with 5% aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a colorless oil. Chromatographic separation on SiO_2 (EtOAc/hexanes, 1:1) gave 37.2 mg (26%) of a 7.9:1 mixture of **17α** and **18β** as white solids and 82.8 mg (58%) of **19** as a colorless oil. R_f, ^{1}H NMR, and ^{13}C NMR data for **17α** were identical to those of the sample prepared earlier from **16α** and literature[16] values. **18β**: [16] R_f (EtOAc/hexanes, 1:1) = 0.28; ^{1}H NMR δ 5.80 (s, 4 H), 1.32 (s, 6 H); ^{13}C NMR δ 133.3, 65.3, 28.3. **19**: R_f (EtOAc/hexanes, 1:1) = 0.61; mp 50−51 °C; IR (neat) 3391, 2971, 2942, 2886, 1663, 1505, 1455, 1424, 1379, 1267, 1198, 1129, 1086, 1013, 932, 853, 793, 725, 685 cm^{-1}; ^{1}H NMR δ 6.67 (d, 1 H, J = 10.0 Hz), 5.83 (d, 1 H, J = 10.0 Hz), 2.73 (bs, 1 H), 2.41 (dd, 1 H, J = 16.6, 10.1 Hz), 2.30 (dd, 1 H, J = 16.6, 4.4 Hz), 2.09 (dddq, 1 H, J = 10.1, 6.8, 4.4, 1.6 Hz), 1.38 (s, 3 H), 1.02 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 200.4, 154.1, 128.0, 69.1, 42.0, 38.8, 27.1, 14.7; MS (EI) *m/e* (relative intensity) 140 (M$^+$, 20), 125 ([M − CH_3]$^+$, 20), 107 (25), 98 (100), 91 (100), 79 (20), 70 (30), 55 (40), 40 (60); HRMS (EI) calcd for $C_8H_{12}O_2$ 140.0837, found 140.0827.

(5*RS*,10*RS*)-10-Methyl-1-oxaspiro[4.5]dec-6-en-8-one (21), (5*SR*,6*RS*,7*SR*,8*SR*,9*SR*,10*RS*)-6,7:9,10-Diepoxy-8-hydroxy-8-methyl-1-oxaspiro[4.5]decane (22α), and (5*SR*,6*RS*,7*SR*,8*SR*,9*RS*,10*SR*)-6,7:9,10-Diepoxy-8-hydroxy-8-methyl-1-oxaspiro[4.5]decane (22β). To a solution of **6** (30 mg, 0.2 mmol) in dry THF (3 mL) was added dropwise for 10 min at −78 °C 0.3 mL (2.0 mmol) of CH_3MgBr (1.5 M solution in THF/toluene, 1:3). After 30 min, the reaction mixture was quenched with 5% aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The colorless residue was chromatographed on SiO_2 (EtOAc/hexanes, 1:1) to give 10.6 mg (32%) of an inseparable 8.6:1 mixture of **20α,β** as a colorless liquid and 13.9 mg (42%) of **21** as a colorless oil. **20α**: R_f (EtOAc/hexanes, 1:1) = 0.4; ^{1}H NMR δ 5.82 (d, 2 H, J = 10.0 Hz), 5.70 (d, 2 H, J = 10.0 Hz), 3.91 (t, 2 H, J = 6.7 Hz), 2.57 (bs, 1 H), 2.06−1.97 (m, 2 H), 1.78 (t, 2 H, J = 7.3 Hz), 1.25 (s, 3 H); ^{13}C NMR δ 133.5, 129.9, 76.2, 68.0, 65.3, 38.4, 28.3, 26.4; MS (EI) *m/e* (relative intensity) 166 (M$^+$, 30), 151 (50), 123 (100), 121 (30), 108 (20), 95 (20), 77 (20), 65 (15), 55 (12); HRMS (EI) calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0987. **20β**: R_f (EtOAc/hexanes, 1:1) = 0.4; ^{1}H NMR δ 1.31 (s, 3 H); ^{13}C NMR δ 134.0, 130.5. **21**: R_f (EtOAc/hexanes, 1:1) = 0.6; IR (neat) 2967, 2874, 1682, 1462, 1385, 1281, 1237, 1200, 1140, 1067, 1034, 926, 864, 77, 737 cm^{-1}; ^{1}H NMR δ 6.61 (d, 1 H, J = 10.0 Hz), 5.87 (d, 1 H, J = 10.0 Hz), 4.0−3.85 (m, 2 H), 2.47 (dd, 1 H, J = 16.8, 2.4 Hz), 2.42 (dd, 1 H, J = 16.8, 3.0 Hz), 2.21 (ddq, 1 H, J = 6.8, 3.0, 2.4 Hz), 2.16−2.10 (m, 1 H), 2.05−1.95 (m, 2 H), 1.93−1.85 (m, 1 H), 1.03 (d, 3 H, J = 6.8 Hz); ^{13}C NMR δ 199.4, 152.2, 127.4, 81.5, 68.8, 43.3, 38.2, 35.8, 26.2, 14.9; MS (EI) *m/e* (relative intensity) 166 (M$^+$, 0.3), 151 (0.3), 147 (0.1), 138 (10), 124 ([M − C_3H_6]$^+$, 100), 96 (20), 82 (20), 77 (10), 68 (15), 55 (50); HRMS (EI) calcd for $C_7H_8O_2$ (M − C_3H_6) 124.0524, found 124.0517. A solution of **20α,β** (9.0 mg, 0.05 mmol) in 2 mL of CCl_4 was treated with 47 mg (0.27 mmol) of MCPBA and 6 mg (0.02 mmol) of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide. The resulting suspension was heated to 65 °C for 4 h, the solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2. Chromatography on SiO_2 (EtOAc/hexanes, 1:1) gave 6.6 mg (61%) of a 8.6:1 mixture of **22α,β** as a viscous oil. **22α**: R_f (EtOAc/hexanes, 1:1) = 0.1; IR (neat) 3403, 2957, 2886, 1460, 1383, 1291, 1161, 1127, 1067, 1048, 922, 885, 868, 853, 714 cm^{-1}; ^{1}H NMR δ 4.07 (t, 2 H, J = 6.6 Hz), 3.16 (s, 4 H), 2.99 (bs, 1 H), 2.15−2.05 (m, 2 H), 2.0−1.9 (m, 2 H), 1.34 (s, 3 H); ^{13}C NMR δ 78.5, 69.0, 66.9, 60.3, 59.8, 33.7, 26.3, 22.5; MS (EI) *m/e* (relative intensity) 198 (M$^+$, 30), 169 (10), 149 (17), 137 (15), 113 (100), 100 (35), 87 (50), 71 (60), 58 (30); HRMS (EI) calcd for $C_{10}H_{14}O_4$ 198.0892, found 198.0909. **22β**: ^{1}H NMR δ 4.12 (t, 2 H, J = 6.6 Hz), 3.09 (s, 4 H), 2.34−2.29 (m, 2 H), 1.54 (s, 3 H); ^{13}C NMR δ 70.2, 58.3, 56.2, 34.5, 25.5, 23.8.

(5*SR*,6*RS*)-6-Methyl-1-oxaspiro[4.5]dec-6-en-8-one (23). A solution of 46 mg (0.28 mmol) of enone **21** in MeOH (5 mL) was treated with 10 mg of 10% Pd/C. Hydrogen gas was bubbled for 30 min through the suspension. The reaction mixture was filtered through a short plug of Celite, the solvent was removed, and the oily residue was diluted with 20 mL of hexanes and washed with brine. The organic layer was dried (Na_2SO_4), concentrated *in vacuo*, and chromatographed on SiO_2 (EtOAc/hexanes, 1:10) to give 39 mg (83%) of **23** as a colorless oil: R_f (EtOAc/hexanes, 1:1) = 0.72; ^{1}H NMR δ 3.94−3.79 (m, 2 H), 2.63 (ddd, 1 H, J = 14.5, 13.0, 6.4 Hz), 2.42 (dd, 1 H, J = 14.3, 12.2 Hz), 2.24−2.16 (m, 2 H), 2.07−1.84 (m, 5 H), 1.72−1.61 (m, 2 H), 0.93 (d, 3 H, J = 6.6 Hz); ^{13}C NMR δ 212.1, 82.0, 68.3, 46.3, 40.4, 38.3, 36.8, 34.4, 26.5, 15.7.

***syn*-4-(Benzoyloxy)-1,4-dimethyl-2,5-cyclohexadien-1-ol (24α) and *anti*-4-(Benzoyloxy)-1,4-dimethyl-2,5-cyclohexadien-1-ol (24β).** To a solution of **7** (100 mg, 0.44 mmol) in 5 mL of dry THF was added dropwise for 10 min at −78 °C 0.3 mL (0.5 mmol) of CH_3MgBr (1.5 M solution in THF/toluene, 1:3). After 30 min, the reaction mixture was quenched with 5% aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give an >8:1 mixture of **24α,β** as a light yellow oil that decomposed rapidly at 21 °C. **24α**: R_f (EtOAc/hexanes, 1:1) = 0.5; ^{1}H NMR δ 7.96 (d, 2 H, J = 8.0 Hz), 7.6−7.5 (m, 1 H), 7.40 (t, 2 H, J = 8.0 Hz), 6.01 (d, 2 H, J = 9.9 Hz), 5.82 (d, 2 H, J = 9.9 Hz), 3.48 (bs, 1 H), 1.53 (s, 3 H), 1.36 (s, 3 H). A solution of 10 mg of crude **24α,β** in THF (5 mL) was treated at −78 °C with 10 mg (0.27 mmol) of $LiAlH_4$. The reaction mixture was slowly warmed to 21 °C, and stirring was continued for 20 min at this temperature. The solution was cooled to −10 °C, quenched with a mixture of the saturated aqueous $NaHCO_3$ and brine, and washed with EtOAc (2 × 10 mL), and the organic layer was separated, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was chromatographed on SiO_2 (EtOAc/hexanes, 1:1) to give 5.6 mg of a 10.1:1 mixture of **17α** and **18β**.

***syn*-8-Hydroxy-8-methyl-1-oxaspiro[4.5]deca-6,9-dien-2-one (25α) and *anti*-8-Hydroxy-8-methyl-1-oxaspiro[4.5]deca-6,9-dien-2-one (25β).** To a solution of **8** (95 mg, 0.58 mmol) in dry THF (7 mL) was added dropwise for 10 min at −78 °C 0.6 mL (0.87 mmol) of CH_3MgBr (1.4 M solution in THF/toluene, 1:3). After 30 min, the reaction mixture was quenched with 5% aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give a 32:1 mixture of **25α,β** as a colorless oil according to ^{1}H NMR analysis. Chromatographic separation on SiO_2 (benzene/acetone, 3:1) gave 57.4 mg (55%) of **25α** as a colorless liquid and 2.5 mg (2.4%) of **25β** as a white solid. **25α**: R_f (benzene/acetone, 1:1) = 0.45; IR (neat) 3413, 2970, 1769, 1698, 1682, 1455, 1410, 1361, 1302, 1181, 1123, 1071, 1015, 967, 912, 860, 810, 781, 756, 668 cm^{-1}; ^{1}H NMR δ 5.92 (d, 2 H, J = 10.1 Hz), 5.70 (d, 2 H, J = 10.1 Hz), 3.22 (bs, 1 H), 2.57 (t, 2 H, J = 8.3 Hz), 2.04 (t, 2 H, J = 8.3 Hz), 1.20 (s, 3 H); ^{13}C NMR δ 176.5, 136.0, 126.5, 79.1, 65.1, 34.4, 28.5, 28.3; MS (EI) *m/e* (relative intensity) 180 (M$^+$, 20), 165 (30), 134 (2.5), 121 (35), 108 (15), 91 (10), 77 (13), 65 (7), 56 (10), 55 (100), 53 (10), 51 (10), 43 (30), 41 (10); HRMS (EI) calcd for $C_{10}H_{12}O_3$ 180.0786, found 180.0786. **25β**: R_f (benzene/acetone, 1:1) = 0.40; mp 112 °C; IR (neat) 3260, 3017, 2980, 1769, 1451, 1414, 1364, 1304, 1207, 1184, 1123, 1084, 1008, 968, 911, 789 cm^{-1}; ^{1}H NMR δ 6.06 (d, 2 H, J = 9.3 Hz), 5.80 (d, 2 H, J = 9.3 Hz), 2.68 (t, 2 H, J = 8.3 Hz), 2.20 (t,

2 H, J = 8.3 Hz), 1.83 (bs, 1 H), 1.37 (s, 3 H); ^{13}C NMR δ 176.4, 137.2, 127.1, 79.1, 65.5, 34.1, 28.8, 27.9; MS (EI) *m/e* (relative intensity) 180 (M^+, 2), 165 ([M − CH_3]$^+$, 40), 125 (25), 108 (20), 91 (10), 77 (11), 65 (10), 55 (100).

(5*SR*,6*RS*,7*SR*,8*SR*,9*SR*,10*RS*)-6,7:9,10-Diepoxy-8-hydroxy-8-methyl-1-oxaspiro [4.5]decan-2-one (26α). A solution of alcohol **25**α (101 mg, 0.56 mmol) in 3 mL of CCl_4 and 0.3 mL of CH_2Cl_2 was treated with 970 mg (5.62 mmol) of MCPBA. The resulting suspension was heated to 40 °C for 24 h, the solvent was removed under reduced pressure, and CH_2Cl_2 was added to dissolve the solid residue. Chromatography on SiO_2 (EtOAc/hexanes, 1:1, then EtOAc) gave 79 mg (66%) of **26**α as a white solid (recrystallized from acetone and EtOAc for X-ray analysis): R_f (benzene/acetone, 1:1) = 0.17; mp 110 °C; IR (neat) 3430, 2982, 1734, 1701, 1474, 1458, 1375, 1242, 1169, 1111, 1048, 941, 841, 733 cm^{-1}; ^{1}H NMR δ 3.25 (d, 2 H, J = 3.8 Hz), 3.20 (d, 2 H, J = 3.8 Hz), 2.76 (bs, 1 H), 2.70 (t, 2 H, J = 8.6 Hz), 2.19 (t, 2 H, J = 8.6 Hz), 1.33 (s, 3 H); ^{13}C NMR (D_2O/CD_3OD) δ 179.8, 83.8, 67.6, 61.1, 58.7, 28.8, 28.6, 23.5; MS (EI) *m/e* (relative intensity) 212 (M^+, 1), 183 (5), 169 (6), 165 (2), 153 (10), 123 (12), 111 (10), 95 (35), 81 (25), 71 (20), 55 (30); MS (CI) 213 ([M + 1]$^+$, 100), 195 (20), 167 (25), 153 (30), 139 (10), 125 (10), 111 (15), 95 (10).

***syn*-4-Methoxy-4-methyl-2,5-cyclohexadien-1-ol (27α) and *anti*-4-Methoxy-4-methyl-2,5-cyclohexadien-1-ol (27β).** To a solution of 20 mg (0.14 mmol) of **5** and 108 mg (0.28 mmol) of $CeCl_3$·$7H_2O$ in 5 mL of MeOH was added 6 mg (0.14 mmol) of $NaBH_4$ in three portions at 0 °C. The reaction mixture was quenched by addition of 0.1 mL of acetone and diluted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give 20 mg (92%) of an inseparable mixture of **27**α,β as a white solid: R_f (EtOAc/hexanes, 3:2) = 0.5; IR (neat) 3339, 3029, 2977, 2934, 2824, 1516, 1451, 1408, 1366, 1266, 1221, 1132, 1090, 1048, 889, 862, 820, 756, 698, 652 cm^{-1}; ^{1}H NMR δ 6.10 (dd, 2 H, J = 10.2, 3.1 Hz), 6.02 (dd, 2 H, J = 10.2, 3.0 Hz), 5.69−5.63 (m, 4 H), 4.41 (bs, 2 H), 3.09 (s, 3 H), 2.99 (s, 3 H), 2.26 (bs, 2 H), 1.30 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR δ 132.8, 132.5, 131.9, 103.8, 70.9, 70.6, 62.4, 62.1, 51.9, 51.3, 28.2, 28.0; MS (EI) *m/e* (relative intensity) 107 ([M − CH_3OH − H]$^+$, 100), 90 (12), 77 (18), 59 (10), 51 (9), 45 (9); HRMS (EI) calcd for C_7H_7O (M − CH_3OH − H) 107.0497, found 107.0494.

***syn*-1-Ethynyl-4-methoxy-4-methyl-2,5-cyclohexadien-1-ol (28α) and *anti*-1-Ethynyl-4-methoxy-4-methyl-2,5-cyclohexadien-1-ol (28β).** To a solution of **5** (35 mg, 0.25 mmol) in 5 mL of dry THF was added dropwise for 10 min at −78 °C 0.75 mL (0.75 mmol) of C_2HMgBr (1.0 M solution in THF). The reaction mixture was slowly warmed to 0 °C. After 30 min, the reaction mixture was quenched with 5% aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and chromatographed on SiO_2 (EtOAc/hexanes, 1:3) to give an inseparable mixture of 29 mg (70%) of **28**α,β as a colorless yellow solid: R_f (EtOAc/hexanes, 1:1) = 0.5; IR (neat) 3312, 3245, 2936, 2830, 2363, 2350, 1470, 1372, 1092, 1049, 768, 683, 652, 617 cm^{-1}; ^{1}H NMR δ 6.09 (d, 2 H, J = 10.0 Hz), 6.04 (d, 2 H, J = 10.0 Hz), 5.73 (d, 2 H, J = 10.0 Hz), 5.70 (d, 2 H, J = 10.0 Hz), 3.09 (s, 3 H), 3.06 (s, 3 H), 2.76 (s, 2 H), 2.53 (s, 2 H), 1.30 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR δ 132.1, 131.2, 84.7, 84.3, 72.9, 72.7, 70.8, 70.4, 61.5, 61.1, 52.2, 51.9, 27.6; MS (EI) *m/e* (relative intensity) 164 (M^+, 3), 149 ([M − CH_3]$^+$, 95), 133 (100), 115 (55), 105 (60), 91 (30), 77 (45), 63 (20), 51 (20); HRMS (EI) calcd for $C_9H_9O_2$ (M − CH_3) 149.0603, found 149.0603.

***syn*-1-(1-Hexynyl)-4-methoxy-4-methyl-2,5-cyclohexadien-1-ol (29α) and *anti*-1-(1-Hexynyl)-4-methoxy-4-methyl-2,5-cyclohexadien-1-ol (29β).** To a solution of 1-hexyne (45 mg, 0.36 mmol) in dry THF (5 mL) was added dropwise for 5 min at −78 °C 0.85 mL of *t*-BuLi (1.7 M solution in pentane, 1.8 mmol). A solution of **5** in 2 mL of THF was added to the reaction mixture at −78 °C. The solution was slowly warmed to 0 °C over 30 min, quenched by addition of 5% aqueous $NaHCO_3$ solution, and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and chromatographed on SiO_2 (EtOAc/hexanes, 1:3) to give 9.7 mg (14%) of **29**α and 8.6 mg (12%) of **29**β as colorless liquids. **29**α: R_f (EtOAc/hexanes, 1:1) = 0.55; IR (neat) 3692, 3677, 3652, 3631, 3569, 3384, 3031, 2959, 2934, 2874, 2824, 2200, 1460, 1406, 1366, 1152, 1090, 1049, 862, 781 cm^{-1}; ^{1}H NMR δ 6.03 (dd, 2 H, J = 8.2, 1.7 Hz), 5.68 (dd, 2 H, J = 8.2, 1.8 Hz), 3.19 (s, 3 H), 2.24 (bs, 1 H), 2.19 (t, 2 H, J = 7.1 Hz), 1.50−1.33 (m, 4 H), 1.29 (s, 3 H), 0.89 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 132.2, 131.2, 85.8, 81.0, 70.8, 61.5, 52.2, 30.5, 27.8, 22.0, 18.5, 13.6; MS (EI) *m/e* (relative intensity) 220 (M^+, 50), 205 (100), 187 (30), 177 (60), 171 (20), 159 (90), 145 (60), 135 (50), 129 (55), 121 (70), 115 (60), 105 (100), 91 (60), 81 (85), 72 (30), 65 (40), 55 (50), 50 (7); HRMS (EI) calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1459. **29**β: R_f (EtOAc/hexanes, 1:1) = 0.6; IR (neat) 3382, 2959, 2932, 2872, 2200, 1090, 1049 cm^{-1}; ^{1}H NMR δ 6.09 (d, 2 H, J = 11.3 Hz), 5.65 (d, 2 H, J = 11.3 Hz), 3.07 (s, 3 H), 2.19 (t, 2 H, J = 6.7 Hz), 2.17 (bs, 1H), 1.64−1.32 (m, 4 H), 1.31 (s, 3 H), 0.88 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 133.1, 131.2, 86.0, 80.7, 70.3, 61.9, 51.9, 30.5, 27.8, 21.9, 18.4, 13.6; MS (EI) *m/e* (relative intensity) 220 (M^+, 40), 205 (100), 189 (25), 177 (30), 172 (10), 159 (30), 147 (30), 135 (20), 129 (40), 121 (70), 121 (50), 115 (30), 105 (70), 91 (40), 81 (85), 72 (80), 65 (75), 55 (25); HRMS (EI) calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1447.

***syn*-4-Methoxy-4-methyl-1-phenyl-2,5-cyclohexadien-1-ol (30α) and *anti*-4-Methoxy-4-methyl-1-phenyl-2,5-cyclohexadien-1-ol (30β).** To a solution of **5** (24 mg, 0.17 mmol) in dry THF was added dropwise for 10 min at −78 °C 0.35 (0.34 mmol) mL of PhMgBr (1.5 M solution in THF). After 30 min, the reaction mixture was quenched with 5% aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), concentrated *in vacuo*, and chromatographed on SiO_2 (EtOAc/hexanes, 1:1) to give 24 mg (65%) of **30**α as a colorless oil and 6.5 mg (18%) of **30**β as a white solid. **30**α: R_f (EtOAc/hexanes, 1:1) = 0.5; IR (neat) 3403, 2977, 1449, 1130, 1088, 1048, 947, 783, 752, 700 cm^{-1}; ^{1}H NMR δ 7.36−7.16 (m, 5 H), 5.97 (d, 2 H, J = 10.1 Hz), 5.68 (d, 2 H, J = 10.1 Hz), 3.12 (s, 3H), 2.27 (bs, 1 H), 1.28 (s, 3 H); ^{13}C NMR δ 144.2, 134.6, 131.1, 128.5, 127.4, 125.4, 70.9, 69.7, 52.0, 27.9; MS (EI) *m/e* (relative intensity) 216 (M^+, 60), 201 (100), 185 (70), 167 (40), 152 (30), 141 (25), 115 (20), 105 (22), 91 (10), 77 (25); HRMS (EI) calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1168. **30**β: R_f (EtOAc/hexanes, 1:1) = 0.6; mp 109−110 °C; IR (neat) 3402, 2977, 1449, 1130, 1088, 1048, 947, 783, 752, 700 cm^{-1}; ^{1}H NMR δ 7.46−7.19 (m, 5 H), 6.03 (d, 2 H, J = 10.2 Hz), 5.75 (d, 2 H, J = 10.2 Hz), 3.10 (s, 3H), 1.88 (bs, 1 H), 1.32 (s, 3 H); ^{13}C NMR δ 144.4, 135.1, 132.6, 128.5, 127.5, 125.5, 70.7, 69.4, 52.5, 28.3; MS (EI) *m/e* (relative intensity) 216 (M^+, 90), 201 (100), 198 ([M − H_2O]$^+$, 30), 185 (50), 167 (45), 152 (40), 141 (30), 115 (25), 105 (22), 91 (20), 77 (30), 59 (15), 51 (10); HRMS (EI) calcd for $C_{14}H_{14}O$ (M − H_2O) 198.1045, found 198.1017.

***syn*-1-((Benzyloxy)methyl)-4-methoxy-4-methyl-2,5-cyclohexadien-1-ol (31α) and *anti*-1-((Benzyloxy)methyl)-4-methoxy-4-methyl-2,5-cyclohexadien-1-ol (31β).** To a solution of 450 mg (1.1 mmol) of $BnOCH_2SnBu_3$[28] in 10 mL of THF was added dropwise at −78 °C 3.6 mL (1.0 mmol) of 2.5 M nBuLi. The reaction mixture was stirred for 30 min at −78 °C, and a solution of **5** (69 mg, 0.5 mmol) in 3 mL of THF was added by cannula. After 10 min, the reaction mixture was quenched by addition of 5% $NaHCO_3$ solution. The organic layer was washed with brine, dried (Na_2SO_4), and chromatographed on SiO_2 (EtOAc/hexanes, 1:2) to give 109 mg (84%) of an inseparable 3:1 mixture of **31**α,β as a colorless oil. **31**α: R_f (EtOAc/hexanes, 1:2) = 0.55; IR (neat) 3414, 3027, 2977, 2932, 2859, 1455, 1408, 1364, 1215, 1090, 866, 789, 739, 698 cm^{-1}; ^{1}H NMR δ 7.31 (m, 5 H), 5.98 (d, 2 H, J = 10.2 Hz), 5.71 (d, 2 H, J = 10.2 Hz), 4.54 (s, 2 H), 3.41 (s, 1 H), 3.35 (s, 2 H), 3.12 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR δ 137.6, 132.8, 132.3, 131.6, 128.4, 127.4, 76.8, 73.3, 71.0, 67.6, 51.8, 28.1; MS (EI) *m/e* (relative intensity) 260 (M^+, 1), 228 (2), 215 (3), 198 (3), 178 (1.5), 169 (1.2), 152 (5), 139 ([M − $CH_2OCH_2C_6H_5$]$^+$, 80), 124 (20), 108 (30), 91 (100), 77 (10), 65 (15); HRMS (EI) calcd for $C_8H_{11}O_2$ (M − $CH_2OCH_2C_6H_5$) 139.0759, found 139.0750. **31**β: ^{1}H NMR δ 7.31 (m, 5 H), 6.03 (d, 2 H, J = 10.3 Hz), 5.67 (d, 2 H, J = 10.3 Hz), 4.55 (s, 2 H), 3.30 (s, 2 H), 3.27 (s, 1 H), 2.98 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR δ 137.6, 132.8, 132.3, 131.6, 128.4, 127.5, 76.2, 73.3, 71.2, 67.1, 51.4, 27.6.

4-Methoxy-4-(1,1,2,2,2-pentafluoroethyl)-2,5-cyclohexadienone (32). A solution of **35** (276 mg, 0.87 mmol) in 10 mL of dry THF was treated at 0 °C with 1.5 mg (2.62 mmol) of 60% NaH and 372 mg (2.62 mmol) of CH_3I. The reaction mixture was stirred for 7 h at 0 °C and partitioned

(28) (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (b) Johnson, C. R.; Medich, J. R. *J. Org. Chem.* **1988**, *53*, 4131.

between EtOAc and brine. The organic layer was separated, dried (Na_2SO_4), and concentrated *in vacuo* to give a pale yellow oil. A solution of this crude product in 30 mL of THF was treated at 0 °C with 3 mL of 0.1 N HCl, stirred for 1.5 h at 0 °C, diluted with EtOAc, and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and chromatographed on SiO_2 (EtOAc/hexanes, 1:6) to give 166 mg (79%) of **32** as a colorless oil: R_f (EtOAc/hexanes, 1:4) = 0.5; IR (neat) 2946, 2321, 1686, 1676, 1655, 1638, 1619, 1391, 1343, 1283, 1210, 1175, 1105, 1065, 1026, 995, 930, 853, 747, 706; ^{1}H NMR δ 6.78 (d, 2 H, J = 10.3 Hz), 6.53 (d, 2 H, J = 10.3 Hz), 3.25 (s, 3 H); ^{13}C NMR δ 183.4, 140.7, 134.9, 118.8 (qt, J = 276.2 Hz, 35.5 Hz), 112.8 (tq, J = 264.1, 36.2 Hz), 75.5 (t, J = 24.1 Hz), 52.5; MS (EI) *m/e* (relative intensity) 242 (M^+, 1), 211 (2.5), 201 (2.5), 191 (1), 183 (5), 173 (2.2), 163 (20), 123 (100), 114 (20), 95 (20), 81 (10), 74 (10), 69 (13), 59 (12); HRMS (EI) calcd for $C_7H_7O_2$ ($M - C_2F_5$) 123.0446, found 123.0443.

4-Butoxy-4-methoxy-2,5-cyclohexadienone (34). To a solution of 537 mg (4.33 mmol) of *p*-hydroquinone monomethyl ether (**33**) in 30 mL of nBuOH at 0 °C was added 1.71 g (5.20 mmol) of (diacetoxyiodo)benzene. The reaction mixture was stirred for 30 min at 0 °C, diluted with EtOAc, washed with H_2O, saturated aqueous $NaHCO_3$, and brine, and dried ($MgSO_4$). Chromatography on SiO_2 (hexanes/EtOAc, 2:1) gave 587 mg (76%) of **34** as a colorless oil: R_f (EtOAc/hexanes, 1:1) = 0.7; ^{1}H NMR δ 6.85–6.79 (m, 2 H), 6.28–6.24 (m, 2 H), 3.55 (t, 2 H, J = 6.5 Hz), 3.36 (s, 3 H), 1.59–1.52 (m, 2 H), 1.41–1.34 (m, 2 H), 0.91 (t, 3 H, J = 7.3 Hz); MS (EI) *m/e* (relative intensity) 196 (M^+, 3), 165 ([$M - OCH_3$]$^+$, 5), 140 (8), 123 (100), 109 (30), 95 (20), 57 (10); HRMS (EI) calcd for $C_{10}H_{13}O_2$ ($M - OCH_3$) 165.0916, found 165.0929.

4-Butoxy-4-methoxy-1-(1,1,2,2,2-pentafluoroethyl)-2,5-cyclohexadienone (35). To a solution of 3.6 g (18.1 mmol) of pentafluoroethyl iodide in 10 mL of Et_2O was added dropwise at −78 °C 10 mL (18.1 mmol) of CH_3Li·LiBr (1.5 M solution in Et_2O). A solution of **34** (580 mg, 2.96 mmol) in 10 mL of Et_2O was cannulated into the reaction mixture. The solution was slowly warmed to −20 °C, quenched by addition of 5% aqueous $NaHCO_3$ solution, diluted with EtOAc, washed with brine, and dried (Na_2SO_4). Chromatography on SiO_2 (EtOAc/hexanes, 1:10) gave 683 mg (81%) of **35** as a yellowish oil: R_f (EtOAc/hexanes, 1:10) = 0.7; IR (neat) 3360, 2984, 2940, 1341, 1215, 1181, 1148, 1086, 1049, 936, 911 cm^{-1}; ^{1}H NMR δ 6.13 (d, 2 H, J = 10.4 Hz), 6.04 (d, 2 H, J = 10.4 Hz), 3.83 (bs, 1 H), 3.46 (t, 2 H, J = 6.5 Hz), 3.20 (s, 3 H), 1.55–1.45 (m, 2 H), 1.38–1.23 (m, 2 H), 0.84 (t, 3 H, J = 8.3 Hz); ^{13}C NMR δ 131.8, 127.7, 119.0 (qt, J = 285.8, 35.3 Hz), 113.5 (tq, J = 260.3, 34.5 Hz), 92.3, 68.9 (t, J = 24.0 Hz), 62.1, 49.8, 32.0, 19.2, 13.6; MS (EI) *m/e* (relative intensity) 316 (M^+, 2), 285 ([$M - OCH_3$]$^+$, 14), 260 (2), 243 (100), 229 (25), 209 (2.5), 202 (2), 195 (2), 189 (1), 182 (2), 173 (2), 166 (3), 157 (5), 151 (1), 143 (4), 124 (50), 110 (25), 81 (10), 57 (20); HRMS (EI) calcd for $C_{12}H_{14}F_5O_2$ ($M - OCH_3$) 285.0914, found 285.0923.

***syn*-4-Methoxy-1-methyl-4-(1,1,2,2,2-pentafluoroethyl)-2,5-cyclohexadien-1-ol (36α) and *anti*-4-Methoxy-1-methyl-4-(1,1,2,2,2-pentafluoroethyl)cyclohexadien-1-ol (36β) from 32.** To a solution of **32** (21 mg, 0.09 mmol) in 3 mL of dry THF was added dropwise at −78 °C 72 μL of CH_3Li·LiBr (1.5 M solution in Et_2O, 0.11 mmol). After 30 min, the reaction mixture was quenched by addition of 5% aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give 16 mg (72%) of a 1:5 mixture of **36α,β** as a colorless oil. **36β**: R_f (EtOAc/hexanes, 1:4) = 0.4; IR (neat) 3310, 1341, 1179, 1148, 1075, 926 cm^{-1}; ^{1}H NMR δ 6.36 (d, 2 H, J = 10.3 Hz), 5.77 (d, 2 H, J = 10.3 Hz), 3.13 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR 142.1, 122.2, 119.0 (qt), 113.0 (tq), 74.7 (t, J = 24.0 Hz), 64.9, 51.3, 27.2; MS (EI) *m/e* (relative intensity) 258 (M^+, 3), 243 ([$M - CH_3$]$^+$, 50), 227 (10), 207 (0.3), 157 (10), 139 (30), 124 (100), 109 (20), 91 (10), 79 (10), 74 (10), 59 (20), 43 (25); HRMS (EI) calcd for $C_9H_8F_5O_2$ ($M - CH_3$) 243.0444, found 243.0425.

***syn*-4-Methoxy-1-methyl-4-(1,1,2,2,2-pentafluoroethyl)-2,5-cyclohexadien-1-ol (36α) and *anti*-4-Methoxy-1-methyl-4-(1,1,2,2,2-pentafluoroethyl)cyclohexadien-1-ol (36β) from 10.** To a solution of 458 mg (1.86 mmol) of pentafluoroethyl iodide in 10 mL of Et_2O was added dropwise at −78 °C 1.2 mL (1.86 mmol) of CH_3Li·LiBr (1.5 M solution in Et_2O). A solution of **10** (67 mg, 0.37 mmol) in 5 mL of Et_2O was cannulated into the reaction mixture. The solution was slowly warmed to 0 °C, quenched by addition of 5% aqueous $NaHCO_3$ solution, and diluted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), dissolved in 12 mL of THF, and treated at 0 °C with 74 mg (1.86 mmol) of 60% NaH and 264 mg (1.86 mmol) of CH_3I. The reaction mixture was stirred for 2 h at 0 °C and partitioned between EtOAc and brine. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give a bright yellow oil. Unreacted **10** was removed by chromatography on SiO_2 (EtOAc/hexanes, 1:10). A solution of the crude product in 5 mL of THF was treated at 0 °C for 5 min with 0.4 mL (0.4 mmol) of TBAF (1 M solution in THF), diluted with EtOAc, and washed with brine. The organic layer was dried (Na_2SO_4) and chromatographed on SiO_2 (EtOAc/hexanes, 1:10) to give 57 mg (61%) of a 3:1 mixture of **36α,β**. **36α**: R_f (EtOAc/hexanes, 1:4) = 0.3; IR (neat) 3306, 2988, 1406, 1341, 1213, 1179, 1148, 1123, 1105, 1075, 999, 926, 774, 673 cm^{-1}; ^{1}H NMR δ 6.34 (d, 2 H, J = 10.3 Hz), 5.73 (d, 2 H, J = 10.3 Hz), 3.20 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR δ 141.8, 121.6, 119.0 (qt, J = 322.5, 36.0 Hz), 113.3 (tq, J = 258.0, 35.3 Hz), 74.9 (t, J = 24.0 Hz), 65.7, 51.5, 28.1; MS (EI) *m/e* (relative intensity) 258 (M^+, 2), 243 ([$M - CH_3$]$^+$, 60), 227 (10), 207 (0.5), 157 (10), 139 (30), 124 (100), 109 (20), 79 (10), 74 (20), 59 (25), 45 (35); HRMS (EI) calcd for $C_{10}H_{11}F_5O_2$ 258.0679, found 258.0672.

***syn*-1-(Benzyloxy)-4-methoxy-1-methyl-4-(1,1,2,2,2-pentafluoroethyl)-2,5-cyclohexadiene (37α) and *anti*-1-(Benzyloxy)-4-methoxy-1-methyl-4-(1,1,2,2,2-pentafluoroethyl)cyclohexadiene (37β).** A solution of 23 mg (0.09 mmol) of a 3:1 mixture of **36α,β** in 7 mL of THF was treated at 0 °C with 11 mg (0.27 mmol) of 60% NaH, 46 mg (0.27 mmol) of benzyl bromide, and 4 mg (0.01 mmol) of tetrabutylammonium iodide. The reaction mixture was stirred at 0 °C for 5 h, diluted with hexanes, washed with H_2O and brine, and dried (Na_2SO_4). Chromatography on SiO_2 (EtOAc/hexanes, 1:50) gave 24 mg (76%) of a 3:1 mixture of **37α,β** as a colorless oil. **37α**: R_f (EtOAc/hexanes, 1:10) = 0.7; IR (neat) 2938, 1553, 1501, 1466, 1451, 1399, 1339, 1213, 1175, 1146, 1088, 1069, 1026, 1001, 926, 772, 743, 718, 695, 681 cm^{-1}; ^{1}H NMR δ 7.30–7.18 (m, 5 H), 6.29 (d, 2 H, J = 10.0 Hz), 5.87 (d, 2 H, J = 10.0 Hz), 4.28 (s, 2 H), 3.23 (s, 3 H), 1.32 (s, 3 H); ^{13}C NMR (500 MHz) δ 141.6, 138.6, 128.5, 127.6, 124.3, 119.3 (qt, J = 283.8, 36.4 Hz), 115.9 (tq, J = 208.7, 48.5 Hz), 75.0 (t, J = 48.5 Hz), 71.1, 67.1, 51.8, 27.7; MS (EI) *m/e* (relative intensity) 333 ([$M - CH_3$]$^+$, 1), 257 (1), 241 ([$M - OCH_2C_6H_5$]$^+$, 22), 227 (2), 221 (2), 210 (22), 171 (4), 141 (20), 122 (40), 107 (20), 91 (100), 79 (15), 65 (10), 45 (10); HRMS (EI) calcd for $C_{10}H_{10}F_5O$ ($M - OCH_2C_6H_5$) 241.0651, found 241.0642.

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Supplementary Material Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **5–10**, **14–32**, and **34–37** (71 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.