Formal [3 + 2] Cycloaddition of Benzylic Cations with Alkenes

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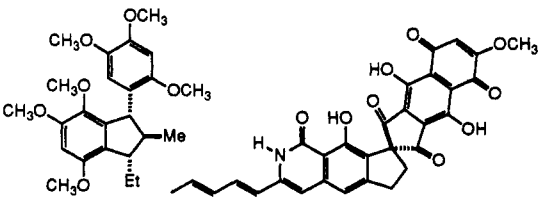
The reaction of benzylic cations with styrenes affords dihydro(1*H*)indenes in good yield via a formal [3 + 2] atom cycloaddition. The cations were generated from quinone methides and benzylic alcohols. (*E*)-Styrenes participate in the reaction with remarkable stereoselectivity affording dihydro(1*H*)indenes with three stereogenic centers with >40:1 diastereoselectivity. A possible transition state for the reaction is discussed. Less activated alkenes such as dihydropyran and methylcyclohexene afforded cycloadducts in 66% and 51% yields, respectively.

Introduction

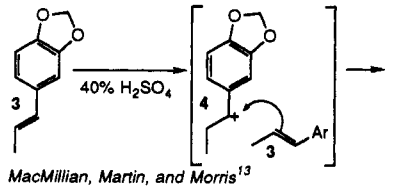
There are numerous natural products that possess the dihydroindene ring system,[1-8] including simple compounds such as **1**, a component of the essential oil of *Acorus calamus*,[1] and complex compounds such as fredericamycin A, **2**.[2] In addition, there are many synthetic compounds possessing the dihydroindene skeleton that show significant biological activity.[3] In accordance with the importance of the compounds possessing this skeleton, there have been a large number of methods developed for their synthesis;[4-8] however, the lack of general stereoselective methods led us to develop a cycloaddition-type strategy for the preparation of highly substituted dihydro(1*H*)-indenes. This strategy takes advantage of the large increase in molecular complexity that can be realized using cycloaddition-based methodology.

At the turn of the century, Tiemann[9] and Angeli and Mole[10] treated propenylbenzenes with acidic reagents to



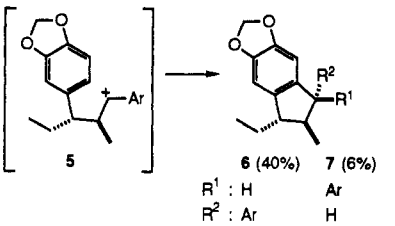
1 2

afford dimeric products. It was believed that these dimers were derivatives of cyclobutane or 9,10-dihydroanthracene.[11] In 1940, Baker and Enderby were the first to propose the dihydro(1*H*)indene structure for these dimers.[12] The correct stereochemical assignments of the dimers derived from (*E*)-isosafrole were finally reported by MacMillan, Martin, and Morris in 1969.[13] An example of this type of styrene dimerization is shown in eq 1.



(1)

MacMillian, Martin, and Morris[13]



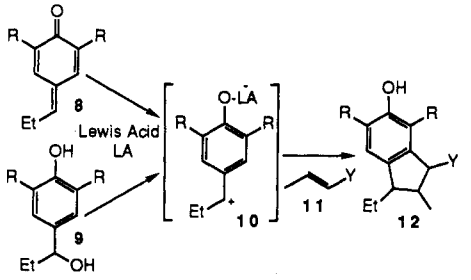
Dihydroindene products **6** and **7** are thought to arise from protonation of styrene **3** to afford benzylic cation **4**, which can then be trapped by a second styrene to afford a new benzylic cation, **5** (eq 1). Cation **5** can then cyclize to afford dihydroindenes **6** and **7**. It should be noted that this method is only applicable to the synthesis of homodimers, where the two aryl rings are the same.

In a mechanistically similar reaction Marcuzzi, Maroni, Melloni, and Modena have reported that the reaction of phenyl-substituted alkenes and alkynes with diphenylmethyl cations afforded good yields of indenes and dihydroindenes.[14]

(1) Saxena, D. B. *Phytochem.* **1986**, *25*, 553.
(2) (a) Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M.; Kalita, C. C.; Aszalos, A. A.; Garretson, A. L.; Wei, T. T.; Byrne, K. M.; Geoghegan, R. F., Jr.; White, R. J. *J. Antibiot.* **1981**, *34*, 1389. (b) Misra, R.; Pandey, R. C.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478.
(3) (a) Kunstmann, R.; Lerch, U.; Gerhards, H.; Leven, M.; Schacht, U. *J. Med. Chem.* **1984**, *27*, 432. (b) Warnick-Pirkle, D. J.; Byrne, K. M.; Pandey, R. C.; White, R. J. *J. Antibiot.* **1981**, *34*, 1402. (c) Cross, B. E.; Galt, R. H. B.; Norton, K. *Tetrahedron* **1968**, *24*, 231.
(4) For leading references to cationic cyclization/cycloaddition routes to dihydro(1*H*)indenes see: (a) Sarkar, A. K.; Sinha, N. C.; Dutta, L. N. *Ind. J. Chem.* **1985**, *24B*, 1061. (b) Ipaktschi, J.; Lauterbauch, G. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 354. (c) Bennett, S. M.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1986**, 878. (d) Morrow, G. W.; Wang, S.; Swenton, J. S. *Tetrahedron Lett.* **1988**, *29*, 3441. (e) Morrow, G. W.; Swenton, J. S. *Tetrahedron Lett.* **1987**, *28*, 5445. (f) Mayr, H.; Pock, R. *Chem. Ber.* **1986**, *119*, 2473. (g) Haack, R. A.; Beck, K. R. *Tetrahedron Lett.* **1989**, *30*, 1605.
(5) For organometallic based routes to dihydro(1*H*)indenes see: (a) Sivavec, T. M.; Katz, T. J. *Tetrahedron Lett.* **1985**, *26*, 2159. (b) Trost, B. M.; Walchli, R. *J. Am. Chem. Soc.* **1987**, *109*, 3487. (c) Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4149. (d) Abelman, M. M.; Taeboem, O.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (e) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919.
(6) For miscellaneous routes to dihydro(1*H*)indenes see: (a) Suzuki, M.; Hart, H.; Dunkelblum, E.; Wolfgang, L. *J. Am. Chem. Soc.* **1977**, *99*, 5083. (b) Bender, C. O.; Elder, J. L. M.; Herbst, A. J.; Miller, L. E. *Can. J. Chem.* **1972**, *50*, 395. (c) Shamma, M.; Slusarchyk, W. A. *Chem. Commun.* **1965**, 528. (d) Kende, A. S.; Koch, K.; Smith, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 2210. (e) Zólyomi, G.; Bánfi, D.; Láng, T.; Körösi, J. *Chem. Ber.* **1974**, *107*, 3904.
(7) For cycloaddition type of approaches to dihydro(1*H*)indenes where two C–C bonds of the five-membered ring are formed in a single step see: (a) Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C. *Tetrahedron Lett.* **1985**, *26*, 4725. (b) Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C. *Tetrahedron Lett.* **1985**, *26*, 4723. (c) Berney, D.; Schuh, K. *Helv. Chim. Acta.* **1975**, *58*, 2228. (d) Parker, K. A.; Koziski, K. A.; Breault, G. *Tetrahedron Lett.* **1985**, *26*, 2181. (e) Franck, R. W.; Gupta, R. B. *Tetrahedron Lett.* **1985**, *26*, 293. (f) Trogen, L.; Edlund, U. *Acta. Chem. Scand. B.* **1979**, *33*, 109.
(8) For a preliminary report of this work see: Angle, S. R.; Arnaiz, D. O. *J. Org. Chem.* **1990**, *55*, 3708.
(9) Tiemann, F. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2870.
(10) Angeli, A.; Mole, P. *Gazz. Ital.* **1894**, *24(II)*, 127.
(11) For reviews see: (a) Müller, A. *Acta. Chim. Acad. Sci. Hung.* **1952**, *2*, 231. (b) McOmie, J. F. W. *Ann. Rep.* **1952**, *49*, 166.
(12) Baker, W.; Enderby, J. *J. Chem. Soc.* **1940**, 1094.
(13) MacMillan, J.; Martin, I. L.; Morris, D. J. *Tetrahedron* **1969**, *25*, 905.
(14) (a) Marcuzzi, F.; Melloni, G.; Modena, G. *J. Org. Chem.* **1979**, *44*, 3022 and references cited therein. (b) Marcuzzi, F.; Melloni, G. *Tetrahedron Lett.* **1975**, 2771. (c) Maroni, R.; Melloni, G. *Tetrahedron Lett.* **1972**, 2869.

0022-3263/92/1957-5937$03.00/0

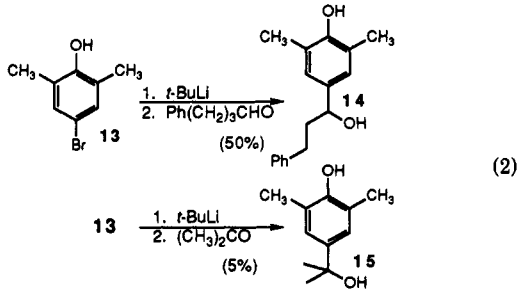
Scheme I. Proposed Dihydroindene Synthesis



We report here the stereoselective synthesis of dihydro(1*H*)indenes in a single step via the reaction of an activated *p*-quinone methide or a benzylic cation with an electron-rich alkene. The success of this formal cycloaddition relies on the selective activation of a quinone methide or benzylic alcohol by a Lewis acid in the presence of nucleophilic alkene (Scheme I). Alkene **11** should add to the activated quinone methide/benzylic cation **10** to afford a new benzylic cation (analogous to **5**, eq 1) which can then undergo cyclization to afford dihydroindene **12** (Scheme I).[15]

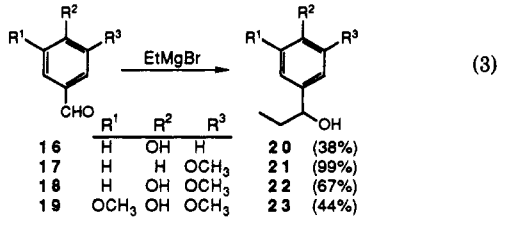
Results and Discussion

Synthesis of Substrates. Bromophenol **13** was treated with 2 equiv of *tert*-butyllithium to give the dianion which was then condensed with hydrocinnamaldehyde to afford **14** (50%) and acetone to afford **15** (5%)[16] (eq 2). The low yield of **15** is likely due to the enolization of acetone; however, in view of the ready availability of the starting materials, no attempt was made to optimize this reaction.



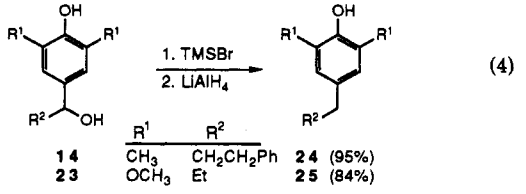
(2)

The other benzylic alcohols were prepared from the corresponding benzaldehydes and ethylmagnesium bromide as shown in eq 3. Phenols **24** and **25** were prepared



(3)

	R¹	R²	R³		
16	H	OH	H	20	(38%)
17	H	H	OCH_3	21	(99%)
18	H	OH	OCH_3	22	(67%)
19	OCH_3	OH	OCH_3	23	(44%)



(4)

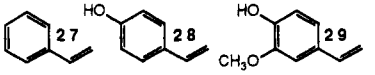
	R¹	R²		
14	CH_3	CH_2CH_2Ph	24	(95%)
23	OCH_3	Et	25	(84%)

via reduction of the corresponding benzylic alcohols (eq 4).[17] The (*Z*)-styrenes were prepared by olefination of the corresponding benzaldehydes using a Still–Modified-Wittig reaction[18] (see Experimental Section for details).

Studies on the Formal Cycloaddition: General Considerations. The formal cycloaddition might employ any alkene that can form a stabilized cation upon reaction with a benzylic cation. In light of the mechanistic similarity of this process to styrene dimerization, we elected to first examine styrenes as the alkene component in the cycloaddition.

We planned to generate the benzylic cations by two methods: (1) activation of a quinone methide with a Lewis acid[19] and (2) treatment of a benzylic alcohol with a Lewis acid.[20] Since Lewis acids are known to promote styrene polymerization,[21] a potential problem with the desired formal cycloaddition is that the styrene might polymerize, particularly if heteroatom functionality is present on the aryl ring of the styrene.[21]

Cycloaddition Studies: Quinone Methides. Earlier work in our laboratory[19] showed $ZnCl_2$ to be an excellent Lewis acid for the activation of quinone methides in cyclization reactions. Accordingly, $ZnCl_2$ has been employed for the selective activation of quinone methides in the presence of styrenes for the formal cycloaddition. Table I presents the results of our initial studies where two different quinone methides were used to screen the reactivity of several different styrenes. Preliminary experiments with three monosubstituted styrenes (**27**, **28**, and **29**) afforded no detectable dihydro(1*H*)indene products. The presence of organic insoluble solids, base-line material on TLC analysis, and broad peaks in the ^1H NMR spectra indicated styrene and quinone methide polymerization might be occurring. The use of activated styrenes (**28** and **29**), and employing large excesses of styrene (>10 equiv) failed to improve the reaction with monosubstituted styrenes.



In stark contrast, β-methylstyrenes afforded good yields of "cycloadducts" (Table I). The change in styrene reactivity is in agreement with work by Higashimura and Hiza who studied the BF_3-OEt_2-mediated polymerization of styrenes in CH_2Cl_2 at 30 °C.[22] These workers found that styrene polymerized twice as fast as β-methylstyrene. In the case of the formal cycloaddition, slowing down styrene polymerization by introduction of a β-methyl substituent must make the formal cycloaddition competitive with polymerization.

Three stereogenic centers are formed in the formal cycloaddition; thus, four different racemic diastereomers might be obtained. (*Z*)-Styrenes afford only two diastereomers and excellent stereocontrol at two of the three stereogenic centers is observed (Table I, entries 1–5). Stereocontrol at the third bis-benzylic center is modest at best. In three of the five (*Z*)-styrene examples (Table I,

(15) For a detailed discussion of these results see: Arnaiz, D. O. Ph.D. Dissertation, University of California, Riverside, 1991.

(16) For the preparation of a series of related compounds see: Popísek, J.; Pisová, M.; Soucek, M. *Collect. Czech. Chem. Commun.* **1975**, *40*, 142.

(17) The benzylic alcohol was converted to the benzylic bromide according to: Jung, M. E.; Hatfield, G. L. *Tetrahedron Lett.* **1978**, 4483.

(18) (a) Sreekumar, C.; Darst, K. D.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260. (b) For an application to the synthesis of (*Z*)-styrenes see: Turnbull, K. D. Ph.D. Dissertation, University of California, Riverside, 1991.

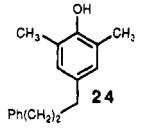
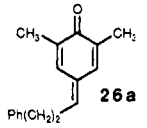
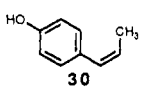
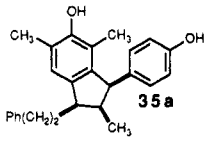
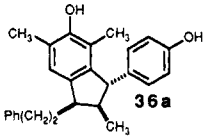
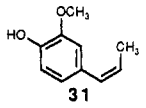
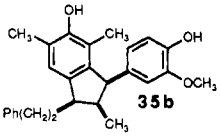
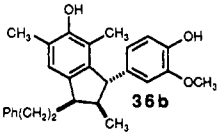
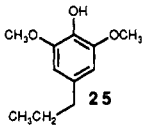
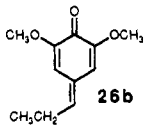
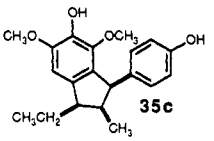
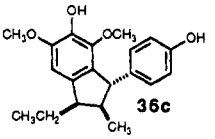
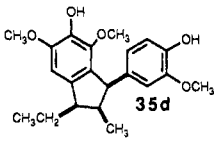
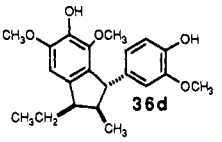
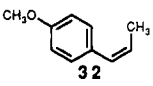
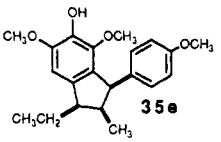
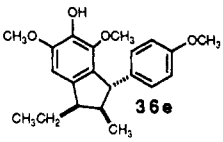
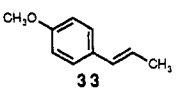
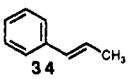
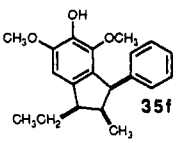
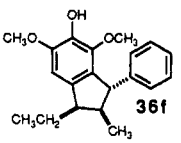
(19) (a) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1989**, *111*, 1136. (b) Angle, S. R.; Louie, M. S.; Mattson, H. L.; Yang, W. *Tetrahedron Lett.* **1989**, *30*, 1193.

(20) Angle, S. R.; Louie, M. S. *J. Org. Chem.* **1991**, *56*, 2853.

(21) (a) Brook, M. A.; Hülser, P.; Sebastian, T. *Macromolecules* **1989**, *22*, 3816. (b) Kennedy, J. P. *Cationic Polymerization of Olefins: a Critical Inventory*; John Wiley & Sons: New York, 1975 and references cited therein.

(22) Higashimura, T.; Hiza, M. *J. Polym. Sci. Polym. Chem. Educ.* **1981**, *19*, 1957.

Table I. Formal [3 + 2] Cycloaddition of Quinone Methides and Styrenes

entry	phenol	quinone methide	styrene	(Z/E)[a]	product	% yield (35:36)[b]
1	 24	 26a	 30	(13:1)	 35a  36a	71 (2.2:1)
2	24	26a	 31	(11:1)	 35b  36b	54 (3:1)
3	 25	 26b	30	(13:1)	 35c  36c	96 (1:1)
4	25	26b	31	(11:1)	 35d  36d	51 (1:1)
5	25	26b	 32	(10:1)	 35e  36e	79[c] (1:1)
6	25	26b	 33	(1:99)	35e/36e	81 (1:43)
7	25	26b	 34	(1:99)	 35f  36f	67 (1:17)

[a] Ratio was determined by GC. [b] Ratio was determined by ^{1}H NMR. [c] In this case, 0.01 equiv of $ZnCl_2$ was employed at room temperature.

entries 3–5) the products are 1:1 mixtures of epimers at the bis-benzylic center. In the other two (Table I, entries 1, 2) the major product is the all-cis diastereomer. This stereoselectivity is in contrast to the results seen in styrene dimerization where the all-cis diastereomer corresponding to **35** is not observed.[9-13]

(*E*)-Styrenes afford excellent stereocontrol at all three stereogenic centers (Table I, entries 6, 7). This high level of stereocontrol is remarkable for what is likely a stepwise reaction (the possible origin of this stereocontrol is discussed later).

It is worth noting that in entries 2 and 4 where the styrene contains a bidentate Lewis base (the *o*-methoxyphenol) a lower yield of adducts is obtained. In these cases the styrene may compete with the quinone methide for the Lewis acid. In support of this notion, polymerization of the styrene was a major side reaction.

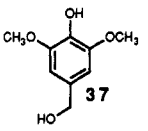
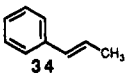
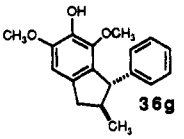
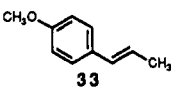
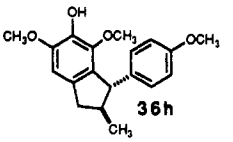
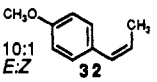
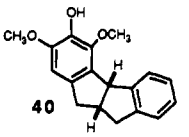
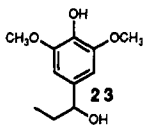
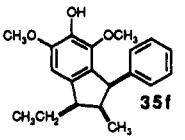
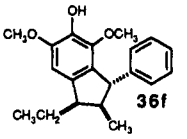
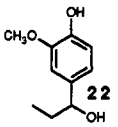
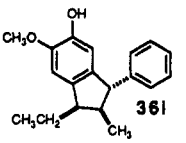
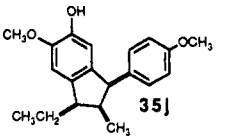
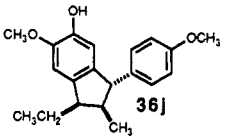
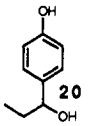
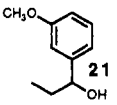
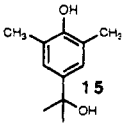
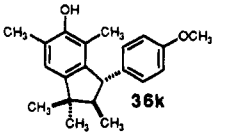
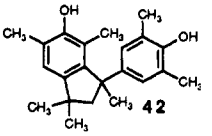
Cycloaddition Studies: Benzylic Cations. Benzylic alcohols can also be used as precursors to benzylic cations in the formal [3 + 2] cycloaddition (Table II). In this case, a stronger Lewis acid, $SnCl_4$, is required for generation of the cationic intermediate. Several different benzylic alcohols of varying substitution were examined (Table II).

Primary and secondary benzylic alcohols afforded good yields of cycloadducts as long as there was a phenol para to the benzylic alcohol *and* at least one meta alkoxy or alkyl group. Styrenes of varying substitution on the aryl ring were screened with primary benzylic alcohol **37**. (*E*)-Styrenes **33** and **34** both afford products where the trans orientation of the aryl and methyl substituents is retained in the products (Table II, entries 1, 2). (*Z*)-Styrene **32** affords the same product as (*E*)-styrene **33** (Table II, entry 3), showing that styrene geometry has no effect on diastereoselectivity of the reaction with primary benzylic alcohols. Benzylic alcohol **37** was treated with indene **39** to afford tetracyclic indenoindene **40** in 96% yield (Table II, entry 4).

Styrene **34** was used to screen several secondary benzylic alcohols to determine the substitution pattern required for participation in the formal cycloaddition. Benzylic alcohol **23** affords cycloadducts **35f/36f** as a >1:17 mixture by ^{1}H NMR analysis (entry 5). As in the case of quinone methide **26b** (Table I, entry 7), the product **36f** retains the trans relationship between the phenyl and methyl substituents.

Upon reaction with (*E*)-β-methylstyrene, benzylic alcohol **22** (entry 6) affords **36i** in an 87% yield as a *single diastereomer*! This remarkable transformation forms three new stereogenic centers *and* affords a single regioisomer with respect to the methoxy group ortho to the phenol and the bis-benzylic methine in the five-membered ring. Again, the trans orientation of the alkene is retained in the product. In a similar fashion, reaction of **22** with *trans*-anethole afforded **35j/36j** in 95% yield as a 1:10 mixture of diastereomers (entry 7).

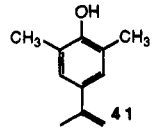
Table II. Formal [3 + 2] Cycloaddition of Benzylic Alcohols and Styrenes

entry	phenol	styrene	reactn cond*	equiv $SnCl_4$	product	% yield (35:36)[b]
1	 37	 34	A	5.7	 36g	77
2	37	 33	B	1.2	 36h	87
3	37	 10:1 E:Z 32	B	1.2	36h	92
4	37	 39	B	1.3	 40	96
5	 23	34	C	5.7	 35f  36f	78[c] (1:17)
6	 22	34	C	5.0	 36l	87
7	22	33	C	4.2	 35j  36j	95 (1:10)
8	 20	34	C	4.8	———	no rxn
9	 21	34	C	5.0	———	no rxn
10	 38	34	B,C	1.3	———	no rxn
11	 15	33	C	5.1	 36k	60
12	15	34	C	4.8	 42	70[c]

*Conditions: A = add $SnCl_4$ at −78 °C and then warm to 25 °C, 1.2 equiv of styrene, 1 h; B = 0 °C, 20–40 min; C = −78 °C, 1 h. [a] Ratio was determined by GC. [b] Ratio was determined by ^1H NMR. [c] This product is a dimer of the starting quinone methide; see text for structure and discussion.

When both methoxy groups ortho to the phenol were removed, no dihydroindene products were isolated (Table II, entry 8). Benzylic alcohols **21** and **38**, lacking a *p*-hydroxy group, also did not afford adducts upon reaction with styrene **34** (entries 9, 10). Running these reactions under more forcing conditions, higher reaction temperatures, longer reaction times and employing titanium(IV) chloride afforded intractable mixtures of products.

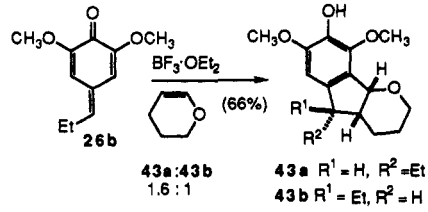
Tertiary alcohol **15** affords the desired cycloadduct **36k** in 60% yield when *trans*-anethole **33** is employed as the nucleophilic alkene (Table II, entry 11). However, *trans*-β-methylstyrene affords none of the desired cycloadduct; the major product is **42**, a dimer of alcohol **15** (Table II, entry 12). The formation of **42** presumably occurs via dehydration of **15** to styrene **41**, which then reacts with the benzylic cation corresponding to **15**.



41

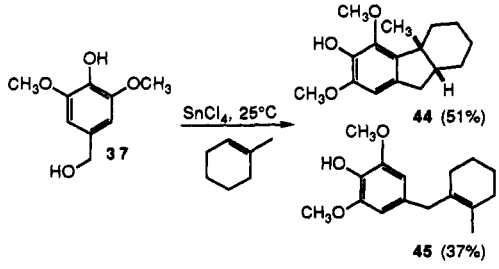
The source of the benzylic cation, quinone methide or benzylic alcohol, had no effect on the stereoselectivity but did have a modest effect on the yield of the reaction. Styrene **34** afforded adducts **35f/36f** in 67% yield with quinone methide **26b** and 78% with benzylic alcohol **23** (Table I, entry 7, Table II, entry 5).

The generality of the formal cycloaddition with nonstyrene alkenes was briefly examined with two representative alkenes, dihydropyran and methylcyclohexene. Treatment of a solution of quinone methide **26b** and dihydropyran with $ZnCl_2$ under the standard conditions utilized for styrenes resulted in intractable product mixtures. A series of Lewis acids ($Ti(O\text{-}i\text{-}Pr)_4$, $TiCl_4$, $SnCl_4$) were screened with similar results. However, employing $BF_3{\cdot}O(C_2H_5)_2$ (10 equiv, −78 °C) resulted in the formation of indenopyrans **43** (1.6:1 mixture **43a/43b**, HPLC) in 66% isolated yield (eq 5).



(5)

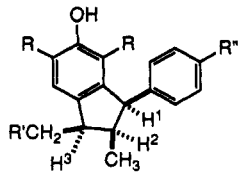
Treatment of benzylic alcohol **37** with excess methylcyclohexene and $SnCl_4$ (1 equiv) afforded **44** and **45** in 51% and 37% yields, respectively (eq 6). Alkene **45** must be derived from a tertiary cation that underwent elimination, rather than intramolecular electrophilic aromatic substitution.



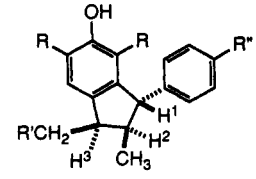
(6)

Stereochemical Assignments. The sterochemical assignments for the adducts follow directly from ^1H NMR coupling constants and difference NOE experiments. MacMillan, Martin, and Morris showed that cis,cis-1,2,3-trisubstituted dihydro(1*H*)indenes show characteristic values for J[H(1)–H(2)] and J[H(2)–H(3)] of approximately 7.0 Hz for each pair.[13] Compounds **35** show nearly identical values for these same coupling constants (Table III) and have been assigned as having this same cis,cis orientation. An NOE experiment on **35e** (C_6D_6) supports this assignment. Irradiation of the H(1) methine hydrogen resonance at δ 3.78 caused a 35.4% enhancement for the H(3) methine hydrogen resonance at δ 2.55 (see Table III for the numbering system).[23] No enhancement of the resonance for the hydrogens of methylene group attached to C(3) was seen.

Table III. Selected Coupling Constants (Hz) for Dihydro(1*H*)indenes 35 and 36



35



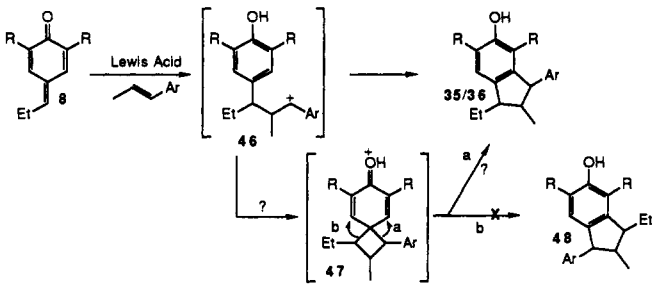
36

	dihydro-1*H*-indene **36**		dihydro-1*H*-indene **36**	
compd	J[H(1)–H(2)]	J[H(2)–H(3)]	J[H(1)–H(2)]	J[H(2)–H(3)]
35a	6.5	7.2		
36a			3.6	6.9
35b	6.6	obscured		
36b			4.2	6.5
35c	7.5	7.2		
36c			5.4	7.2
35d	7.5	6.9		
36d			obscured	7.2
35e	7.5	6.9		
36e			5.4	7.2
36f			5.4	7.2
36i			9.3	6.9
36j			9.3	7.2

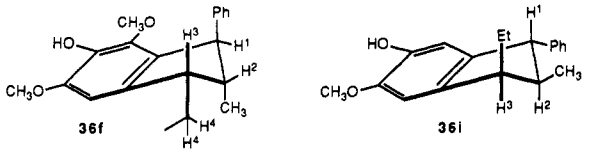
The trans,cis isomers **36a–36i**, which are predicted to have similar conformations to each other, show J[H(1)–H(2)] and J[H(2)–H(3)] of 3.6–5.4 Hz and 6.5–7.2 Hz, respectively. These values are consistent with those seen for **36f** whose stereochemistry was independently assigned by the NOE studies as follows.[23] Irradiation of the resonance for the H(1) methine hydrogen at δ 3.99 caused a 14% enhancement of the signal for the exocyclic methylene attached to C(3) at δ 1.59 (see Table III for the numbering system). No enhancement to the H(3) methine hydrogen resonance at δ 2.46 was observed. Thus, the exocyclic methylene attached to C(3) must be on the same face of the molecule as H(1), and H(3) must be on the opposite face of the molecule. The small J[H(1)–H(2)] for **36a–36f** must be due to a conformation where the nonfused aryl group is in a pseudoaxial position to minimize steric interactions due to $A^{1,3}$ strain[24] with the adjacent substituent on the fused aryl ring. An examination of Table III shows that adducts **36i** and **36j** have very different values for J[H(1)–H(2)] and J[H(2)–H(3)] than other dihydroindenes **36**. This difference is thought to be due to a change in conformation of the five-membered ring which puts the nonfused aryl ring in a pseudoequatorial position (rather than the pseudoaxial position seen in **36a–36f**, see below). This change in conformation is consistent with lack of an $A^{1,3}$ interaction[24] that is present in **36a–36f** due to the substituent on the fused-aryl ring. The coupling constants for **36i** and **36j** are consistent with those reported by McMillian for similar compounds with substituents in a

(23) See supplementary material for details.
(24) For reviews on allylic strain see: (a) Johnson, F. *Chem. Rev.* **1968**, *64*, 375. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

Scheme II. Possible Mechanism for the Formal Cycloaddition



trans,cis orientation[13] and with difference NOE experiments.[23]



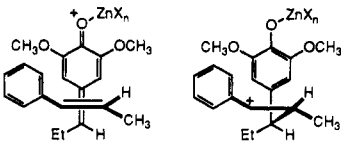
Mechanism and Origin of Stereocontrol. The stereochemistry of the products was believed to arise from kinetic control, and not from thermodynamic control. To test the reversibility of the reaction the dihydroindenes and styrenes were resubmitted to the reaction conditions. Resubmission of dihydroindene **35a** to the reaction conditions ($ZnCl_2$) resulted in the recovery of **35a**; no other dihydroindene products had been formed. Although the *trans,cis*-dihydroindenes of the **36** series should be more thermodynamically stable than the *cis,cis*-dihydroindenes of the **35** series, their stability was tested also. A solution of dihydroindene **36f** was resubmitted to the reaction conditions ($ZnCl_2$) and recovered unchanged. These experiments imply that the reaction of quinone methides and styrenes in the presence of zinc(II) chloride is under kinetic control. In the presence of the stronger Lewis acid, tin(IV) chloride, reversibility may be more of a problem. This possibility was investigated by treating dihydroindene **35a** with tin(IV) chloride for 25 min at 0 °C. Aqueous workup afforded dihydroindene **35a** unchanged. A solution of dihydroindene **36f** was also treated with tin(IV) chloride to afford unchanged **36f** after aqueous workup. These experiments show that the products are stable to the reaction conditions.

Another possible way to rationalize the different stereochemical results between cis and trans styrenes is that the styrene may isomerize under the reaction conditions. *cis*-Anethole (**32**) and *cis*-β-methylstyrene were treated with $ZnCl_2$ (0.1 and 1.0 equiv, respectively, of a 1.0 M solution in ether; 0.01 M in CH_2Cl_2) at room temperature. After 1 h no isomerization had occurred (^1H NMR analysis). Stannic chloride, a very strong Lewis acid, is much more likely to facilitate the cis/trans interconversion of styrenes. A solution of *cis*-anethole (**32**) [12.4:1 (*Z*/*E*)] and CH_2Cl_2 (0.016 M) at 0 °C was treated with 0.81 equiv of tin(IV) chloride and stirred for 1 h. These reaction conditions are the same as those used in the reaction. Aliquots were removed at 18, 33, and 60 min. Examination of the ^1H NMR spectra showed that the ratio had changed to 9.1:1 (*Z*/*E*) after 18 min, 6:1 (*Z*/*E*) after 33 min, and 3:1 (*Z*/*E*) after 1 h. This experiment indicates that styrene isomerization is a possibility although isomerization appears too slow to significantly affect the reaction.

Thus far, the mechanistic details of the formal [3 + 2] cycloaddition have been neglected. As depicted in Scheme II, addition of a styrene to an activated quinone methide/benzylic cation should afford a new benzylic cation, **46**. Ring closure via electrophilic aromatic substitution would then afford dihydroindenes **35/36**. Alternatively, ipso attack on cation **46** would afford spiro[3.5]nonadienone **47**, which is poised to undergo a dienone–phenol rearrangement.[25] Migration of the benzylic carbon would afford dihydroindenes **35/36**; however, migration of the secondary alkyl group will afford the regioisomeric dihydroindene **48**. The formation of **47** is not likely due to the known difficulty of forming spiro[3.5]nonadienones by this type of reaction.[26] Since the migratory aptitude of a benzylic carbon can be similar to that of a secondary alkyl carbon,[27] regioisomeric dihydroindenes **35/36** *and* **48** might be expected if **47** were an intermediate. This led us to consider the possibility that the isomeric products in the cycloaddition might be regioisomers, **48**, not stereoisomers **35/36**. Difference NOE experiments unambiguously proved the mixtures of products arise from stereoisomers not regioisomers.[23] While the intermediacy of **47** is viewed as unlikely, it cannot be ruled out as an intermediate from the available information.

One might expect *cis*- and *trans*-styrenes to afford the same cationic intermediate and thus the same ratio of diastereomers **35** and **36**. This is clearly not observed. It is possible that the (*E*)- and (*Z*)-styrenes react via different transition states, and this is responsible for the different stereoselectivities for each isomer. Assuming a stepwise pathway, there are several different transition states that could account for the stereoselectivity of the formal [3 + 2] cycloadditions.

One of these possible transition state structures for *trans*-styrenes is **49** which offers the advantage of minimizing nonbonded interactions and allowing some degree of π–π interactions between the electron-rich styrene and electron-deficient benzylic cation. Carbon–carbon bond



formation would then afford cation **50** which could then rapidly cyclize to products **36** prior to bond rotations that result in loss of the trans orientation between the aryl and methyl substituents of the styrene. Given the present information there is no experimental evidence that excludes any of the other possible transition states that would also give the same stereochemical outcome.

Conclusion

The reaction of benzylic cations with styrenes affords dihydro(1*H*)indenes in good yield and appears to be a general reaction for activated alkenes. The origin of the high stereoselectivities seen for (*E*)-styrenes and application of this methodology to natural product synthesis is currently under investigation.

Experimental Section

General Information. NMR spectra were recorded on a General Electric QE-300 NMR or a GE GN-500 NMR; shifts

(25) For a review of the dienone–phenol rearrangement see: (a) Wedemeyer, K. F. In *Houben-Weyl Methoden der Organischen Chemie*; Mueller, E.; Bayer, O., Eds.; G. Thieme Verlag: Stuttgart, 1976; Vol. VI/1c, p 810. See also: (b) Darling, S. F.; Spanagel, E. W. *J. Am. Chem. Soc.* **1931**, *53*, 1117. (c) Yanagita, M.; Inayama, S.; Hirakura, M.; Seki, F. *J. Org. Chem.* **1958**, *23*, 690. (d) Arnold, R. T.; Buckley, J. S., Jr.; Richter, R. *J. Am. Chem. Soc.* **1947**, *69*, 2322.

(26) (a) Murphy, W. S.; Wattanasin, S. *Chem. Soc. Rev.* **1983**, 213. (b) Ie Noble, W. J.; Gabrielsen, B. *Tetrahedron Lett.* **1970**, 45. (c) Dorling, S.; Harley-Mason, J. *Chem. Ind.* **1959**, 1551.

(27) Hedaya, A. E.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1661.

reported are relative to internal $CHCl_3$; coupling constants, J, are reported in Hz and refer to apparent peak multiplicities and not true coupling constants. Abbreviations used are as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = pentuplet. Mass spectra were recorded at the UCR-MS facility on a VG-7070EHF or a VG-ZAB1FHF and are reported as percent relative intensity to the parent peak. IR spectra were recorded on a Nicolet-5DX FT-IR. Microanalyses were performed by Desert Analytics, Tucson, AZ. Flash chromatography was done on E. Merck Silica Gel no. 60, 230–400 mesh, and analytical TLC was preformed on E. Merck glass-backed silica gel 60 plates, 0.250-mm thickness, with a 254-nm fluorescent indicator. HPLC was carried out on a Rainin HPLC system with HPX pumps and a Knauer model 198 RI detector using a 25-cm column (4.6-mm or 1-cm i.d.) packed with 8-μm silica gel. Capillary GC was carried out on a Hewlett-Packard 5890 equipped with a HP-3393A computing integerator using a 25 m HP-101 (methyl silicone) column. The following standard GC parameters were used unless indicated otherwise: flow rate 60 mL/min; injector temperature 200 °C; detector temperature 280 °C; temperature program 40–280 °C at 18 °C/min, initial time 1 min, final time 5 min. THF and ether were distilled from sodium/benzophenone. CH_2Cl_2 was distilled from CaH_2. Solvents for chromatography and recrystallization were distilled prior to use. Commercial compounds were purchased from Fischer Scientific or Aldrich Chemical Co. unless stated otherwise. Alcohol **20** is commercially available from Sharpe Chemicals, Burbank, CA. The molarities indicated for alkyllithiums were established by titration with 2,5-dimethoxybenzyl alcohol.[28] Melting points are uncorrected. In cases where synthetic intermediates or products were isolated by "aqueous workup (aqueous solution, organic solvent)", the procedure was to quench the reaction mixture with the indicated aqueous solution, dilute with the indicated organic solvent, separate the organic layer, extract the aqueous layer several times with the organic solvent, dry the combined organic extracts over $MgSO_4$, and remove the solvent under reduced pressure (water aspirator) with a Büchi Rotavapor. Unless stated otherwise, all reactions were run under an atmosphere of nitrogen or argon in oven-dried glassware. The pH 8.5 buffer solution was prepared from saturated aqueous NH_4Cl/concentrated NH_4OH (9:1, v/v).

1-(3,5-Dimethyl-4-hydroxyphenyl)-3-phenylpropanol (14). *t*-BuLi (36.6 mL of a 1.7 M solution in pentane, 62.2 mmol) was added dropwise over 4 min to a solution of 4-bromo-2,6-dimethylphenol (4.05 g, 15.8 mmol) and THF (100 mL) at −78 °C. The resulting mixture was then slowly warmed to 0 °C. After 25 min, saturated aqueous NH_4Cl (40 mL) was added. Aqueous workup (pH 8.5 buffer, ether) followed by crystallization from hexane/ether afforded 2.57 g (50%) of **14** as white crystals: mp 114–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.16 (m, 5 H, Ar), 6.97 (s, 2 H, Ar), 4.62–4.54 (m, 2 H, ArO*H*, C*H*OH), 2.80–2.60 (m, 2 H, CH_2Ph), 2.25 (s, 6 H, $ArCH_3$), 2.20–1.95 (m, 2 H, CH_2CH_2Ph), 1.71 (d, J = 3.2 Hz, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 141.9, 136.0, 128.4, 128.3, 126.3, 125.7, 123.1, 73.7, 40.2, 32.2, 16.0; IR (CCl_4) 3367, 3168, 2946, 1602, 1488, 1453, 1375, 1217, 1071, 690 cm^{-1}; MS (EI, 70 eV) m/z 256 (M$^+$, 12), 238 (5), 151 (100), 91 (24); HRMS calcd for $C_{17}H_{20}O_2$ 256.1463, found 256.1461. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.62; H, 7.86. Found: C, 79.72; H, 7.87.

2-(3,5-Dimethyl-4-hydroxyphenyl)-2-propanol (15). The same procedure given for the preparation of **14** was carried out with acetone. 4-Bromo-2,6-dimethylphenol (4.27 g, 21.2 mmol) was treated with *tert*-butyllithium (48 mL of a 0.91 M solution in pentane, 43.2 mmol) and acetone (1.60 mL, 21.8 mmol) to afford 4.18 g of crude **15**. Recrystallization (hexane/ether) afforded 180 mg (5%) of alcohol **15** as a white solid: mp 156–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 2 H, Ar), 4.57 (s, 1 H, OH), 2.26 (s, 6 H, $ArCH_3$), 1.54 (s, 6 H, CCH_3).

1-(3-Methoxyphenyl)-1-propanol (21). Ethylmagnesium bromide (14.0 mL of a 2 M solution in THF, 28 mmol) was added dropwise to a stirred solution of *m*-anisaldehyde (**17**, 2.00 mL, 13.1 mmol) at −78 °C. The resulting solution was stirred at −78 °C for 10 min and then allowed to warm to room temperature. After the solution was stirred for 2 h at room temperature, CH_3OH (3 mL) was added. Aqueous workup (H_2O, ether) afforded 2.58 g (99%) of **21** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.24 (m, 1 H, Ar), 6.94–6.81 (m, 3 H, Ar), 4.61 (br s, 1 H, C*H*CH_2), 3.82 (s, 3 H, OMe), 1.90–1.65 (m, 3 H, CHO*H*, CHCH_2), 0.93 (t, J = 7.5 Hz, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 146.3, 129.4, 118.3, 112.9, 111.4, 76.0, 55.2, 31.8, 10.1.

1-(4-Hydroxy-3-methoxyphenyl)-1-propanol (22). The same procedure described for the preparation of **21** was carried out with vanillin (**18**, 3.00 g, 19.7 mmol) and EtMgBr (29.0 mL of a 2 M solution in THF, 58.0 mmol, 2.9 equiv) to afford crude **22**. Flash chromatography (3:1 hexane/ethyl acetate) gave 2.40 g (67%) of **22** as a white solid: mp 79–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91–6.80 (m, 3 H, Ar), 5.58 (s, 1 H, ArOH), 4.54 (dt, J = 3, 6.6 Hz, 1 H, C*H*OH), 3.90 (s, 3 H, OCH_3), 1.90–1.65 (m, 2 H, CH_2CH$_3$), 0.92 (t, J = 7.5 Hz, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 145.0, 136.7, 119.0, 114.0, 108.3, 76.0, 55.9, 31.8, 10.2.

1-(3,5-Dimethoxy-4-hydroxyphenyl)-1-propanol (23). The same procedure described for the preparation of **21** was carried out with syringaldehyde (**19**, 1.98 g, 10.9 mmol) and EtMgBr (27.2 mL of a 2.0 M solution in THF, 54.3 mmol) to afford 1.66 g of crude alcohol. Recrystallization (hexane/ether) afforded 1.01 g (44%) of **23** as white crystals: mp 96–96.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (s, 2 H, Ar), 5.48 (s, 1 H, ArOH), 4.51 (t, J = 5.7 Hz, 1 H, C*H*OH), 3.89 (s, 6 H, OCH_3), 1.77–1.65 (m, 3 H, CHO*H*, CH_2CH$_3$), 0.91 (t, J = 7.4 Hz, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 135.8, 133.9, 102.5, 76.2, 56.2, 31.9, 10.2; IR (CCl_4) 3613, 3557, 2959, 2938, 1618, 1464, 1429, 1371 cm^{-1}; MS (EI, 20 eV) m/z 212 (M$^+$, 21), 194 (100), 183 (67), 123 (34).

2,6-Dimethyl-4-(3-phenylpropyl)phenol (24). Bromotrimethylsilane (0.21 mL, 1.59 mmol) was added to a solution of alcohol **14** (207 mg, 0.78 mmol) and THF (5 mL) to give a yellow solution. After 10 min, the reaction solution was cooled to 0 °C and lithium aluminum hydride (163 mg, 4.30 mmol) was added. After 30 min, ether was added and the resulting mixture was filtered through silica gel. Drying ($MgSO_4$) and concentration afforded 202 mg of crude **24**. Flash chromatography (10:1 hexane/ethyl acetate) gave 169 mg (95%) of phenol **24** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5 H, Ar), 6.86 (s, 2 H, Ar), 4.54 (s, 1 H, OH), 2.71 (t, J = 7.6 Hz, 2 H, CH_2Ar), 2.59 (t, J = 7.6 Hz, 2 H, CH_2Ar), 2.28 (s, 6 H, $ArCH_3$), 1.95 (p, J = 7.6 Hz, 2 H, CH_2CH_2Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 142.4, 133.8, 128.4, 128.4, 128.2, 125.6, 122.8, 35.4, 34.5, 33.2, 15.8; IR (CCl_4) 3580, 3042, 2882, 1600, 1487, 1452, 1232, 1192, 902, 692 cm^{-1}; MS (EI, 20 eV) m/z 240 (M$^+$, 65), 148 (17), 135 (100), 91 (15); HRMS calcd for $C_{17}H_{20}O$ 240.1514, found 240.1521.

2,6-Dimethoxy-4-propylphenol (25). The same procedure described for the preparation of **24** was carried out with alcohol **19** (209 mg, 0.98 mmol), bromotrimethylsilane (0.26 mL, 2.0 mmol), and lithium aluminum hydride (187 mg, 5.0 mmol) to afford crude **25**. Flash chromatography (10:1 hexane/ethyl acetate) afforded 165 mg (84%) of **25** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40 (s, 2 H, Ar), 5.38 (s, 1 H, OH), 3.87 (s, 6 H, OCH_3), 2.51 (t, J = 7.7 Hz, 2 H, ArCH_2), 1.07 (m, 2 H, CH_2CH$_3$), 0.94 (t, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 133.8, 132.5, 104.9, 56.1, 38.2, 24.8, 13.8; IR (CCl_4) 3557, 2959, 2931, 1616, 1457, 1215, 1120 cm^{-1}; MS (EI, 20 eV) m/z 196 (M$^+$, 59), 182 (11), 167 (100), 135 (18).

General Procedure for Quinone Methide Formation: 2,6-Dimethyl-4-(3-phenylpropylidene)-2,5-cyclohexadien-1-one (26a). Ag_2O (323 mg, 1.39 mmol, 10 equiv) was added to a solution of phenol **24** (33.5 mg, 0.14 mmol) and $CDCl_3$ (1 mL) to give a yellow solution of quinone methide **26a** after 10 min (monitored by ^{1}H NMR). Solutions of **26a** were stable for several days with no sign of decomposition (^{1}H NMR). Filtration through a plug of glass wool afforded a $CDCl_3$ solution of **26a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4–7.2 (m, 6 H, HC=CH, Ar), 6.88 (s, 1 H, HC=CH), 6.31 (t, J = 6.0 Hz, 1 H, CH_2CH=C), 2.84 (s, 4 H, CH_2), 2.02 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.7, 146.3, 140.4, 138.4, 136.5, 134.8, 132.2, 129.7, 128.5, 128.4, 126.3, 35.3, 30.7, 16.7, 16.0; IR (CCl_4) 3082, 2872, 1629, 1601, 1577, 1496, 1477, 1452, 1207, 902, 687 cm^{-1}; MS (EI, 20 eV) m/z 238 (M$^+$, 52), 223 (34), 135 (7), 104 (10), 91 (100); HRMS calcd for $C_{17}H_{18}O$ 238.1358, found 238.1362. The $CDCl_3$ was then removed and the quinone methide was dried by chasing with benzene (3 × 3 mL) or filtration through a plug of Na_2SO_4 before use in the formal cycloaddition. This identical procedure was used with

(28) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.

(29) Commercially available from Fluka Chemie, Ronkonkama, NY.

CH_2Cl_2 to prepare solutions of **26a** in this solvent.

2,6-Dimethoxy-4-propylidene-2,5-cyclohexadien-1-one (26b). Ag_2O (298 mg, 1.29 mmol, 7.1 equiv) was added to a solution of phenol **25** (35.3 mg, 0.180 mmol) and $CDCl_3$ (2 mL) to give a yellow solution of quinone methide **26b** after 10 min (monitored by ^1H NMR). Solutions of **26b** were unstable and showed signs of decomposition within 10 min of forming (^1H NMR). Due to instability, it was not fully characterized. Filtration of the solution through a plug of glass wool afforded a $CDCl_3$ solution of **26b**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.57 (s, 1 H, HC=CH), 6.31 (partially obscured t, J = 8.1 Hz, 1 H, CH_2CH=C), 6.25 (s, 1 H, HC=CH), 3.81 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 2.52 (apparent p, J = 8.0 Hz, 2 H, CH_2CH_3), 1.17 (t, J = 8.0 Hz, 3 H, CH_3). This identical procedure was used with CH_2Cl_2 to prepare solutions of **26b** in this solvent. Concentration of solutions of **26b** resulted in the formation of a solid polymer.

(*Z*)-1-(4-Hydroxyphenyl)propene (30).[30] Using the general procedure of Still et al., KH (1.95 g of a 35% wt solution in oil, 17.0 mmol) was washed with hexane (3 × 10 mL). THF (17.7 mL) was then added followed by addition of hexamethyldisilazane (3.6 mL, 17 mmol). The reaction mixture was stirred for 30 min. It was then added over 10 min into a solution of ethyltriphenylphosphonium bromide (7.05 g, 19.0 mmol), hexamethylphosphoramide (7.2 mL), and THF (62 mL) to afford an orange solution. The resulting solution was stirred at room temperature for 10 min and then cooled to −78 °C. After 20 min, a solution of *p*-hydroxybenzaldehyde (490 mg, 4.0 mmol) and THF (3 mL) was added. The reaction mixture was allowed to warm to room temperature over 1 h. After the mixture was stirred for 1 h at room temperature, H_2O (50 mL) was added to quench the reaction. Aqueous workup (H_2O, ether) followed by flash chromatography (4:1 hexane/ethyl acetate) afforded 479 mg (89%) of **30**[30] (13:1 *Z*/*E*, GC, *Z*-isomer t_R = 7.80 min) a clear oil. Major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J = 8.4 Hz, 2 H, Ar), 6.80 (d, J = 8.4 Hz, 2 H, Ar), 6.35 (d, J = 11.7 Hz, 1 H, *H*C=CHCH$_3$), 5.69 (dt, J = 7.2, 14.1 Hz, 1 H, HC=C*H*CH$_3$), 5.46 (s, 1 H, OH), 1.88 (dd, J = 1.4, 7.2 Hz, 3 H, CHC*H*$_3$).

(*Z*)-1-(4-Hydroxy-3-methoxyphenyl)propene (31).[31] The same procedure described for the preparation of **30** was carried out with vanillin (610 mg, 4.01 mmol) to afford crude **31**. Flash chromatography (6:1 hexane/ethyl acetate) of the crude styrene afforded 530 mg (80%) of **31**[31] (11:1 *Z*/*E*, GC, *Z*-isomer t_R = 5.70 min, temperature program 100–280 °C at 15 °C/min) as a clear oil. Major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 6.90–6.80 (m, 3 H, Ar), 6.35 (d, J = 11.4 Hz, 1 H, *H*C=CHCH$_3$), 5.71–5.69 (m, 1 H, HC=C*H*CH$_3$), 5.60 (s, 1 H, OH), 3.89 (s, 3 H, OCH_3), 1.90 (dd, J = 1.2, 6.0 Hz, 3 H, HC=CHC*H*$_3$).

(*Z*)-1-(4-Methoxyphenyl)propene (32).[32] The same procedure described for the preparation of **30** was carried out with *p*-anisaldehyde (2.56 g, 21.0 mmol) to afford crude **32**.[32] Flash chromatography (4:1 hexane/ethyl acetate) gave 635 mg (99%) of **32** (10:1 *Z*/*E*, GC, *Z*-isomer t_R = 7.36 min) as a clear oil. Major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.4 Hz, 2 H, OC*H*C=CH), 6.86 (d, J = 8.7 Hz, 2 H, OCCH=C*H*), 6.35 (d, J = 11.7 Hz, 1 H, *H*C=CHCH$_3$), 5.75–5.64 (m, 1 H, HC=C*H*CH$_3$), 3.81 (s, 3 H, OCH_3), 1.88 (dd, J = 1.8, 7.2 Hz, HC=CHC*H*$_3$).

General Procedure for the Formal [3 + 2] Cycloaddition of a Quinone Methide and Styrene in the Presence of Zinc(II) Chloride: (1*R,2*S**,3*R**)- and (1*S**,2*S**,3*R**)-6-Hydroxy-1-(4-hydroxyphenyl)-2,5,7-trimethyl-3-(2-phenylethyl)-2,3-dihydroindene [35a (1*R**,2*S**,3*R**) and 36a (1*S**,2*S**,3*R**)].** A CH_2Cl_2 solution of quinone methide **26a** (prepared from 38.6 mg, 0.161 mmol of phenol **24** and 2 mL of CH_2Cl_2) was filtered through Na_2SO_4 into a two-necked round-bottomed flask, diluted with additional CH_2Cl_2 (10 mL), and cooled to −78 °C. Styrene **30** (0.82 mL of a 0.255 M solution in CH_2Cl_2, 0.21 mmol) and $ZnCl_2$ (0.20 mL of a 1 M solution in ether, 0.20 mmol) were added sequentially to give a bright yellow solution. The reaction mixture was stirred for 5 min at −78 °C and then allowed to warm to room temperature. The resulting soultion was stirred for 1 h. Aqueous workup (saturated aqueous $NaHCO_3$, CH_2Cl_2) afforded crude **35a** and **36a**. HPLC (1-cm diameter 8-μm silica gel column; 3:1 hexane/ethyl acetate, 9 mL min^{-1}, t_R = 22 min) afforded 44 mg (71%) of **35a** and **36a** as a clear oil in a 2.2:1 ratio: ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereomers **35a** and **36a**) δ 153.7, 151.2, 151.0, 142.8, 142.8, 142.7, 142.4, 138.8, 138.4, 136.7, 128.9, 128.7, 128.3, 125.7, 125.7, 123.3, 123.0, 122.0, 121.4, 120.1, 119.9, 115.3, 115.1, 58.1, 56.6, 51.3, 50.9, 47.8, 45.3, 36.6, 34.2, 33.4, 31.3, 19.6, 16.4, 15.1, 12.3, 12.2; IR (CCl_4) 3612, 3345, 2979, 2867, 1614, 1471, 1442, 1381, 1265, 1216, 873, 775, 699 cm^{-1}; MS (EI, 20 eV) m/z 372 (M^+, 28), 280 (13), 267 (100), 252 (6), 91 (4). Anal. Calcd for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 83.87; H, 7.72. Analytical samples of the two diastereomers were prepared by HPLC (4.6-mm i.d. column, 9:1 hexane/ethyl acetate, 0.5 mL min^{-1}) purification to afford the major diastereomer **35a** as white crystals (t_R = 71 min) and the minor diastereomer **36a** as an oil (t_R = 75 min). Diastereomer **35a**: mp 154–154.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.15 (m, 5 H, Ar), 6.96 (d, J = 8.4 Hz, 2 H, Ar), 6.89 (s, 1 H, Ar), 6.73 (s, J = 8.4 Hz, 2 H, Ar), 4.42 (br s, 1 H, OH), 3.74 (d, J = 6.6 Hz, 1 H, $CHAr_2$), 2.80–2.60 (m, 3 H, CHAr, CH_2Ar), 2.26 (s, 3 H, $ArCH_3$), 2.13–1.97 (m, 2 H, C*H*CH$_3$, C*H*HCH$_2$Ar), 1.95–1.83 (m, 1 H, CH*H*CH$_2$Ar), 1.71 (s, 3 H, $ArCH_3$), 1.19 (d, J = 6.9 Hz, 3 H, CHC*H*$_3$). Diastereomer **36a**: oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.18 (m, 5 H, Ar), 6.89 (m, 3 H, Ar), 6.70 (d, J = 8.4 Hz, 2 H, Ar), 4.45 (br s, 1 H, OH), 3.89 (d, J = 3.6 Hz, 1 H, $CHAr_2$), 3.14 (q, J = 6.9 Hz, 1 H, CHAr), 2.65 (t, J = 7.8 Hz, 2 H, CH_2Ar), 2.51–2.40 (m, 1 H, C*H*CH$_3$), 2.26 (s, 3 H, $ArCH_3$), 1.95–1.84 (m, 5 H, C*H*$_2$CH$_2$Ar, $ArCH_3$), 1.03 (d, J = 6.9 Hz, 3 H, CHC*H*$_3$).

(1*R,2*S**,3*R**)- and (1*S**,2*S**,3*R**)-6-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2,5,7-trimethyl-3-(2-phenylethyl)-2,3-dihydroindene [35b (1*R**,2*S**,3*R**) and 36b (1*S**,2*S**,3*R**)].** The same procedure described for the preparation of **35a** and **36a** was carried out with quinone methide **26a** [from phenol **24** (9.9 mg, 0.040 mmol)], styrene **31** (8.9 mg, 0.052 mmol), and $ZnCl_2$ (0.05 mL of a 1.0 M solution in ether, 0.050 mmol) to afford 17.6 mg of crude product. HPLC (4.6-mm i.d. column; 3:1 hexane/ethyl acetate, 0.5 mL min^{-1}, t_R = 15 min) afforded 8.9 mg (54%) of **35b** and **36b** (clear oil) as an inseparable 3:1 (**35b**/**36b**) mixture.[33] Major diastereomer **35b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–6.40 (m, 9 H, Ar), 5.49 (s, 1 H, OH), 4.49 (s, overlaps with diastereomer 1 H, OH), 3.79 (s, overlaps with diastereomer, 3 H, OMe), 3.72 (d, J = 6.6 Hz, 1 H, CHAr), 2.77–2.63 (m, overlaps with diastereomer, 3 H, CH_2Ar, CHAr), 2.27 (s, overlaps with diastereomer, 3 H, $ArCH_3$), 2.17–1.79 (m, overlaps with diastereomer, 3 H, C*H*$_2$CH$_2$Ar,C*H*CH$_3$), 1.74 (s, 3 H, $ArCH_3$), 1.20 (d, J = 6.6 Hz, 3 H, CHC*H*$_3$). Minor diastereomer **36b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–6.40 (m, 9 H, Ar), 5.48 (s, 1 H, OH), 4.49 (s, overlaps with diastereomer, 1 H, OH), 3.89 (d, J = 4.2 Hz, 1 H, $CHAr_2$), 3.80 (s, overlaps with diastereomer, 3 H, OMe), 3.15 (q, J = 6.9 Hz, 1 H, CHAr), 2.77–2.63 (m, 2 H, CH_2Ar), 2.52–2.41 (m, 1 H, C*H*CH$_3$), 2.27 (s, overlaps with diastereomer, 3 H, $ArCH_3$), 1.97–1.78 (m, 5 H, C*H*$_2$CH$_2$CH$_3$, Ar*CH*$_3$) 1.04 (d, J = 6.9 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$, the mixture of diastereomers **35b** and **36b**) δ 151.3, 151.0, 146.6, 146.5, 143.8, 142.8, 142.8, 142.6, 142.3, 138.7, 138.4, 138.4, 136.5, 128.3, 125.7, 123.3, 123.0, 122.0, 121.4, 120.6, 120.3, 120.2, 120.0, 114.2, 114.0, 110.1, 58.7, 57.2, 56.0, 55.9, 51.4, 50.8, 47.9, 45.3, 36.6, 34.2, 33.4, 31.3, 19.6, 16.4, 15.1, 12.2, 12.2; IR (CCl_4) 3619, 3556, 3028, 2958, 2930, 1604, 1464, 1452, 1374, 1264, 1230, 1215, 874 cm^{-1}; MS (EI, 70 eV) m/z 402 (M^+, 14), 311 (8), 297 (100), 123 (3), 105 (32), 91 (88), 77 (28). Anal. Calcd for $C_{27}H_{30}O_3$: C, 80.56; H, 7.51. Found: C, 80.56; H, 7.81.

(1*R,2*S**,3*R**)- and (1*S**,2*S**,3*R**)-5,7-Dimethoxy-3-ethyl-6-hydroxy-1-(4-hydroxyphenyl)-2-methyl-2,3-dihydroindene [35c (1*R**,2*S**,3*R**) and 36c (1*S**,2*S**,3*R**)].** The same procedure described for the preparation of **35a** and **36a** was carried out with quinone methide **26b** [from phenol **25** (35.3 mg, 0.180 mmol)], styrene **30** (1.0 mL of a 0.254 M solution in CH_2Cl_2, 0.255 mmol), and $ZnCl_2$ (0.20 mL of a 1.0 M solution in

(30) A known compound: Lee Da Silva, J.-C.; Marechal, E. *Bull. Soc. Chim. Fr.* **1974**, 779.

(31) Commercially available as a mixture of isomers from Aldrich Chemical Co., Milwaukee, WI.

(32) A known compound: Davies, D. E.; Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1275.

(33) In cases where an inseparable mixture of **35** and **36** was obtained the assignment of ^1H NMR spectra and coupling constants was made on chromatography fractions enriched in one of the diastereomers in conjunction with decoupling experiments.

ether, 0.20 mmol). HPLC (1-cm i.d. column; 1:1 hexane/ethyl acetate, 9 mL min^{-1}, t_R = 14 min) afforded 56.8 mg (96%) of **35c** and **36c** as an inseparable 1:1 mixture[33] (white crystals), mp 151–152 °C. **35c**: ^1H NMR (300 MHz, C_6D_6) δ 6.94 (d, J = 8.1 Hz, 2 H, Ar), 6.60–6.50 (m, overlaps with diastereomer, 2 H, Ar), 6.34 (s, 1 H, Ar), 5.40 (br s, 1 H, OH), 3.70 (d, J = 7.5 Hz, 1 H, $CHAr_2$), 3.29 (s, overlaps with diastereomer, 3 H, OMe), 3.26 (s, 3 H, OMe), 2.51 (m, 1 H, CHAr), 1.96 (sextet, J = 7.2 Hz, 1 H, $CHCH_3$), 1.80–1.50 (m, overlaps with diastereomer, 2 H, CH_2CH_3), 1.03 (d, J = 6.6 Hz, 3 H, $CHCH_3$), 0.90–0.80 (m, overlaps with diastereomer, 3 H, CH_2CH_3); **36c** 6.87 (d, J = 8.4 Hz, 2 H, Ar), 6.60–6.50 (m, overlaps with diastereomer, 2 H, Ar), 6.38 (s, 1 H, Ar), 5.80 (br s, 1 H, OH), 3.94 (d, J = 5.4 Hz, 1 H, $CHAr_2$), 3.36 (s, 3 H, OMe), 3.29 (s, overlaps with diastereomer, 3 H, OMe), 2.90 (q, J = 7.2 Hz, 1 H, CHAr), 2.41–2.35 (m, 1 H, $CHCH_3$), 1.80–1.50 (m, overlaps with diastereomer, 2 H, CH_2CH_3), 0.90–0.80 (m, overlaps with diastereomer, 6 H, $CHCH_3$, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereomers **35c** and **36c**) δ 154.0, 147.5, 147.1, 144.0, 143.6, 138.6, 138.2, 138.1, 137.3, 137.1, 136.8, 128.9, 128.7, 115.1, 103.2, 102.3, 60.0, 59.5, 56.7, 56.5, 55.2, 53.0, 50.9, 48.2, 26.2, 22.2, 18.8, 14.4, 12.2, 11.1; IR (CCl_4) 3610, 3547, 2961, 2933, 1595, 1465, 1445, 1373, 1261, 1234, 1206, 864 cm^{-1}; MS (EI, 20 eV) m/z 328 (M^+, 69), 313 (3), 299 (100), 284 (5), 267 (11), 234 (12), 205 (8), 91 (9); HRMS calcd for $C_{20}H_{24}O_4$ 328.1675, found 328.1676.

(1*R,2*S**,3*R**)- and (1*S**,2*S**,3*R**)-5,7-Dimethoxy-3-ethyl-6-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-methyl-2,3-dihydroindene [35d (1*R**,2*S**,3*R**) and 36d (1*S**,2*S**,3*R**)].** The same procedure described for the preparation of **35a** and **36a** was carried out with quinone methide **26b** [from phenol **25** (9.81 mg, 0.050 mmol)], styrene **31** (0.72 mL of a 0.10 M solution in CH_2Cl_2, 0.072 mmol, 1.5 equiv), and $ZnCl_2$ (0.09 mL of a 1.0 M solution in ether, 0.09 mmol, 1.8 equiv) to afford 19.6 mg of crude product. HPLC (4.6-mm i.d. column; 3:1 hexane/ethyl acetate, 1.5 mL min^{-1}, t_R = 9.5 min) afforded 9.2 mg (51%) of **35d** and **36d** as an inseparable 1:1 mixture[33] (white powder), mp 74–77 °C. **35d**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.70–6.50 (m, overlaps with diastereomer, 4 H, Ar), 5.60–5.40 (m, overlaps with diastereomer, 2 H, OH), 3.91 (s, overlaps with diastereomer, 3 H, OMe), 3.82 (s, 3 H, OMe), 3.74 (d, J = 7.5 Hz, 1 H, $CHAr_2$), 3.39 (s, 3 H, OMe), 2.64 (q, J = 6.9 Hz, 1 H, CHAr), 2.05–1.50 (m, overlaps with diastereomer, 3 H, CH_2CH_3, $CHCH_3$), 1.16 (d, J = 6.6 Hz, 3 H, $CHCH_3$), 1.01–0.93 (m, overlaps with diastereomer, 3 H, CH_2CH_3); **36d** 6.70–6.50 (m, overlaps with diastereomer, 4 H, Ar), 5.60–5.40 (m, overlaps with diastereomer, 2 H, OH), 3.91 (m, overlaps with diastereomer, 4 H, $CHAr_2$, OMe), 3.81 (s, 3 H, OMe), 3.49 (s, OMe, 3 H), 2.99 (q, J = 7.2 Hz, 1 H, CHAr), 2.42 (sextet, J = 6.6 Hz, 1 H, $CHCH_3$), 2.05–1.50 (m, overlaps with diastereomer, 2 H, CH_2CH_3), 1.01–0.93 (m, overlaps with diastereomer, 6 H, $CHCH_3$, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereomers **35d** and **36d**) δ 147.3, 146.9, 146.3, 143.8, 143.7, 143.4, 138.5, 138.0, 137.8, 137.0, 136.8, 136.5, 129.3, 128.9, 120.5, 120.2, 113.8, 113.8, 110.2, 110.1, 102.8, 101.9, 60.0, 59.7, 57.1, 56.3, 55.9, 55.9, 55.5, 52.6, 50.7, 48.2, 47.9, 26.0, 22.1, 18.9, 14.5, 12.2, 11.0; IR (CCl_4) 3556, 2979, 2867, 1608, 1464, 1443, 1149, 1119, 1039, 809 cm^{-1}; MS (EI, 20 eV) m/z 358 (M^+, 75), 343 (4), 329 (100), 314 (6), 234 (44), 137 (11); HRMS calcd for $C_{21}H_{26}O_5$ 358.1780, found 358.1794. Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.12; H, 7.41.

(1*R,2*S**,3*R**)- and (1*S**,2*S**,3*R**)-5,7-Dimethoxy-3-ethyl-6-hydroxy-1-(4-methoxyphenyl)-2-methyl-2,3-dihydroindene [35e (1*R**,2*S**,3*R**) and 36e (1*S**,2*S**,3*R**)]. From 32.** The same procedure described for the preparation of **35a** and **36a** was carried out with quinone methide **26b** [from phenol **25** (39.3 mg, 0.200 mmol)], styrene **32** (35.7 mg, 0.24 mmol), and $ZnCl_2$ (0.020 mL of a 1.0 M solution in ether, 0.020 mmol). Since catalytic $ZnCl_2$ was used, the addition of Lewis acid was carried out at room temperature. Stirring for 1 h followed by aqueous workup as before afforded 69.9 mg of crude product. Flash chromatography (6:1 hexane/ethyl acetate) afforded 53.6 mg (79%) of **35e** and **36e** as a 1:1 mixture (clear oil).

From 33. The same procedure described for the preparation of **35a** and **36a** was carried out with quinone methide **26b** [from phenol **25** (39.3 mg, 0.200 mmol)], styrene **33** (0.26 mL of a 1.0 M solution in CH_2Cl_2, 0.26 mmol, 1.3 equiv), and $ZnCl_2$ (0.20 mL of a 1.0 M solution in ether, 0.20 mmol, 1.0 equiv) to afford 72.5 mg of crude product. Flash chromatography (6:1 hexane/ethyl acetate) afforded 55.0 mg (81%) of **35e** and **36e** as a 1:42 (**35e**/**36e**) mixture (clear oil). HPLC of the 1:1 mixture of diastereomers (1-cm i.d. column, 20:3:1 $CHCl_3$/hexane/ethyl acetate, 7 mL min^{-1}) afforded diastereomer **35e** (t_R = 18 min, 11:1 mixture **35e**:**36e**) and diastereomer **36e** (t_R = 17 min, > 1:20, **35e**:**36e**). Diastereomer **35e**: ^1H NMR (C_6D_6, 300 MHz) δ 7.08 (d, J = 8.7 Hz, 2 H, Ar), 6.75 (d, J = 8.7 Hz, 2 H, Ar), 6.36 (s, 1 H, Ar), 5.40 (s, 1 H, OH), 3.78 (d, J = 7.5 Hz, 1 H, $CHAr_2$), 3.35 (s, 3 H, OMe), 3.28 (s, 3 H, OMe), 3.26 (s, 3 H, OMe), 2.55 (dt, J = 5.1, 6.9 Hz, 1 H, CHAr), 2.03 (ddq, J = 6.9, 6.9, 7.2 Hz, 1 H, $CHCH_3$), 1.79–1.58 (m, 2 H, CH_2CH_3), 1.07 (d, J = 6.6 Hz, 3 H, $CHCH_3$), 0.91 (t, J = 7.5 Hz, 3 H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.9, 147.3, 143.4, 138.1, 137.8, 137.1, 129.4, 128.7, 113.5, 101.9, 59.6, 56.5, 56.4, 55.2, 52.6, 50.8, 26.0, 18.7, 11.0. IR (CCl_4) 3550, 3000, 2937, 1612, 1465, 1445, 1375, 1247, 1208, 1042, 831, 755 cm^{-1}; MS (EI, 70 eV) m/z 342 (M^+, 78), 327 (5), 313 (100), 298 (6), 253 (3), 234 (11), 149 (10), 91 (5); HRMS calcd for $C_{21}H_{26}O_4$ 342.1831, found 342.1839. Diastereomer **36e**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.01 (d, J = 8.4 Hz, 2 H, Ar), 6.80 (d, J = 8.7 Hz, 2 H, Ar), 6.58 (s, 1 H, Ar), 5.50 (s, 1 H, OH), 3.97 (d, J = 5.4 Hz, 1 H, $CHAr_2$), 3.91 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.00 (q, J = 7.2 Hz, 1 H, CHAr), 2.43 (ddq, J = 6.0, 6.9, 6.9 Hz, 1 H, $CHCH_3$), 1.64–1.55 (m, 2 H, CH_2CH_3), 1.00 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 0.96 (t, J = 7.2 Hz, 3 H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.8, 146.8, 143.8, 138.4, 136.8, 136.5, 129.0, 128.4, 113.4, 102.8, 59.9, 56.3, 55.1, 54.9, 48.1, 47.9, 22.0, 14.4, 12.2; IR (CCl_4) 3548, 3031, 2962, 1612, 1489, 1465, 1374, 1263, 1246, 1206, 1041, 1017, 834, 727, 709 cm^{-1}; MS (EI, 70 eV) m/z 342 (M^+, 41), 327 (5), 313 (100), 298 (7), 234 (44), 149 (5); HRMS calcd for $C_{21}H_{26}O_4$ 342.1831, found 342.1839.

(1*R,2*S**,3*R**)- and (1*S**,2*S**,3*R**)-5,7-Dimethoxy-3-ethyl-6-hydroxy-2-methyl-1-phenyl-2,3-dihydroindene [35f (1*R**,2*S**,3*R**) and 36f (1*S**,2*S**,3*R**)]. From 26b.** The same procedure described for the preparation of **35a** and **36a** was carried out with quinone methide **26b** [from phenol **25** (103.1 mg, 0.525 mmol)], styrene **34** (5.0 mL of a 0.140 M solution in CH_2Cl_2, 0.694 mmol, 1.3 equiv), and $ZnCl_2$ (0.53 mL of a 1.0 M solution in ether, 0.53 mmol, 1.1 equiv) to afford 153.1 mg of crude product. Flash chromatography (6:1 hexane/ethyl acetate) afforded 109.6 mg (67%) of **35f** and **36f** as a 1:17 (**35f**/**36f**) mixture (clear oil).

From 23. Styrene **34** (0.34 mL of a 1.03 M solution in CH_2Cl_2, 0.350 mmol, 1.6 equiv) and $SnCl_4$ (0.13 mL, 1.11 mmol) were sequentially added to a −78 °C solution of alcohol **23** (46.5 mg, 0.219 mmol) and CH_2Cl_2 (22 mL). The resulting solution was stirred for 20 min at −78 °C and then poured into a rapidly stirred solution of saturated aqueous $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL). Aqueous workup ($NaHCO_3$, CH_2Cl_2) followed by flash chromatography (6:1 hexane/ethyl acetate) afforded 54.9 mg (78%) of **35f** and **36f** as a 1:17 (**35f**/**36f**) mixture (clear oil). Major diastereomer **36f**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5 H, Ar), 6.58 (s, 1 H, Ar), 5.44 (s, 1 H, OH), 3.99 (d, J = 5.4 Hz, 1 H, $CHAr_2$), 3.91 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.00 (q, J = 7.2 Hz, 1 H, CHAr), 2.46 (m, 1 H, $CHCH_3$), 1.59 (m, 2 H, CH_2CH_3), 1.00 (d, J = 7.2 Hz, 3 H, $CHCH_3$), 0.95 (t, J = 7.2 Hz, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 144.5, 143.8, 138.6, 136.8, 128.9, 128.1, 127.6, 126.0, 102.8, 60.0, 56.3, 55.8, 48.2, 48.0, 22.1, 14.5, 12.2; IR (CCl_4) 3550, 3023, 2966, 2938, 1613, 1470, 1453, 1375, 1122, 1108, 956, 908, 699 cm^{-1}; MS (EI, 20 eV) m/z 312 (M^+, 100), 283 (84), 117 (4); HRMS calcd for $C_{20}H_{34}O_3$ 312.1725, found 312.1735. Anal. Calcd for $C_{20}H_{34}O_3$: C, 76.89; H, 7.74. Found: C, 76.08; H, 7.76.

(1*S,2*S**)-5,7-Dimethoxy-6-hydroxy-1-phenyl-2-methyl-1,2-dihydroindene (36g).** The same procedure described for the preparation of **36f** from **23** was carried out with alcohol **37**[29] (22.1 mg, 0.120 mmol), styrene **34** (0.19 mL of a 1.03 M solution in CH_2Cl_2, 0.247 mmol), and $SnCl_4$ (0.08 mL, 0.684 mmol). Rather than quenching at −78 °C the reaction mixture was allowed to warm to room temperature for 1 h and then quenched as before. Flash chromatography (8:1 hexane/ethyl acetate) afforded 26.2 mg (77%) of **36g** as a white powder: mp 108–109 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5 H, Ar), 6.61 (s, 1 H, Ar), 5.43 (s, 1 H, OH), 3.94 (d, J = 6 Hz, 1 H, $CHAr_2$), 3.91 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3), 3.16 (dd, J = 7.5, 15 Hz, 1 H, $CHCHH$), 2.52 (dd, J = 6.6, 15 Hz, 1 H, $CHCHH$), 2.46–2.37 (m, 1 H, $CHCHH$), 1.17 (d, J = 6.6 Hz, 3 H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 145.2, 143.7, 136.8, 134.6, 129.6, 128.1, 127.5, 126.0, 102.8,

59.7, 57.8, 56.3, 45.6, 40.3, 19.9; IR (CCl_4) 3550, 2957, 1615, 1472, 1226, 893, 773, 700 cm^{-1}; MS (EI, 20 eV) m/z 284 (M^+, 100), 269 (7), 253 (5), 207 (10), 91 (4); HRMS calcd for $C_{18}H_{20}O_3$ 284.1412, found 284.1423.

(1*S,2*S**)-5,7-Dimethoxy-6-hydroxy-1-(4-methoxyphenyl)-2-methyl-1,2-diydroindene (36h). From 33.** The same procedure described for the preparation of **36f** from **23** was carried out with alcohol **37**[29] (46.1 mg, 0.250 mmol), styrene **33** (0.37 mL of a 1.067 M solution in CH_2Cl_2, 0.40 mmol), and $SnCl_4$ (0.035 mL, 0.30 mmol). The reaction was carried out at 0 °C (30 min) rather than −78 °C. Flash chromatography (4:1 hexane/ethyl acetate) afforded 65.3 mg (87%) of **36h** as a clear oil.

From 32. The same procedure described for the preparation of **36f** from **23** was carried out with alcohol **37**[29] (46.1 mg, 0.250 mmol), styrene **32** (0.37 mL of a 1.07 M solution in CH_2Cl_2, 0.46 mmol), and $SnCl_4$ (0.035 mL, 0.30 mmol). The reaction was carried out at 0 °C (30 min) rather than −78 °C. Flash chromatography (4:1 hexane/ethyl acetate) afforded 74.2 mg (92%) of **36h** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, J = 8.4 Hz, 2 H, Ar), 6.82 (d, J = 8.4 Hz, 2 H, Ar), 6.60 (s, 1 H, Ar), 5.49 (s, 1 H, OH), 3.89 (s, 4 H, OCH_3, $CHAr_2$), 3.79 (s, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3), 3.14 (dd, J = 7.5, 15.3 Hz, 1 H, CHC*H*H), 2.49 (dd, J = 6.9, 15.3 Hz, 1 H, CHCH*H*), 2.44–2.03 (m, 1 H, C*H*CHH), 1.15 (d, J = 6.9 Hz, 3 H, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 147.1, 143.7, 137.2, 136.8, 134.5, 129.7, 128.4, 113.5, 102.9, 59.8, 57.0, 56.2, 55.1, 45.6, 40.1, 19.7; IR (CCl_4) 3549, 3000, 2955, 1613, 1465, 1443, 1245, 896, 805, 750 cm^{-1}; MS (EI, 20 eV) m/z 314 (M^+, 100), 299 (7), 283 (9), 206 (11); HRMS calcd for $C_{19}H_{22}O_4$ 314.1518, found 314.1510.

(1*S,2*R**,3*S**)-3-Ethyl-6-hydroxy-1-phenyl-5-methoxy-2-methyl-1,2-dihydroindene (36i).** The same procedure described for the preparation of **36f** from **23** was carried out with alcohol **22** (52.5 mg, 0.288 mmol), styrene **34** (0.445 mL of a 1.03 M solution in CH_2Cl_2, 0.458 mmol), and $SnCl_4$ (0.168 mL, 1.44 mmol). Flash chromatography (8:1 hexane/ethyl acetate) afforded 70.9 mg (87%) of **36i** as a white crystals: mp 105–106 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.03 (m, 5 H, Ar), 6.69 (s, 1 H, Ar), 6.39 (s, 1 H, Ar), 5.41 (s, 1 H, OH), 3.79 (s, 3 H, OCH_3), 3.71 (d, J = 9.3 Hz, 1 H, $CHAr_2$), 2.82 (ddd, J = 6.9, 7.2, 7.5 Hz, 1 H, CHAr), 2.41 (sex, J = 6.9 Hz, 1 H, C*H*CH$_3$), 1.69–1.55 (m, 1 H, C*H*HCH$_3$), 1.39–1.25 (m, 1 H, CH*H*CH$_3$), 0.94 (d, J = 6.9 Hz, 3 H, CHCH_3), 0.89 (t, J = 7.2 Hz, 3 H, CHHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 144.5, 144.0, 138.9, 138.8, 128.5, 128.2, 126.2, 111.0, 107.4, 57.0, 56.1, 49.2, 48.6, 22.4, 13.8, 12.2; IR (CCl_4) 3557, 2961, 1602, 1465, 1453, 879, 765, 701 cm^{-1}; MS (EI, 20 eV) m/z 282 (M^+, 52), 253 (100), 221 (7); HRMS calcd for $C_{19}H_{22}O_2$ 282.1620, found 282.1610.

(1*S,2*S**,3*R**)-3-Ethyl-6-hydroxy-5-methoxy-1-(4-methoxyphenyl)-2-methyl-2,3-dihydroindene (36j).** The same procedure described for the preparation of **36f** from **23** was carried out with alcohol **22** (0.300 mL of a 0.405 M solution in CH_2Cl_2, 0.122 mmol), styrene **33** (0.49 mL of a 0.352 M solution in CH_2Cl_2, 0.142 mmol), and $SnCl_4$ (0.060 mL, 0.513 mmol) to afford 44.5 mg of crude product. Flash chromatography (3:1 hexane/ethyl acetate) afforded 35.9 mg (95%) of **36j** an inseparable 1:10 mixture (**35j**/**36j**) (white solid). Major diastereomer, **36j**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, J = 8.7 Hz, 1 H, Ar), 6.84 (d, J = 8.7 Hz, 1 H, Ar), 6.79 (s, 1 H, Ar), 6.48 (s, 1 H, Ar), 5.51 (s, 1 H, OH), 3.90 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.76 (d, J = 9.3 Hz, 1 H, $CHAr_2$), 2.92 (dt, J = 6.0, 7.2 Hz, 1 H, CHAr), 2.54–2.41 (m, 1 H, C*H*CH$_3$), 1.79–1.65 (m, 1 H, C*H*HCH$_3$), 1.48–1.35 (m, 1 H, CH*H*CH$_3$), 1.03 (d, J = 7.2 Hz, 3 H, CHCH_3), 0.99 (t, J = 7.5 Hz, 3 H, CHHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 145.1, 144.5, 139.2, 138.7, 136.0, 129.4, 113.6, 111.0, 107.5, 56.1, 55.2, 49.2, 48.5, 29.7, 22.4, 13.7, 12.2; IR (CCl_4) 3557, 2959, 1612, 1465, 1457, 826 cm^{-1}; MS (EI, 70 eV) m/e 312 (M^+, 58), 297 (3), 283 (100), 268 (7), 205 (5); HRMS calcd for $C_{20}H_{24}O_3$ 312.1725, found 312.1718.

(1*S,2*S**)-6-Hydroxy-1-(4-methoxyphenyl)-2,3,3,5,7-pentamethyl-1,2-dihydroindene (36k).** The same procedure described for the preparation of **36f** from **23** was carried out with alcohol **15** (22.8 mg, 0.127 mmol), styrene **33** (0.202 mL of a 1.00 M solution in CH_2Cl_2, 0.202 mmol), and $SnCl_4$ (0.075 mL, 0.64 mmol). Flash chromatography (20:1 hexane/ethyl acetate) afforded 23.7 mg (60%) of **36k** as a white solid: mp 119–120 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, J = 8.7 Hz, 2 H, Ar), 6.86–6.83 (m, 3 H, Ar), 4.46 (s, 1 H, OH), 3.82 (s, 3 H, OCH_3), 3.72 (d, J = 9.9 Hz, 1 H, $CHAr_2$), 2.28 (s, 3 H, $ArCH_3$), 1.97–1.87 (m, 1 H, C*H*CH$_3$), 1.65 (s, 3 H, $ArCH_3$), 1.31 (s, 3 H, CH_3), 0.98–0.96 (m, 6 H, CH_3, CHCH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.9, 151.1, 145.6, 141.2, 137.6, 129.0, 121.8, 121.3, 119.8, 113.7, 57.1, 55.9, 55.2, 44.1, 27.0, 24.6, 16.4, 12.4, 11.5; IR (CCl_4) 3621, 2958, 1613, 1465, 1372, 1231, 873 cm^{-1}; MS (EI, 20 eV) m/z 310 (MH^+, 35), 295 (100), 280 (4), 265 (3); HRMS calcd for $C_{21}H_{26}O_2$ 310.1933, found 310.1931.

(4b*S,9b*S**)-2,4-Dimethoxy-3-hydroxy-4b,5,9b,10-tetrahydroindeno[1,2-*a*]indene (40).** The same procedure described for the preparation of **36f** from **23** was carried out with alcohol **37** (42.7 mg, 0.232 mmol), indene (**39**, 0.361 mL of a 1.03 M solution in CH_2Cl_2, 0.371 mmol), and $SnCl_4$ (0.035 mL, 0.30 mmol). The reaction was carried out at 0 °C (30 min) rather than −78 °C. Flash chromatography (4:1 hexane/ethyl acetate) afforded 63.2 mg (96%) of **40** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.60–7.57 (m, 1 H, Ar), 7.17–7.13 (m, 3 H, Ar), 6.47 (s, 1 H, Ar), 5.46 (s, 1 H, OH), 4.83 (d, J = 7.8 Hz, 1 H, $CHAr_2$), 4.02 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.47–3.35 (m, 1 H, CHHC*H*CHH), 3.27–3.12 (m, 2 H, C*HH*CHCHH), 2.83 (dd, J = 2.7, 15.9 Hz, 1 H, CHHCHC*H*H), 2.64 (dd, J = 6.6, 15.6 Hz, 1 H, CHHCHCH*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 144.2, 143.5, 142.4, 136.8, 134.3, 129.2, 126.6, 126.6, 125.9, 124.6, 102.6, 60.1, 56.3, 54.6, 43.4, 39.4, 38.4; IR (CCl_4) 3547, 3039, 2940, 1616, 1476, 1445, 1233, 899 cm^{-1}; MS (EI, 20 eV) m/e 282 (M^+, 100), 267 (4), 251 (5), 191 (10), 167 (59), 91 (6); HRMS calcd for $C_{18}H_{18}O_3$ 282.1256, found 282.1252.

1-(3,5-Dimethyl-4-hydroxyphenyl)-6-hydroxy-1,3,3,5,7-pentamethyl-1,2-dihydroindene (42). The same procedure described for the preparation of **36f** from **23** was carried out with alcohol **15** (28.8 mg, 0.16 mmol), β-methylstyrene (**34**, 0.25 mL of a 1.03 M solution, 0.258 mmol), and $SnCl_4$ (0.09 mL, 0.769 mmol). Flash chromatography (6:1 hexane/ethyl acetate) afforded 20.0 mg (70%) of **42** as a white solid: mp 150–152 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1 H, Ar), 6.79 (s, 2 H, Ar), 4.52 (s, 1 H, OH), 4.49 (s, 1 H, OH), 2.30 (s, 3 H, $ArCH_3$), 2.20 (s, 6 H, $ArCH_3$), 2.13–2.10 (m, 2 H, CH_2), 1.80 (s, 3 H, $ArCH_3$), 1.71 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 149.7, 146.4, 144.3, 142.7, 126.4, 122.4, 122.1, 121.8, 119.3, 62.0, 50.6, 41.9, 31.8, 31.6, 28.1, 16.5, 16.1, 11.9; IR (CCl_4) 3621, 2956, 1475, 1222 cm^{-1}; MS (EI, 20 eV) m/z 324 (M^+, 44), 309 (100); HRMS calcd for $C_{22}H_{28}O_2$ 324.2089, found 324.2090.

(4a*R,5*S*,9b*R**)- and (4a*R**,5*R**,9b*R**)-7,9-Dimethoxy-5-ethyl-8-hydroxy-2,3,4,4a,5,9b-hexahydroindeno[1,2-*b*]pyran [43a (4a*R**,5*S*,9b*R**) and 43b (4a*R**,5*R**,9b*R**)].** A solution of quinone methide **26b** [from phenol **25** (0.98 mL of a 0.25 M solution in CH_2Cl_2, 0.25 mmol)] was filtered through Na_2SO_4 into a round-bottom flask and cooled to −78 °C. Dihydropyran (0.03 mL, 0.33 mmol, 1.3 equiv) and $BF_3{\cdot}OEt_2$ (0.23 mL, 2.50 mmol, 10.0 equiv) were added sequentially. The resulting solution was stirred for 15 min at −78 °C and then poured into a rapidly stirred solution of saturated aqueous $NaHCO_3$ (15 mL) and CH_2Cl_2 (15 mL). Aqueous workup (CH_2Cl_2, $MgSO_4$) afforded crude **43**. Flash chromatography (3:1 hexane/ethyl acetate) afforded 45.7 mg (66%) of **43** as a clear oil (1.6:1 ratio of **43a**:**43b** by HPLC). The diastereomers were separated by HPLC (4.6-mm i.d. column, 3:1 hexane/ethyl acetate, 0.5 mL min^{-1}) to afford analytical samples of each diastereomer. Major diastereomer, **43a**: HPLC t_R = 33 min; oil; ^1H NMR (300 MHz, $CDCl_3$) δ 6.53 (s, 1 H, Ar), 5.45 (s, 1 H, OH), 5.10 (d, J = 5.3 Hz, 1 H, CHArO), 3.98 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 3.69–3.60 (m, 2 H, OCH_2), 2.71 (q, J = 6.9 Hz, 1 H, CHAr), 2.45 (p, J = 6.3 Hz, 1 H, C*H*CH$_2$), 1.80–1.40 (m, 6 H, CH_2CH$_3$, $OCH_2CH_2CH_2CH$,$OCH_2CH_2CH_2CH_2CH$), 1.05 (t, J = 6.3 Hz, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 144.3, 138.7, 136.3, 124.3, 103.0, 79.2, 64.2, 60.7, 56.3, 47.8, 41.0, 23.9, 22.7, 20.8, 12.7; IR (CCl_4) 3548, 2958, 2867, 1614, 1464, 1445, 1379, 1116, 908, 881 cm^{-1}; MS (EI, 20 eV) m/z 278 (M^+, 100), 249 (23), 233 (14), 220 (12), 219 (18), 205 (55); HRMS calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1506. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.05; H, 8.14. Minor diastereomer **43b**: HPLC t_R = 35 min; oil; ^1H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 1 H, Ar), 5.47 (s, 1 H, OH), 4.93 (d, J = 4.3 Hz, 1 H, CHArO), 4.01 (s, 3 H, OMe), 3.88 (br s, 4 H, OMe, OCH_2), 3.51 (t, J = 11 Hz, 1 H, OCH_2), 3.11 (dt, J = 5.0, 9.3 Hz, 1 H, CHAr), 2.00–1.40 (m, 7 H, $OCH_2CH_2CH_2CH$, $OCH_2CH_2CH_2CH$, $OCH_2CH_2CH_2CH$, CH_2CH_3), 0.93 (t, J = 7.5 Hz, 3 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 143.6, 139.5, 136.3, 126.7, 102.4, 77.7, 66.2, 61.1,

56.4, 44.8, 43.1, 23.5, 23.3, 21.7, 10.6; IR (CCl_4) 3550, 2938, 1616, 1465, 1451, 1348, 1219, 1126, 885 cm^{-1}; MS (EI, 20 eV) m/z 278 (M^+, 100), 249 (20), 233 (20), 220 (18), 219 (12), 205 (58); HRMS calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1520.

(4b*S,8a*S**)-2,4-Dimethoxy-3-hydroxy-4b-methyl-4b,5,6,7,8,8a-hexahydro-9*H*-fluorene (44) and 1-[(3,5-Dimethoxy-4-hydroxyphenyl)methyl]-2-methyl-1-cyclohexene (45).** The same procedure described for the preparation of **36f** from **23** was carried out with alcohol **37** (103 mg, 0.560 mmol), 1-methylcyclohexene (2.7 mL of a 1.014 M solution in CH_2Cl_2, 2.74 mmol, 4.9 equiv), and $SnCl_4$ (0.08 mL, 0.684 mmol, 1.2 equiv). The reaction was carried out at 25 °C (95 min) rather than −78 °C. Flash chromatography (6:1 hexane/ethyl acetate) afforded 75.5 mg (51%) of **44** and 54.5 mg (37%) of **45** as clear oils. Spectral data for **44**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.56 (s, 1 H, Ar), 5.45 (s, 1 H, OH), 3.91 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 2.78 (dd, J = 7.2, 15 Hz, 1 H, CHC*H*H), 2.60 (dd, J = 7.8, 15 Hz, 1 H, CHCH*H*), 2.06–1.98 (m, 1 H, C*H*CHH), 1.84–1.43 (m, 8 H, $CCH_2CH_2CH_2CH_2CH$), 1.40 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2, 144.1, 137.0, 136.4, 133.1, 103.5, 77.2, 60.4, 56.2, 48.5, 35.9, 34.8, 26.3, 25.1, 22.7, 22.0; IR (CCl_4) 3551, 2928, 1613, 1471, 1447, 1233, 887 cm^{-1}; MS (EI, 20 eV) m/z 262 (M^+, 69), 247 (100), 219 (49); HRMS calcd for $C_{19}H_{22}O_3$ 262.1569, found 262.1573. Spectral data for **45**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.39 (s, 2 H, Ar), 5.39 (s, 1 H, OH), 3.88 (s, 6 H, OCH_3), 3.28 (s, 2 H, CH_2Ar), 2.32–1.20 (m, 11 H, $CH_3C{=}C$, $CH_2CH_2CH_2CH_2$); IR (CCl_4) 3559, 2931, 1618, 1515, 1463, 1213 cm^{-1}; MS (EI, 20 eV) m/z 262 (M^+, 100), 247 (10), 167 (42).

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Supplementary Material Available: ^1H NMR spectra for the following compounds: **14, 15, 21, 22, 23, 24, 25, 26a, 26b, 32, 35a/36a, 35b/36b, 35c/36c, 35d/36d, 35e/36e, 36f, 36g, 36i, 36j, 36k, 40, 42, 43a, 43b, 44,** and **45** (35 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.

An Efficient Stereoselective Synthesis of $\Delta^{4,5}$-Pipecolic Esters

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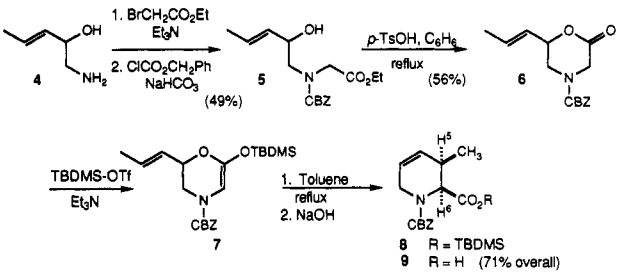
The synthesis of racemic and enantiomerically homogeneous pipecolic esters from 1-amino-3-buten-2-ols is reported. The synthesis of enantiomerically homogeneous *N*-methylpipecolic esters requires four chemical steps from *N*-*t*-BOC-protected amino esters. The key step of the sequence is a conformationally restricted Claisen rearrangement. The method affords complete control of the absolute and relative stereochemistry of all three stereogenic centers in pipecolic ester **22** which is obtained in 33% overall yield from *N*-*t*-BOC-L-alanine ethyl ester **16a**.

Introduction

The piperidine ring is a structural subunit found in a large number of naturally occurring alkaloids.[1] Due to the broad range of biological activity possessed by these compounds[1] and their versatility as key synthetic intermediates, the stereoselective synthesis of highly functionalized piperidines has received considerable attention.[2,3] As a part of our program to develop general routes

Scheme I



to piperidine-containing natural products, we report here a general method for the synthesis of 1,2,5,6-tetrahydro-

(1) (a) Glasby, J. S. *Encyclopedia of the Alkaloids*; Plenum Press: New York, 1975, Vols. 1 and 2; 1977, Vol. 3; 1983, Vol. 4. (b) For naturally occurring pipecolic acid derivatives, see: Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816 and references cited therein.

(2) For recent examples and leading references on the synthesis of tetrahydropyridines, see: (a) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097. (b) Bailey, P. D.; McLay, N. R. *Tetrahedron Lett.* **1991**, *32*, 3895. (c) Bosch, J.; Rubiralta, M.; Bolos, J. *Tetrahedron* **1987**, *43*, 391. (d) Kuriharra, T.; Matsubara, Y.; Osaki, H.; Harusawa, S.; Yoneda, R. *Heterocycles* **1990**, *30*, 885. (e) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *Tetrahedron Lett.* **1989**, *30*, 6781. (f) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1991**, *113*, 6672. (g) Shono, T.; Matsumura, Y.; Onomura, O.; Yamada, Y. *Tetrahedron Lett.* **1987**, *28*, 4073. (h) Wuts, P. G. M.; Jung, Y.-W. *J. Org. Chem.* **1988**, *53*, 5989. (i) Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Org. Synth.* **1991**, *70*, 54. (j) Bonin, M.; Chiaroni, A.; Riche, C.; Beloeil, J.-C.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1987**, *52*, 382. (k) Royer, J.; Husson, H.-P. *J. Org. Chem.* **1985**, *50*, 670. (l) Wang, C. J.; Calabrese, J. C. *J. Org. Chem.* **1991**, *56*, 4341. (m) Comins, D. L.; Zeller, E. *Tetrahedron Lett.* **1991**, *32*, 5889. (n) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1991**, *32*, 5697. (o) Comins, D. L.; Morgan, L. A. *Tetrahedron Lett.* **1991**, *32*, 5919. (p) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1991**, *56*, 4976.

(3) For recent examples and leading references on the synthesis of pipecolic acids and their derivatives, see: (a) Bailey, P. D.; Bryans, J. S. *Tetrahedron Lett.* **1988**, *29*, 2231. (b) Kurihara, T.; Matsubara, Y.; Osaki, H.; Harusawa, S.; Yoneda, R. *Heterocycles* **1990**, *30*, 885. (c) Adams, D. R.; Carruthers, W.; Williams, M. J.; Crowley, P. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1507. (d) Esch, P. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1990**, *31*, 759. (e) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (f) Hanson, G. J.; Russell, M. A. *Tetrahedron Lett.* **1989**, *30*, 5751. (g) Esch, P. M.; Boska, I. M.; Hiemstra, H.; Speckamp, W. N. *Syn. Lett.* **1989**, 38. (h) Shuman, R. T.; Ornstein, P. L.; Paschal, J. W.; Gesellchen, P. D. *J. Org. Chem.* **1990**, *55*, 738. (i) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068. (j) Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239. (k) Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 3882.

0022-3263/92/1957-5947$03.00/0