Synthesis of (−)-Monoterpenylmagnolol and Magnolol

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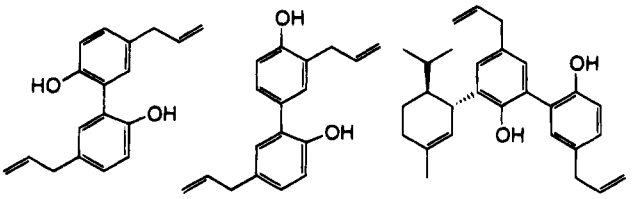
(−)-Monoterpenylmagnolol (**3**) was synthesized in eight steps from (+)-3,9-dibromocamphor (**4**) and the bis(methoxymethyl) ether (**22**) of 3-(4-hydroxyphenyl)-1-propanol. Fragmentation of an *endo*-3-aryl-9-bromocamphor (**27**) provided the correct absolute stereochemistry. In this total synthesis, dissolving metal conditions were developed to reduce enol phosphate and isopropenyl functions without concomitant reduction of an attached phenol. Palladium(0)-catalyzed cross-coupling of an arylzinc chloride with 4-allyl-2-iodophenyl methoxymethyl ether (**34**) provided the desired tricyclic 1,2,3,5-tetrasubstituted biaryl **41** in fair yield without optimization and with little isomerization of the allyl group. Magnolol (**1**) was also synthesized by aryl coupling of **34** and the methoxymethyl ether of 4-allyl-2-lithiophenol *via* the zinc chloride method as above, as well as from 5,5′-dibromo-2,2′-dimethoxybiphenyl (**37**) by allylation with allyltributylstannane followed by ether cleavage.

The bark of *Magnolia officinalis* Rehd. et Wils. (Magnoliaceae) has been used in Chinese and Japanese folk medicine for the treatment of bronchitis and emphysema.[1] The methanol extract of this bark was found to show significant inhibitory effects on Epstein–Barr virus early antigen (EBV-EA) activation on Raji cells.[2] Isolation and characterization of the active extract gave three neolignans, magnolol (**1**),[2c] honokiol (**2**), and (−)-monoterpenylmagnolol (**3**).[2b] This paper describes the synthesis of compounds **3** and **1**.

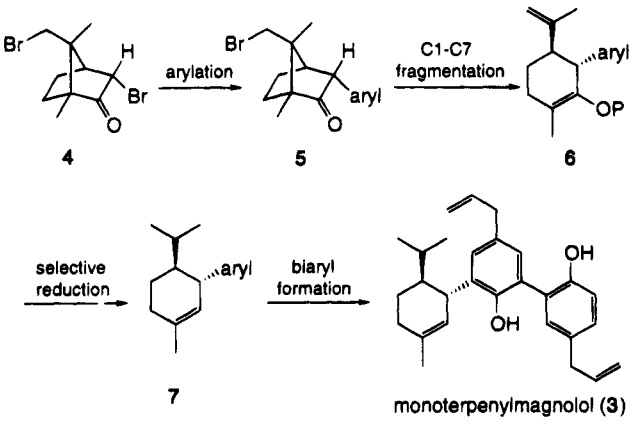


1 **2** **3**

Results and Discussion

Our synthetic plan for (−)-monoterpenylmagnolol (**3**) is shown in Scheme 1. This route involves four processes: (A) arylation of 3,9-dibromocamphor (**4**), (B) fragmentation of the *endo*-α-arylcamphor **5** to the enol phosphate **6**, (C) selective reduction of both the 2-propenyl and the enol phosphate moieties of **6**, and (D) aryl coupling of intermediate **7**. Recent work has shown that (+)-3,9-dibromocamphor (**4**) can be arylated to give α-arylated analogs **5** using aryl cuprates in a dimethyl sulfoxide–tetrahydrofuran mixed solvent system.[3] This arylation proceeds with preferential *endo* selectivity depending on the steric bulk of the aryl cuprate and in good chemical yield (60–80%). Fragmentation of 9-bromocamphor derivatives such as **5** and trapping of the resulting enolate with diethyl chlorophosphate was also reported.[3]

Scheme 1. Proposed Synthesis of 3



The first order of business was to find an efficient method for the simultaneous removal of the diethyl phosphate group and reduction of the isopropenyl group of limonene derivative **6** while leaving the aromatic ring intact (Scheme 1). This aspect of the synthetic sequence was examined using methoxymethyl-protected phenols. Cuprate **9** was generated from phenyl methoxymethyl ether (**8**) with *tert*-butyllithium and copper(I) iodide in tetrahydrofuran. Reaction of the cuprate with (+)-3,9-dibromocamphor (**4**) in a 1:1 mixture of tetrahydrofuran and dimethyl sulfoxide afforded ketone **10**. Integration of the α-hydrogen resonances in the ^{1}H NMR spectrum of **10** showed the ratio of *endo*- to *exo*-arylated products as 4.6:1. Addition of excess sodium naphthalenide to **10** in tetrahydrofuran followed by trapping of the resulting enolate with diethyl chlorophosphate resulted in fragmented product **11** in 81% yield.

With intermediate **11** in hand, selective reductions with a variety of lithium–ammonia conditions were examined. Reaction at −78 °C in the absence of a proton source only led to the reduction of the enol phosphate group and produced compound **12**. Aryl-substituted limonene **12** was also prepared *via* a second route to confirm its structure. Ketone **10** was reduced with diisobutylaluminum hydride to the *endo* alcohol which was converted to the mesylate **13** (90% overall). Addition of **13** to an excess of sodium naphthalenide in tetrahy-

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1995.

(1) Tokyo Syoyaku Kyokai. *Shin Joyo Wakanyaku*; Nankodo Publication: Tokyo, 1973; p 42.

(2) (a) Konoshima T.; Takasaki, M.; Kozuka, M.; Tokuda, H.; Nishino, H.; Iwashima, A.; Haruna, M.; Ito, K.; Tanabe, M. In Proceedings of the International Joint Symposium of Biology and Chemistry of Active Natural Substances; Bonn, West Germany, 1990; p 168. (b) Konoshima, T.; Kozuka, M.; Tokuda, H.; Nishino, H.; Iwashima, A.; Haruna, M.; Ito, K. *J. Nat. Prod.* **1991**, *54*, 816. (c) Ito, K.; Iida, T.; Ichino, K.; Masao, T.; Namba, T. *Chem. Pharm. Bull.* **1982**, *30*, 3347.

(3) Vaillancourt, V.; Albizati, K. F. *J. Org. Chem.* **1992**, *57*, 3627.

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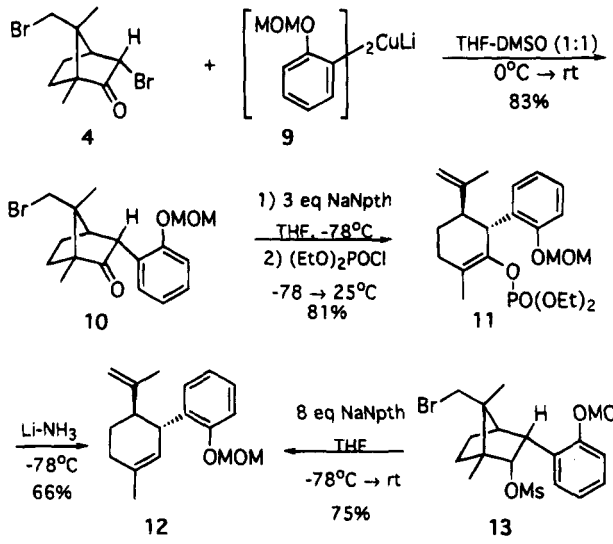
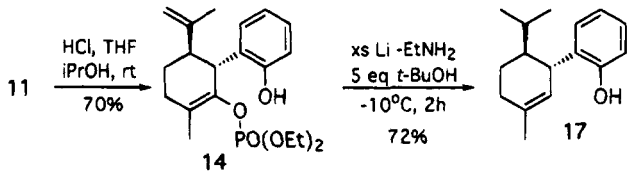


drofuran resulted in **12**. The spectral properties of **12** synthesized by both routes were identical.

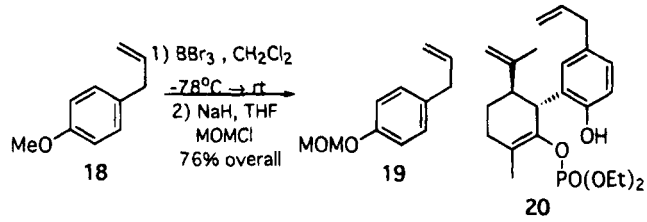
When **11** was treated with lithium and ethylamine, again without a proton source, a mixture of **12** and over-reduced adducts was obtained. NMR analysis of this mixture indicated that the aromatic ring was fully reduced, and the isopropenyl group was left intact.

Phenols are not expected to undergo facile reduction under Birch conditions due to the high energy barrier for electron transfer to the phenolate anion to generate a dianion radical intermediate.[4] Therefore, the methoxymethyl protecting group of **11** was removed with hydrochloric acid in a 1:1 mixture of tetrahydrofuran and isopropyl alcohol to give phenol **14**.



Reduction of **14** was then examined under various conditions. A 70:30 mixture of starting material **14** and a product (**15**) resulting from mono de-ethylation of the phosphate group was obtained using 5 equiv of lithium in ammonia (0.1 M) in the absence of a proton source. When excess lithium in ammonia (2.5 M) was used, the sole product was the de-ethylated material. Reduction with excess lithium in ethylamine (2.5 M) with 3 equiv of *tert*-butyl alcohol as the proton source resulted in reduction only of the enol phosphate to give *trans*-3-(*o*-hydroxyphenyl)limonene (**16**). Five equiv of *tert*-butyl alcohol was required to reduce *both* the enol phosphate and the isopropenyl group. Thus, compound **17** was obtained in 72% yield using lithium-ethylamine and 5 equiv of *tert*-butyl alcohol.

With these results in hand, the synthesis of monoterpenylmagnolol (**3**) was continued using an aryl group that corresponded to that of the natural product. 4-Allylphenyl methoxymethyl ether (**19**) was synthesized from 4-allylanisole (**18**) in 76% overall yield. The sequence described earlier, namely **4** + **8** → **10** → **11** → **14**, was repeated using **19** (instead of **8**) to give the allyl-substituted derivative **20** (*via* the 4-allyl analogs **10a** and **11a** of **10** and **11**, respectively). However, lithium ethylamine–*tert*-butyl alcohol reduction of **20** gave *trans*-3-(2-hydroxy-5-propylphenyl)dihydrolimonene (**21**) as the ultimate product in which the allyl group had also been reduced. Not unexpectedly, when the dissolving metal reduction was stopped before completion, the allyl group had disappeared but the isopropenyl double bond was mostly unaffected as seen in the ^{1}H NMR spectrum.



These results demonstrated that the reduction of the allyl group (probably by way of the 1-propenyl isomer) occurs before the isopropenyl group, and it was necessary to modify the sequence so that the allyl group would not be present during the metal–amine reduction. Therefore, a good method was required for the generation of the allyl group at later stage. Obviously, harsh reaction conditions, especially the use of strong acid or base which might cause isomerization to the conjugated 1-propenylbenzene, had to be excluded. The phenylseleno functionality has become useful in organic synthesis to introduce terminal unsaturation by its oxidative removal. In these organoselenium operations, the first and the most crucial step is the introduction of the phenylseleno group, and *N*-phenylselenophthalimide (*N*-PSP) appears to be the reagent of choice for conversion of alcohols to phenylselenides.[5]

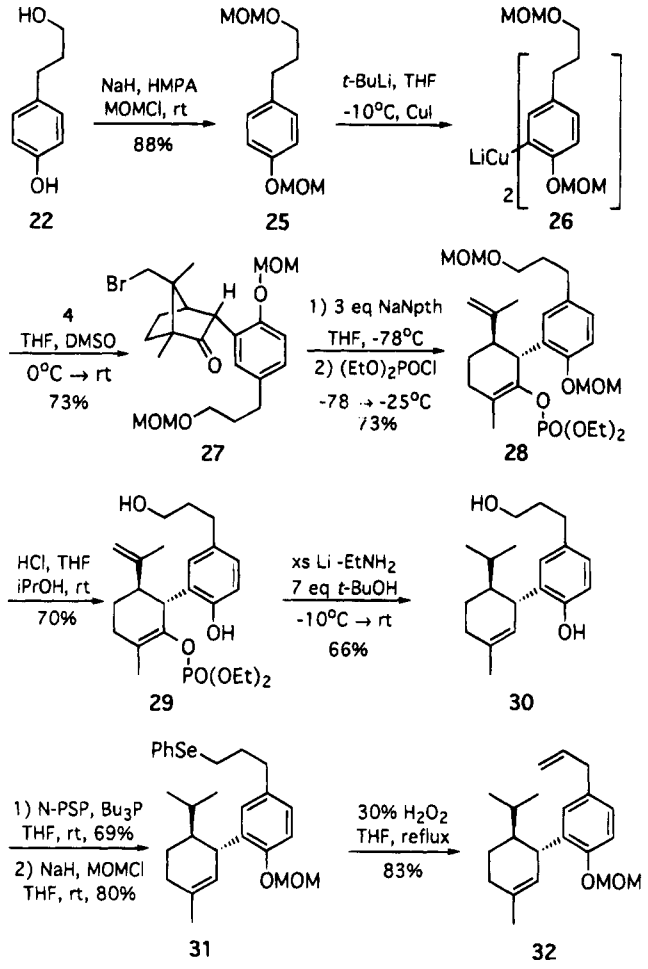
A substrate was needed to develop the conditions required for the formation of the allyl group. 3-(4-Hydroxyphenyl)-1-propanol (**22**) provided a monooxygenated phenyl ring attached to a three-carbon chain which contains a hydroxyl group for subsequent replacement by phenylselenide. Compound **22** was monoprotected at the phenol hydroxyl as the methoxymethyl ether **23**, and the alcohol group was allowed to react with *N*-PSP and tributylphosphine in tetrahydrofuran to produce the phenyl selenide **24**. Oxidation with 30% hydrogen peroxide was accompanied by facile elimination of the selenoxide and gave the previously prepared **19** in a respectable 61% overall yield. In a similar manner 4-allylphenol itself was prepared directly from **22** in 75% overall yield.

For continuation of the total synthesis of **3** it was necessary to convert **22** into the bis(methoxymethyl) ether **25** by treatment with sodium hydride in hexamethylphosphoramide and then chloromethyl methyl ether. Cuprate **26** was generated, and reaction with 3,9-dibromocamphor (**4**) resulted in the 2-*endo*-aryl-9-bromocamphor analog **27** as a single stereoisomer. Compound **27** was subjected to fragmentation conditions as before to give **28**, and the protecting methoxymethyl groups were

(4) (a) Zimmerman, H. E.; Wang, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 1280. (b) Zimmerman, H. E.; Wang, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 2205. (c) Birch, A. J.; Subba Rao, G. S. R. *Tetrahedron Lett.* **1967**, 857. (d) Fried, J.; Abraham, N. A. *Tetrahedron Lett.* **1965**, 3505. (e) Benkeser, R. A.; Arnold, C.; Lambert, R. F.; Thomas, O. H. *J. Am. Chem. Soc.* **1955**, *77*, 6042.

(5) Grieco, P. A.; Jaw, J. Y.; Claremon, D. A.; Nicolaou, K. C. *J. Org. Chem.* **1981**, *46*, 1215.

removed to liberate the required **29**.



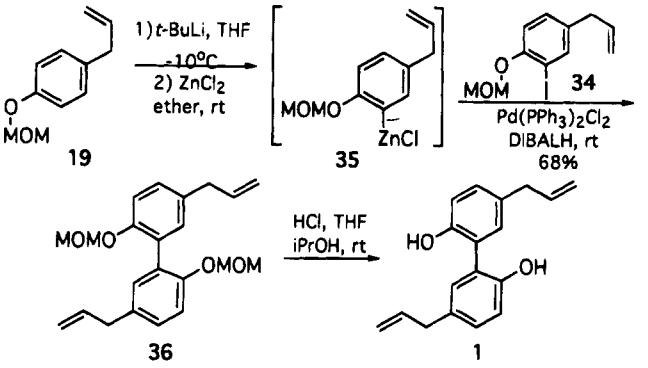
Enol phosphate **29** was reduced with lithium, ethylamine, and *tert*-butyl alcohol to give **30** in 66% yield. Intermediate **30** had a specific rotation of -101.2 (c = 0.015, $CHCl_3$). The primary alcohol was selenated using *N*-PSP and tributylphosphine, and the phenolic hydroxyl group was protected to give the methoxymethyl ether **31**. Oxidation of selenide **31** with 30% hydrogen peroxide produced **32**.

Conditions for biaryl formation were developed next. Palladium(0) complexes catalyze the coupling of aryltin compounds with aryl halides.[6] Many functional groups are tolerated, and the yields of the cross-coupled products are usually high. To this end, 4-allylphenyl methoxymethyl ether (**19**) was lithiated and converted into the 2-tributylstannyl **33** (with Bu_3SnCl) and 2-iodo **34** (with I_2) derivatives. Aryl iodide **34** and the organotin derivative **33** were allowed to react with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) using several different reaction conditions. Unfortunately, the cross-coupled products had one or both of the allyl groups isomerized. Several other methods for biaryl formation were tried, but either no coupling was seen or the allyl groups of the product were isomerized.

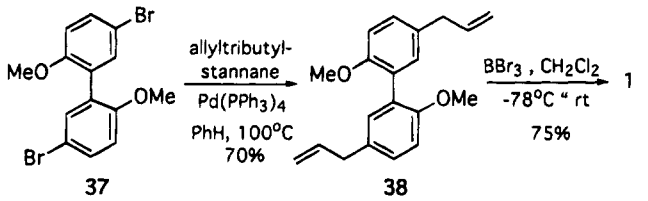
Organozinc compounds readily participate in palladium- or nickel-catalyzed aryl cross-coupling reactions. This mild procedure for the preparation of unsymmetrical biaryls features high chemo- and regioselectivity, as well

(6) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

Scheme 2. Synthesis of Magnolol (1) *via* Arylzinc Coupling



Scheme 3. Synthesis of Magnolol by bis-Allylation



as high cross-coupling to homocoupling ratios.[7] Compound **19** was lithiated and converted to the arylzinc **35** by addition to a solution of zinc chloride in ether. Reaction of organozinc **35** with aryl iodide **34** in the presence of palladium(0) generated *in situ* at room temperature resulted in formation of biaryl **36**, and no isomerization of the allyl groups was observed. When the coupling was attempted using nickel(0) as a catalyst at higher temperature, the allyl groups of the coupled product were isomerized to a large extent. Finally, the methoxymethyl groups of **36** were removed with hydrochloric acid in a 1:1 mixture of isopropyl alcohol and tetrahydrofuran to give magnolol (**1**) in 70% yield (Scheme 2).[8]

Magnolol (**1**) was also synthesized *via* a second route. 2,2′-Dimethoxybiphenyl was brominated with *N*-bromosuccimide in dimethylformamide to give 5,5′-dibromo-2,2′-dimethoxybiphenyl (**37**) in 85% yield. Allylation using allyltributylstannane and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) gave **38.** Cleavage of the methyl ethers with boron tribromide at low temperature produced magnolol (**1**) (Scheme 3).[9]

With a method in hand to generate biaryls without isomerization of an allyl group, the coupling reaction was examined with intermediate **32**. Several attempts to couple the arylzinc derived from **32** with aryl iodide **34** failed. Close examination of the ^1H NMR spectrum of compound **32** revealed trace amounts of a selenium-containing impurity. This accounted for the lack of reactivity, as it is known that selenium byproducts poison the palladium catalyst in such coupling reactions. Several different procedures to purify compound **32** were

(7) Negishi, E.-i.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

(8) A synthesis of magnolol has been reported: Runenberg, J. *Acta Chem. Scand.* **1958**, *12*, 188. The mp of "purified" magnolol is given as 100.0–101.5 °C, after sublimation of the pyrolysis product of the bis(phenylurethane). However, ref 2c describes magnolol (**1**) as a viscous oil.

(9) The intermediate for allylation in the synthesis described in ref 8 was claimed to be 5,5′-dibromo-2,2′-dimethoxybiphenyl (**37**). However, the mp 127–129 °C is much higher than the mp 101–102 °C obtained in this study.

tried. All proved to be unsuccessful except for repeated column chromatography, which made this step of the synthetic sequence highly inefficient.

To overcome this problem the allyl group was generated directly from the dihydroxy compound **30**. This variation produced the free phenol analog of **32,** namely **32-OH.** The latter should be more polar than methoxymethyl ether **32** and allow for more efficient chromatographic purification. Unfortunately, it was again necessary to carry out multiple chromatography to remove all selenium byproducts from this intermediate as well.

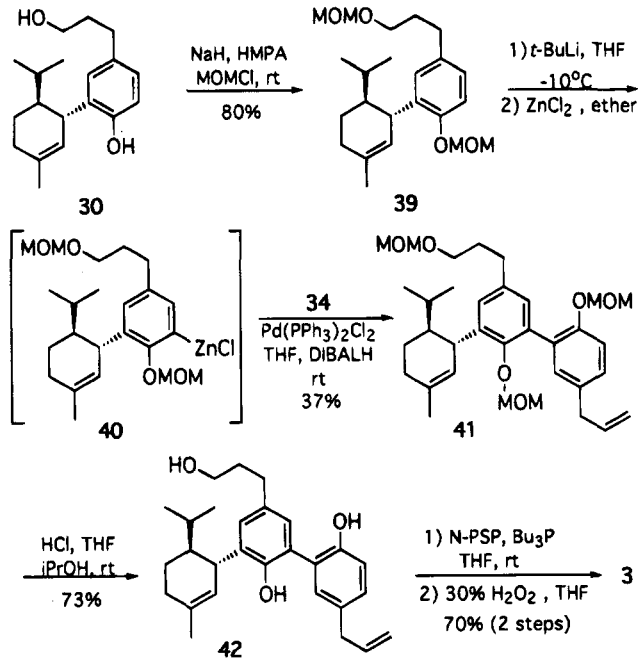
Obviously, aryl−aryl coupling could be carried out before the generation of the allyl group, and the intermediate most suitable for this task was **39** in which both hydroxyl groups of **30** were protected as methoxymethyl ethers by using sodium hydride in hexamethylphosphoramide. Lithiation of **39** with *tert*-butyllithium followed by transmetalation with zinc chloride gave **40**. Coupling of aryl iodide **34** with arylzinc **40** in the presence of palladium(0) at room temperature gave biaryl **41**, albeit in modest yield. Both the recovered aryl iodide **34** and the coupled product **41** showed that less than 5% of the allyl group (^{1}H NMR analysis) had been isomerized to the conjugated isomer. The methoxymethyl groups were removed carefully in the usual manner to provide **42** in 73% yield. Treatment of precursor biaryl **42** with *N*-(phenylseleno)phthalimide followed by oxidative removal of the selenium with hydrogen peroxide *via* the selenoxide gave (−)-monoterpenylmagnolol (**3**), $[\alpha]^{25}_D$ = −129.1 in 70% yield. The ^{1}H NMR, ^{13}C NMR, and IR spectral data were in full agreement with those reported for the isolated natural product (−)-**3**,[2b] and therefore, the absolute configuration of **3** was established as *S*,*S*.

(−)-Monoterpenylmagnolol (**3**) was synthesized in eight steps from (+)-3,9-dibromocamphor (**4**) and the bis(methoxymethyl) ether (**25**) of 3-(4-hydroxyphenyl)-1-propanol (**22**) with an overall yield of 3.7% according to the sequence **25** + **4** → **27** → **28** → **29** → **30** → **39** + **34** → **41** → **42** → **3**. One of the key reactions, which was not optimized, was the palladium(0)-catalyzed coupling of the arylzinc **40** with the aryl iodide **34** to provide the desired 1,2,3,5-tetrasubstituted biaryl in modest yield without isomerization of the allyl group. In the course of model studies, a similar biaryl synthesis provided the naturally-occurring magnolol (**1**).

Experimental Section

^{1}H NMR spectra were recorded at 300 or 500 MHz and ^{13}C NMR spectra at 75 or 125 MHz with $CDCl_3$ solutions unless otherwise specified. IR spectra were obtained using a Nicolet 20DX FTIR with a resolution of 2 cm^{-1}. Mass spectra were determined at 20 or 70 eV. Microanalyses were by Midwest Microlabs, Indianapolis, IN, and Galbraith Laboratories, Knoxville, TN.

Most reactions were conducted in flame-dried glassware under a positive pressure of nitrogen. Alkyllithium reagents were purchased from Aldrich Chemical Co. as standardized solutions. Anhydrous dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) also were obtained from Aldrich. Tetrahydrofuran (THF) and ether were freshly distilled from sodium−benzophenone ketyl. Ammonia was freshly distilled from sodium, and ethylamine was dried over potassium hydroxide pellets and condensed into the reaction vessel. Chromatographic purification refers to flash chromatography using silica gel 60 (230−400 mesh, Kiesgel, EM Reagents) eluting with hexane−EtOAc in the stated v/v proportions.



Phenyl Methoxymethyl Ether (8). To a suspension of sodium hydride (3.16 g, 131.7 mmol) in 100 mL of anhyd THF was added a solution of phenol (11.30 g, 119.7 mmol) in 150 mL of THF over 15 min. The mixture was stirred for 1 h at rt, and chloromethyl methyl ether (10.0 mL, 131.7 mmol) was added slowly. After being stirred for an additional 12 h, the mixture was poured into 500 mL of water and extracted three times with 70 mL of ether. The combined organic layer was washed twice with 50 mL of saturated sodium bicarbonate and once with brine and dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude product was purified by chromatography on silica gel and eluted with hexane-EtOAc (95:5, v/v) to afford 13.4 g (81%) of phenyl methoxymethyl ether: ^{1}H NMR δ 7.35 (dd, J = 8.1, ~0.9 Hz, 2 H), 7.09 (overlapping m, 3 H), 5.23 (s, 2 H), 3.54 (s, 3 H); ^{13}C NMR δ 157.2, 129.4, 121.8, 116.2, 94.3, 55.8; IR (neat) 1591, 1485, 1224, 1189, 1147, 1084 cm^{-1}; HRMS calcd for $C_8H_{10}O_2$ 138.0680$_7$, found 138.0677.

(1*R*,3*R*,4*R*,7*R*)-7-(Bromomethyl)-3-(2-(methoxymethoxy)phenyl)-1,7-dimethylbicyclo[2.2.1]heptan-2-one (10). A solution of *tert*-butyllithium in hexane (8.82 mL of a 1.7 M solution, 15 mmol) was added to 1.382 g (10.0 mmol) of phenyl methoxymethyl ether (**8**) in 10 mL of THF at −10 °C. After being stirred at −10 °C for 2 h, this solution was transferred dropwise *via* cannula to a solution of CuI (0.952 g, 5.0 mmol) in 5 mL of THF at 0 °C. The solution was stirred for an additional 30 min, and 15 mL of anhyd DMSO was added. This solution was then transferred dropwise *via* cannula to 1.41 g (4.54 mmol) of (+)-3,9-dibromocamphor (**4**) in 5 mL of THF and 5 mL of anhyd DMSO at 0 °C. The mixture was allowed to stir at rt overnight. The reaction was quenched by addition of 10 mL of saturated ammonium chloride. The aqueous mixture was extracted three times with 15 mL of ether. The combined organic extract was washed with brine and dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude product was purified by chromatography (hexane−EtOAc, 90:10) to give 2.0 g (83%) of product **10**: ^{1}H NMR δ 7.23 (overlapping m, 2 H), 7.08 (d, J = 8.1 Hz, 1 H)), 6.96 (m, 1 H), 5.21 (s, 2 H), 4.04 (d, J = 4.2 Hz, 1 H), 3.70 (d, J = 10.5 Hz, 1H), 3.49 (s, 3H), 3.31 (d, J = 10.2, 1 H), 2.79 (m, 1 H), 1.76 (m, 1 H), 1.57 (broad m, 2 H), 1.29 (m, 1H), 1.21 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR δ 218.5, 155.4, 128.7, 127.7, 121.5, 113.6, 94.3, 59.7, 50.4, 50.5, 46.2, 39.9, 41.1, 29.4, 20.7, 16.7, 9.9; IR (neat) 1732, 1591, 1485, 1450, 1225, 1254, 1076 cm^{-1}; HRMS calcd for $C_{18}H_{23}O_3Br$ 366.0831, found 366.0825.

(3*R*,4*R*)-2-(Diethoxy(oxyphosphoryl))-4-isopropenyl-3-(2-(methoxymethoxy)phenyl)-1-methyl-1-cyclohexene (11). A solution of 367 mg (1.0 mmol) of **10** in 5 mL of THF at −78 °C was titrated with 0.4 M sodium naphthalenide in tetra-

ethylene glycol dimethyl ether in THF until a deep green color persisted (ca. 8 mL). After the solution was stirred at −78 °C for 10 min, 0.22 mL (1.5 mmol) of diethyl chlorophosphate and 0.30 mL (1.7 mmol) of anhyd HMPA were added. The resulting solution was warmed to −25 °C and quenched with 5 mL of saturated ammonium chloride. The aqueous layer was extracted three times with 10 mL of ether. The combined extract was washed three times with 20 mL of saturated sodium bicarbonate and once with brine and dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude product was chromatographed on silica gel, eluting with hexane−EtOAc first with 95:5 then 75:25 to afford 344 mg (81%) of enol phosphate **11** as an oil: ^{1}H NMR δ 7.13 (dt, J = 7.5, 1.8 Hz, 2 H), 7.03 (d, J = 7.5 Hz, 1 H), 6.92 (t, J = 6.9 Hz, 1 H), 5.14 (s, 2 H), 4.68 (s, 2 H), 4.20 (overlapping m, 1 H), 3.90 (m, 2 H), 3.63 (t, J = 6.9 Hz, 2 H), 3.47 (s, 3 H), 2.37 (m, 1 H), 2.12 (m, 2 H), 1.79 (s, 3 H), 1.71 (s, 3 H), 1.19 (t, J = 6.0 Hz, 2 H), 1.19 (t, J = 6.6 Hz, 3 H), 1.05 (t, J = 6.9 Hz, 3 H); ^{13}C NMR δ 155.5, 146.2, 140.9, 141.0, 127.9, 127.2, 121.1, 113.9, 113.5, 110.9, 94.3, 63.3, 55.7, 55.9, 49.2, 49.0, 28.8, 20.5, 16.6, 15.7; IR (neat) 1698, 1645, 1592, 1485, 1445, 1259, 1226, 1146, 900 cm^{-1}; HRMS calcd for $C_{22}H_{33}O_6P$ 424.2014$_6$, found 424.2019.

(3*S*,4*R*)-4-Isopropenyl-3-(2-(methoxymethoxy)phenyl)-1-methyl-1-cyclohexene (12). A round-bottomed flask in a −78 °C bath was charged with ca. 400 mg (57.5 mmol) of lithium foil and 20 mL of anhyd ammonia. To this was added a solution of 90 mg (0.212 mmol) of **11** in 1 mL of THF. The mixture was stirred at −78 °C for 2 h and then quenched by addition of 5 mL of saturated ammonium chloride. The aqueous mixture was made acidic with 10% hydrochloric acid and extracted with three 10-mL portions of ether. The combined extract was washed with brine, and the solvent was removed *in vacuo*. Flash chromatography (hexane−EtOAc, 95:5) gave 58 mg (66%) of **12**: ^{1}H NMR δ 7.12 (m, 2 H), 7.07 (d, J = 7.2 Hz, 1 H), 6.95 (d, J = 7.5 Hz, 1 H), 5.27 (s, 1 H), 5.15 (s, 2 H), 4.55 (s, 1 H), 4.46 (s, 1 H), 3.91 (m, 1 H), 3.48 (s, 3 H), 2.32 (m, 1 H), 1.71 (s, 2 H), 1.67 (s, 2 H), 1.26 (s, 3 H), 0.86 (m, 3 H); ^{13}C NMR δ 148.0, 134.8, 133.7, 128.7, 126.8, 125.2, 121.7, 114.0, 110.4, 94.8, 55.9, 48.7, 38.4, 31.9, 23.5, 19.9, 14.1; IR (neat) 1611, 1564, 1340, 1280, 1165, 1100 cm^{-1}; EIMS m/z (rel intensity) 273 (12), 272 (M$^+$, 55), 271 (2), 270 (9), 257 (2), 243 (8), 230 (4), 229 (19).

(1*R*,2*S*,3*R*,4*R*,7*R*)-7-(Bromomethyl)-2-(mesyloxy)-3-(2-(methoxymethoxy)phenyl)-1,7-dimethylbicyclo[2.2.1]heptane (13). To a solution of 422 mg (1.15 mmol) of ketone **10** in 3 mL of anhyd toluene at 0 °C was added dropwise 2.30 mL of DIBALH (1.0 M solution in toluene, 2.30 mmol). The resulting mixture was allowed to stir for 1 h and then quenched by addition of 0.20 mL of methanol and 0.10 mL of saturated aqueous ammonium chloride. The mixture was stirred for an additional 1 h, diluted with 5 mL of ether, and dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude product was dissolved in 5 mL of CH_2Cl_2 and cooled to 0 °C. Ten mg of DMAP was added followed by 0.92 mL (11.5 mmol) of pyridine and 0.44 mL (5.7 mmol) of MsCl. The mixture was allowed to warm to rt and stirred for 18 h. The reaction was quenched with 5 mL of saturated aqueous sodium bicarbonate. The aqueous layer was extracted with three 10-mL portions of ether. The combined extract was washed two times with 10 mL of sodium bicarbonate and once with brine. The organic layers were dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude product was chromatographed (hexane−EtOAc, 90:10) to afford 463 mg (90%) of **13** as a colorless oil: ^{1}H NMR δ 7.42 (d, J = 7.2 Hz, 1 H), 7.21 (m, 1 H), 7.05 (m, 2 H), 5.19 (s, 2 H), 5.05 (dd, J = 10.5, 1.2 Hz, 1 H), 4.28 (dd, J = 12.0, 2.4 Hz, 1 H), 3.74 (d, J = 10.2 Hz, 1 H), 3.49 (s, 3 H), 3.27 (d, J = 10.2 Hz, 1 H), 2.48 (s, 3 H), 2.21 (m, 1 H), 2.10 (m, 1 H), 1.81 (m, 1 H), 1.60 (m, 1 H), 1.46 (m, 1 H), 1.33 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR δ 155.8, 131.6, 127.8, 126.3, 121.1, 114.5, 95.2, 87.2, 56.3, 51.5, 51.2, 48.0, 40.5, 38.0, 35.9, 26.5, 20.2, 15.6, 13.7; IR (neat) 1485, 1443, 1351, 1210, 1168, 1076 cm^{-1}; HRMS calcd for $C_{19}H_{27}O_5SBr$ 446.0762$_9$, found 446.0768.

(3*R*,4*R*)-2-(Diethoxy(oxyphosphoryl))-3-(2-hydroxyphenyl)-4-isopropenyl-1-methyl-1-cyclohexene (14). To a solution of 442 mg (1.04 mmol) of **11** in 4 mL of a 1:1 mixture of THF and isopropyl alcohol was added 0.4 mL of concd hydrochloric acid. The solution was stirred at rt for 18 h, poured into 10 mL of water, and extracted with three 10-mL portions of ether. The combined organic extract was washed with brine and dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude product was purified by chromatography (hexane−EtOAc, 60:40) to afford 304 mg (77%) of enol phosphate **14**: ^{1}H NMR δ 7.61 (s, 1 H), 7.03 (dd, J = 7.5, 1.5 Hz, 1 H), 6.96 (dd, J = 7.8, 0.9 Hz, 1 H), 6.81 (m, 2 H), 4.48 (s, 1 H), 4.46 (s, 1 H), 4.19 (m, 1 H), 4.02 (m, 2 H), 3.53 (m, 1 H), 3.39 (m, 1 H), 2.40 (q, J = 8.1 Hz, 1 H), 2.24 (m, 1 H), 2.03 (m, 1 H), 1.66 (s, 5 H), 1.55 (s, 3 H), 1.23 (t, J = 7.2 Hz, 3 H), 0.92 (t, J = 7.8 Hz, 3 H); ^{13}C NMR δ 155.2, 146.4, 141.6, 129.6, 128.0, 127.4, 121.1, 119.1, 111.2, 102.1, 64.3, 51.6, 41.3, 30.3, 27.8, 19.8, 16.5, 15.9; IR (neat) 3246 (br), 1689, 1647, 1598, 1443, 1365, 1231, 1027, 971 cm^{-1}; HRMS calcd for $C_{20}H_{29}O_5P$ 380.1752$_5$, found 380.1747.

(3*S*,4*S*)-3-(2-Hydroxyphenyl)-4-isopropyl-1-methyl-1-cyclohexene (17). To 15 mL of freshly-distilled ethylamine at −78 °C was added 300 mg (43.1 mmol) of lithium foil. The solution was stirred until the lithium was dissolved. To this was slowly added a solution of 105 mg (0.276 mmol) of **14** in 0.5 mL of THF and 0.13 mL of *tert*-butyl alcohol. The mixture was stirred at −10 °C for 1 h and then at rt for 2 h. The reaction was quenched by addition of 5 mL of saturated ammonium chloride. The aqueous mixture was acidified with 20% hydrochloric acid and extracted three times with 10-mL portions of ether. The combined extract was washed with brine and dried over sodium sulfate, and the solvent was removed *in vacuo*. Chromatography (hexane−EtOAc, 95:5) gave 46 mg (72%) of **17**: ^{1}H NMR δ 7.14 (dt, J = 7.8, 1.5 Hz, 1 H), 7.05 (dd, J = 7.5, 1.2 Hz, 1 H), 6.85 (m, 2 H), 5.63 (s, 1 H), 5.52 (s, 1 H), 3.37 (d, J = 6.6 Hz, 1 H), 2.12 (m, 2 H), 1.78 (s, 4 H), 1.62 (m, 2 H), 1.40 (m, 2 H), 0.86 (t, J = 6.9 Hz, 4 H); ^{13}C NMR δ 154.5, 138.7, 130.8, 129.9, 127.6, 124.3, 120.1, 116.6, 43.9, 43.0, 30.5, 27.2, 23.5, 21.7, 21.5, 16.1; IR (neat) 3443 (br), 1598, 1577, 1492, 1478, 1443, 1358, 1267, 1210, 1064, 1034 cm^{-1}; HRMS calcd for $C_{16}H_{22}O$ (M$^+$) 230.1670$_5$, found 230.1666.

4-Allylphenol. To 5.0 mL (32.6 mmol) of 4-allylanisole (**18**) in 100 mL of CH_2Cl_2 at −78 °C was added dropwise 35 mL (1 M in CH_2Cl_2, 35 mmol) of boron tribromide. The mixture was allowed to warm to rt and stirred for 50 min. The reaction was then cooled to 0 °C and quenched by addition of 30 mL of water. The aqueous mixture was extracted three times with 25-mL portions of CH_2Cl_2. The combined extract was washed with brine, and the solvent was removed *in vacuo*. Purification by chromatography (hexane−EtOAc, 90:10) afforded 3.71 g (85%) of 4-allylphenol; ^{1}H NMR δ 7.09 (d, J = 8.4 Hz, 2 H), 6.81 (d, J = 8.4 Hz, 2 H), 5.99 (m, 1 H), 5.56 (broad s, 1 H), 5.10 (m, 2 H), 3.35 (d, J = 6.6 Hz, 2 H); ^{13}C NMR δ 153.6, 137.8, 132.3, 129.7, 115.3, 115.5, 39.3; IR (neat) 3556−3200 (br), 1640, 1605, 1591, 1506, 1436, 1365, 1224, 1168 cm^{-1}; EIMS m/z (rel intensity) 135 (11), 134 (M$^+$, 100), 133 (64), 132 (3), 131 (5), 119 (8), 117 (9), 116 (5), 115 (9), 107 (40), 105 (20); HRMS calcd for $C_9H_{10}O$ 134.0731, found 134.0731.

4-Allylphenyl Methoxymethyl Ether (19). The same procedure used for the preparation of **8** was employed. From 4.0 g (29.8 mmol) of 4-allylphenol there was obtained 6.1 g (89%) of **19** after purification by flash chromatography (hexane−EtOAc, 90:10); ^{1}H NMR δ ($CDCl_3$) 7.08 (d, J = 8.4 Hz, 2 H), 6.96 (d, J = 8.4 Hz, 2 H), 5.91 (m, 1 H), 5.1 (s, 2 H), 6.04 (m, 2 H), 3.45 (s, 3 H), 3.31 (d, J = 6.6 Hz, 2 H); ^{13}C NMR δ ($CDCl_3$) 155.6, 137.7, 133.4, 129.5, 116.2, 115.5, 94.5, 55.8, 39.3; IR (neat) 1640, 1605, 1506, 1429, 1309, 1224, 1196, 1147, 1076, 999, 914 cm^{-1}; HRMS calcd for $C_{11}H_{14}O_2$ 178.0993$_7$, found 178.0990.

3-(4-(Methoxymethoxy)phenyl)propyl Methoxymethyl Ether (25). A solution of 6.08 g (40 mmol) of 3-(4-hydroxyphenyl)-1-propanol (**22**) (Aldrich) in 200 mL of anhyd HMPA was added slowly to a suspension of 2.12 g (88 mmol) of sodium hydride in 80 mL of anhyd HMPA. After the solution was stirred at rt for 1.5 h, 6.68 mL (88 mmol) of chloromethyl methyl ether in 30 mL of anhyd HMPA was added. After 20 h at room temperature, the solution was poured into 250 mL

of water. The aqueous layer was extracted with three 100-mL portions of ether. The combined organic extract was washed twice with 150-mL portions of saturated aqueous sodium bicarbonate and once with brine. The extracts were dried over sodium sulfate, and the solvent was removed *in vacuo*. Purification by flash chromatography (hexane−EtOAc, 90:10) afforded 8.45 g (88%) of bis-ether **25** as a clear oil: ^{1}H NMR δ 7.12 (d, J = 8.4 Hz, 2 H), 6.97 (d, J = 8.1 Hz, 2 H), 5.15 (s, 2 H), 4.63 (s, 2 H), 3.54 (t, J = 6.6 Hz, 2 H), 3.47 (s, 3 H), 3.37 (s, 3 H), 2.66 (t, J = 7.8 Hz, 2 H), 1.90 (m, 2 H); ^{13}C NMR δ 155.3, 135.1, 129.2, 116.1, 96.3, 94.4, 66.9, 55.7, 55.0, 31.4; IR (neat) 1612, 1506, 1436, 1380, 1232, 1154, 1112, 1077, 1034 cm^{-1}; HRMS calcd for $C_{13}H_{20}O_4$ 240.1361$_5$, found 240.1361.

(+)-(1*R*,3*R*,4*R*,7*R*)-7-(Bromomethyl)-3-(2-(methoxymethoxy)-5-(3-(methoxymethoxy)propyl)phenyl)-1,7-dimethylbicyclo[2.2.1]heptan-2-one (27). A solution of *tert*-butyllithium in hexane (4.41 mL of a 1.7 M solution, 7.5 mmol) was added to 1.20 g (5.0 mmol) of **25** in 5 mL of THF at −10 °C. After being stirred at −10 °C for 2 h, this solution was transferred dropwise *via* cannula to a solution of CuI (0.476 g, 2.5 mmol) in 3 mL of THF at 0 °C. The mixture was stirred for an additional 30 min, and then 7 mL of anhyd DMSO was added. This solution was then transferred dropwise *via* cannula to 0.71 g (2.27 mmol) of (+)-3,9-dibromocamphor (**4**) in 3 mL of THF and 3 mL of anhyd DMSO at 0 °C. The mixture was allowed to stir at rt overnight. After the reaction was quenched with 5 mL of saturated ammonium chloride solution, the product was isolated by extraction with ether and purified by chromatography (hexane−EtOAc, 85:15) to give 0.78 g (73%) of **27**, mp 58−59 °C: $[\alpha]^{25}_D$ = +100.9 (c = 0.033, $CHCl_3$); ^{1}H NMR δ 6.90 (m, 2 H), 6.68 (d, J = 1.5 Hz, 1 H), 5.08 (s, 2 H), 4.52 (s, 2 H), 3.92 (d, J = 4.2 Hz, 1 H), 3.59 (d, J = 10.2 Hz, 1 H), 3.42 (t, J = 6.3 Hz, 2 H), 3.37 (s, 3 H), 3.26 (s, 3 H), 3.20 (d, J = 10.2 Hz, 1 H), 2.68 (t, J = 3.9 Hz, 1 H), 2.52 (dt, J = 7.5, 2.4 Hz, 2 H), 1.75 (m, 2 H), 1.64 (m, 1 H), 1.47 (m, 2 H), 1.17 (m, 1 H), 1.10 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR δ 216.9, 153.4, 134.6, 128.5, 127.8, 125.5, 113.4, 96.3, 94.2, 66.8, 59.5, 55.9, 55.0, 50.8, 50.0, 46.0, 39.8, 31.5, 29.2, 20.6, 16.5, 9.9; IR (neat) 1739, 1466, 1434, 1388, 1357, 1248, 1031, 1059 cm^{-1}; HRMS calcd for $C_{23}H_{33}O_5Br$ 468.1511$_7$, found 468.1519. Anal. Calcd for $C_{23}H_{33}O_5Br$: C 58.85, H 7.09. Found: C 59.29, H 7.10.

(−)-(3*R*,4*R*)-2-(Diethoxy(oxyphosphoryl))-4-isopropenyl-3-(2-(methoxymethoxy)-5-(3-(methoxymethoxy)propyl)phenyl)-1-methyl-1-cyclohexene (28). A solution of 1.11 g (2.36 mmol) of **27** in 12 mL of THF was transferred *via* cannula to ca. 25 mL of 0.4 M sodium naphthalenide in tetraethylene glycol dimethyl ether in THF at −78 °C. The mixture was stirred for 15 min, and an additional amount of 0.4 M sodium naphthalenide was added to keep the mixture a deep green color. Next were added 0.51 mL (3.54 mmol) of diethyl chlorophosphate and 0.70 mL (4.0 mmol) of anhyd HMPA. The mixture was warmed to −25 °C and quenched with 10 mL of saturated aqueous ammonium chloride. The aqueous layer was extracted with three 15-mL portions of ether. After the usual workup and purification (see compound **11**), there was obtained 0.91 g (73%) of **28**: $[\alpha]^{25}_D$ = −48.7 (c = 0.026, $CHCl_3$); ^{1}H NMR δ 6.84 (m, 3 H), 4.99 (s, 2 H), 4.57 (s, 2 H), 4.51 (s, 2 H), 3.80 (m, 2 H), 3.54 (m, 2 H), 3.41 (t, J = 6.3 Hz, 2 H), 3.35 (s, 3 H), 3.25 (s, 3 H), 2.51 (t, J = 7.2 Hz, 2 H), 2.01 (m, 2 H), 1.74 (m, 3 H), 1.69 (s, 3 H), 1.59 (overlapping m, 8 H), 1.09 (t, J = 7.8 Hz, 2 H), 0.94 (t, J = 7.2 Hz, 2 H); ^{13}C NMR δ 153.7, 146.1, 146.0, 141.0, 140.9, 134.2, 126.9, 113.5, 110.8, 96.3, 94.4, 66.9, 63.4, 55.6, 55.0, 49.3, 39.8, 31.6, 31.5, 28.7, 20.5, 16.6, 15.9, 15.6; IR (neat) 1492, 1443, 1274, 1232, 1147, 1105, 1034 cm^{-1}; HRMS calcd for $C_{27}H_{43}O_8P$ 526.2695, found 526.2704. Anal. Calcd for $C_{27}H_{43}O_8P$: C 61.58, H 8.23. Found: C 61.27, H 7.90.

(3*S*,4*S*)-2-(Diethoxy(oxyphosphoryl))-3-(2-hydroxy-5-(3-hydroxypropyl)phenyl)-4-isopropenyl-1-methyl-1-cyclohexene (29). To a stirred solution of 547 mg (1.04 mmol) of **28** in 2 mL of THF and 2 mL of isopropyl alcohol at rt was added dropwise 0.5 mL of concentrated hydrochloric acid. The mixture was stirred for 24 h and was poured into 50 mL of water and extracted three times with 15 mL of CH_2Cl_2. The combined extract was washed with brine and dried over sodium sulfate. The solvent was removed *in vacuo*, and the crude product was chromatographed (hexane−EtOAc, 50:50) to afford 314 mg (69%) of **29**: $[\alpha]^{25}_D$ = −77.1 (c = 0.017, $CHCl_3$); ^{1}H NMR δ 7.44 (broad s, 1 H), 6.78 (m, 3 H), 4.45 (d, J = 7.8 Hz, 2 H), 4.13 (d, J = 6.6 Hz, 1 H), 4.00 (m, 2 H), 3.54 (t, J = 6 Hz, 3 H), 3.38 (m, 1 H), 2.51 (t, J = 7.2 Hz, 2 H), 2.37 (q, J = 7.8 Hz, 1 H), 2.24 (m, 1 H), 2.03 (m, 1 H), 1.89 (m, 1 H), 1.73 (t, J = 6.6 Hz, 2 H), 1.66 (s, 4 H), 1.53 (s, 3 H), 1.21 (t, J = 6.9 Hz, 3 H), 0.91 (t, J = 6.9 Hz, 3 H); ^{13}C NMR δ 153.1, 146.5, 141.6, 134.2, 129.2, 127.9, 127.3, 121.4, 118.9, 111.1, 64.5, 64.0, 62.0, 51.4, 34.6, 31.4, 30.2, 27.5, 19.8, 16.5, 16.0; IR (neat) 3300 (br), 1689, 1647, 1612, 1499, 1436, 1365, 1246, 1126, 1027 cm^{-1}; HRMS calcd for $C_{23}H_{35}O_6P$ 438.2171$_1$, found 438.2164.

(3*S*,4*S*)-3-(2-Hydroxy-5-(3-hydroxypropyl)phenyl)-4-isopropyl-1-methyl-1-cyclohexene (30). Freshly-distilled ethylamine (50 mL) was added to ca. 1.80 g (0.259 mg-atom) of lithium foil at −78 °C. The solution was stirred until most of the lithium was dissolved, and a solution of 300 mg (0.685 mmol) of **29** in 3 mL of THF and 0.45 mL of *tert*-butyl alcohol was added slowly. The mixture was stirred at −10 °C for 1 h and then at rt for 4 h, cooled to 0 °C, and quenched with 10 mL of saturated ammonium chloride. The aqueous mixture was acidified with 20% hydrochloric acid and extracted with three 15-mL portions of ether. The combined extract was washed with brine and dried over sodium sulfate, and the solvent was removed *in vacuo*. Chromatography of the crude product (hexane−EtOAc, 85:15) gave 130 mg (66%) of **30**: $[\alpha]^{25}_D$ = −101.2° (c = 0.015, $CHCl_3$); ^{1}H NMR δ 6.92 (dd, J = 8.4, 1.8 Hz, 1 H), 6.85 (d, J = 1.8 Hz, 1 H), 6.73 (d, J = 8.1 Hz, 1 H), 5.76 (s, 1 H), 5.46 (s, 1 H), 3.68 (t, J = 6.6 Hz, 2 H), 3.36 (d, J = 7.2 Hz, 1 H), 2.61 (t, J = 7.5 Hz, 2 H), 2.09 (m, 2 H), 1.86 (m, 2 H), 1.76 (s, 4 H), 1.59 (dt, J = 9.3, 1.8 Hz, 2 H), 1.37 (m, 1 H), 0.85 (m, 6 H); ^{13}C NMR δ 152.6, 138.1, 133.1, 130.5, 130.0, 127.2, 124.5, 116.3, 62.3, 44.0, 42.5, 34.4, 31.2, 30.4, 27.3, 23.5, 21.7, 21.5, 16.2; IR (neat) 3400 (br), 1608, 1506, 1429, 1365, 1260, 1210, 1041 cm^{-1}; HRMS calcd for $C_{19}H_{28}O_2$ 288.2089, found 288.2085.

(3*S*,4*S*)-3-(2-Hydroxy-5-(3-(phenylseleno)propyl)phenyl)-4-isopropyl-1-methyl-1-cyclohexene. To a stirred solution of 210 mg (0.73 mmol) of **30** in 4 mL of THF was added 273 mg (0.95 mmol) of *N*-PSP and 0.35 mL of tributylphosphine. After 5 h at rt, the solvent was removed on a rotary evaporator and the residue was chromatographed (hexane−EtOAc, 90:10) to give 215 mg (69%) of phenyl selenide; ^{1}H NMR δ 7.48 (m, 2 H), 7.24 (m, 3 H), 6.91 (dd, J = 8.1, 2.1 Hz, 1 H), 6.81 (d, J = 1.8 Hz, 1 H), 6.73 (d, J = 8.1 Hz, 1 H), 5.50 (s, 2 H), 3.29 (d, J = 6.6 Hz, 1 H), 2.91 (t, J = 7.5 Hz, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 2.11 (m, 2 H), 1.98 (m, 2 H), 1.77 (s, 4 H), 1.59 (dt, J = 7.2, 2.1 Hz, 2 H), 1.38 (m, 1 H), 0.84 (m, 6 H); ^{13}C NMR δ 152.7, 138.6, 132.7, 132.5, 130.9, 130.4, 129.7, 129.0, 127.4, 126.7, 124.3, 116.6, 43.8, 43.2, 34.8, 31.8, 30.5, 27.3, 27.1, 23.6, 21.7, 21.5, 16.1; IR (neat) 3428 (br), 1572, 1499, 1472, 1432, 1259, 1219, 1186, 1060 cm^{-1}; HRMS calcd for $C_{25}H_{32}OSe$ 428.1618, found 428.1611.

(3*S*,4*S*)-3-(2-(Methoxymethoxy)-5-(3-(phenylseleno)propyl)phenyl)-4-isopropyl-1-methyl-1-cyclohexene (31). The procedure used for MOM ether formation was similar to that for preparation of phenyl methoxymethyl ether (**8**). From 160 mg (0.375 mmol) of the phenyl selenide prepared above there was obtained 142 mg (80%) of methoxymethyl ether **31** after purification by flash chromatography (hexane−EtOAc, 95:5); ^{1}H NMR δ 7.48 (m, 2 H), 7.24 (m, 3 H), 6.95 (m, 3 H), 5.19 (s, 1 H), 5.16 (s, 2 H), 3.78 (m, 1 H), 3.46 (s, 3 H), 2.90 (t, J = 7.5 Hz, 2 H), 2.66 (t, J = 7.2 Hz, 2 H), 1.98 (m, 4 H), 1.72 (s, 4 H), 1.54 (m, 1 H), 1.43 (m, 2 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 153.5, 135.2, 134.3, 134.1, 132.5, 130.4, 129.2, 129.0, 126.7, 126.5, 125.2, 113.8, 94.7, 55.9, 46.0, 37.8, 35.1, 31.8, 29.8, 27.6, 27.2, 23.6, 21.6, 17.4; IR (neat) 1605, 1492, 1464, 1224, 1146, 1076 cm^{-1}; HRMS calcd for $C_{27}H_{36}O_2Se$ 472.1880, found 472.1873.

(−)-(3*S*,4*S*)-3-(5-Allyl-2-(methoxymethoxy)phenyl)-4-isopropyl-1-methyl-1-cyclohexene (32). To a stirred solution of 120 mg (0.255 mmol) of phenyl selenide **31** in 5 mL of THF was added dropwise 0.40 mL (3.82 mmol) of a 30% hydrogen peroxide solution at rt. After being stirred at 40 °C

for 4 h, the mixture was extracted with three 5-mL portions of ether. The combined extract was washed three times with 10 mL of a 1 M solution of $Na_2S_2O_4$ and then with brine. After being dried over sodium sulfate the solvent was removed *in vacuo*. The crude product was purified by chromatography using hexane as eluent to afford 67 mg (83%) of **32**: $[\alpha]^{25}_D$ = −127.2 (c = 0.003, $CHCl_3$); ^{1}H NMR δ 6.99 (m, 3 H), 5.97 (m, 1 H), 5.20 (s, 1 H), 5.16 (s, 2 H), 5.05 (m, 2 H), 3.78 (m, 1 H), 3.47 (s, 3 H), 3.32 (d, J = 6.6 Hz, 2 H), 2.03 (m, 2 H), 1.71 (s, 5H), 1.54 (m, 1 H), 1.44 (m, 2 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.9 Hz, 3 H); ^{13}C NMR δ 153.6, 138.0, 135.2, 134.1, 133.1, 129.3, 126.5, 126.5, 125.3, 115.2, 113.9, 94.7, 55.9, 45.9, 39.5, 37.9, 29.8, 27.6, 23.5, 21.7, 17.4; IR (neat) 1633, 1492, 1443, 1358, 1231, 1196, 1147, 1069 cm^{-1}; HRMS calcd for $C_{21}H_{30}O_2$ 314.2245, found 314.2240.

4-Allyl-2-iodophenyl Methoxymethyl Ether (34). A solution of 2.02 g (11.3 mmol) of **19** in 10 mL of anhyd THF was treated at −78 °C with 10 mL (17.0 mmol of a 1.7 M solution in hexane) of *tert*-butyllithium. After being stirred at −78 °C for 2 h, the mixture was treated with a solution of iodine (4.32 g, 17.0 mmol) in 15 mL of THF. The mixture was stirred for 30 min, allowed to warm to rt, poured into 10 mL of 20% aqueous Na_2SO_3, and extracted three times with 10 mL of ether. The combined extract was washed with brine and dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude product was purified by chromatography (hexane−EtOAc, 95:5) to give 3.1 g (90%) of aryl iodide **34**: ^{1}H NMR δ 7.64 (d, J = 1 Hz, 1 H), 7.12 (d, J = 8.4 Hz, 1 H), 7.01 (d, J = 8.4 Hz, 1 H), 5.92 (m, 1 H), 5.23 (s, 2 H), 5.09 (d, J = 15.9 Hz, 2 H), 3.52 (s, 3 H), 3.31 (d, J = 6.6 Hz, 2 H); ^{13}C NMR δ 154.3, 139.2, 136.8, 135.4, 129.4, 116.2, 114.8, 94.9, 87.2, 56.2, 38.7; IR (neat) 1633, 1596, 1502, 1483, 1233, 1201, 1151, 1076, 1032 cm^{-1}; HRMS calcd for $C_{11}H_{13}O_2I$ 303.9962$_1$, found 303.9957.

5,5′-Diallyl-2,2′-bis(methoxymethoxy)biphenyl (36). A solution of *tert*-butyllithium in hexane (0.88 mL of a 1.7 M solution, 1.5 mmol) was added to 178 mg (1.0 mmol) of **19** in 1 mL of anhyd THF at −78 °C. After 2 h, the mixture was warmed to −10 °C and transferred *via* cannula to 1.0 mL (1.0 mmol, 1.0 M solution in ether) of anhyd zinc chloride at rt. The mixture was stirred for 1 h. The palladium catalyst was prepared in a separate flask by treating 22 mg (0.033 mmol) of $PdCl_2(PPh_3)_2$ in 1.0 mL of THF with 0.066 mL (0.066 mmol) of DIBALH (1 M solution in hexane). To this catalyst solution was added 213 mg (0.70 mmol) of a solution of aryl iodide **34** in 2 mL of THF and the supernatant solution of the arylzinc chloride prepared above. The mixture was stirred for 2 h at rt and quenched with 5 mL of saturated ammonium chloride solution. The aqueous layer was extracted with three 10-mL portions of ether. The combined extract was washed once with brine and dried over sodium sulfate. After removal of the solvent *in vacuo*, the crude product was purified by chromatography (hexane−EtOAc, 95:5) to give 169 mg (68%) of biaryl **36**: ^{1}H NMR δ 7.16 (m, 2 H), 7.12 (s, 1 H), 6.00 (m, 1 H), 5.11 (dd, J = 16.8, 9.0 Hz, 2 H), 5.06 (s, 2 H), 3.40 (d, J = 6.6 Hz, 2 H), 3.36 (s, 3 H); ^{13}C NMR δ 153.2, 137.6, 133.3, 131.6, 129.2, 128.5, 115.8, 115.6, 95.4, 55.8, 39.4; IR (neat) 1478, 1224, 1189, 1154, 1069, 999 cm^{-1}; HRMS calcd for $C_{22}H_{26}O_4$ 354.1830$_9$, found 354.1825.

Magnolol (1). The same procedure used for removal of the methoxymethyl group of **11** to give **14** was employed. From 150 mg (0.423 mmol) of **36** was obtained 79 mg (70%) of **1** as a clear oil[8] after purification by flash chromatography using hexane−EtOAc (90:10): ^{1}H NMR δ 7.12 (dd, J = 8.1, 2.1 Hz, 2 H), 7.08 (s, 2 H), 6.94 (d, J = 8.1 Hz, 2 H), 5.96 (m, 2 H), 5.78 (s, 2 OH), 5.08 (dd, J = 4.3, 2.1 Hz, 4 H), 3.36 (d, J = 6.6 Hz, 4 H); ^{13}C NMR δ 151.1, 137.5, 133.2, 131.2, 129.9, 123.8, 116.6, 115.8, 39.3; IR (neat) 3507, 3300 (br), 1633, 1617, 1492, 1408, 1351, 1224 cm^{-1}; EIMS m/z (rel intensity) 268 (6), 267 (19), 266 (M$^+$, 100), 248 (6), 247 (8), 239 (9), 237 (14), 225 (12), 224 (7), 223 (5); HRMS calcd for $C_{18}H_{18}O_2$ 266.1306$_9$, found 266.1307 (lit.[2c] ^{1}H NMR δ 7.16−6.86 (m, 6 H), 6.16−5.76 (m, 2 H), 5.12 (dd, J = 4, 2 Hz, 4 H), 4.98 (s, 2 OH), 3.34 (d, J = 7 Hz, 4 H); ^{13}C NMR δ 151.0, 137.6, 133.3, 131.4, 129.8, 124.5, 116.8, 115.8, 39.4 ; IR (neat) 3600, 1645, 1610 cm^{-1}); MS m/z 266 (M$^+$, 100), 225, 184, 133)).

5,5′-Dibromo-2,2′-dimethoxybiphenyl (37). 2,2′-Dimethoxybiphenyl (1.79 g, 8.34 mmol) was dissolved in 20 mL of anhyd DMF, and 3.12 g (17.5 mmol) of *N*-bromosuccinimide was added. The resulting solution was stirred at rt for 12 h. Twenty-five mL of water was added, and the aqueous layer was extracted three times with 20 mL of CH_2Cl_2. The combined extract was washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by chromatography (hexane−EtOAc, 85:15) to give 2.78 g (90%) of **37**, mp 101−102 °C (lit.[9] mp 127−129 °C); ^{1}H NMR δ 7.44 (dd, J = 8.7, 2.4 Hz, 1 H), 7.34 (d, J = 2.4 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 1 H), 3.77 (s, 3 H); ^{13}C NMR δ 156.1, 133.8, 131.6, 128.4, 112.7, 112.5, 55.9; IR (Nujol) 1569, 1281, 1238, 1182, 1133, 1020 cm^{-1}; HRMS calcd for $C_{14}H_{12}O_2Br_2$ 369.9205, found 369.9201.

5,5′-Diallyl-2,2′-dimethoxybiphenyl (38). 5,5′-Dibromo-2,2′-dimethoxybiphenyl (**37**) (1.05 g, 3.07 mmol) and allyltributylstannane (1.0 mL, 3.23 mmol) were allowed to react with tetrakis(triphenylphosphine)palladium(0) (38.6 mg, 0.031 mmol) in 10 mL of benzene in a sealed tube at 100 °C for 24 h. The reaction mixture was then diluted with 15 mL of ether and 10 mL of saturated aqueous potassium fluoride. The organic layer was separated, and the aqueous phase was extracted with three 10-mL portions of ether. The combined extract was washed two times with 10 mL of 10% ammonium hydroxide and once with brine. The solvent was removed *in vacuo*, and the crude product was flash chromatographed (hexane−EtOAc, 85:15) to give 0.64 g (69%) of product **38** as a clear oil (lit.[9] bp 165 °C at 0.7 mm); ^{1}H NMR δ 7.19 (dd, J = 8.4, 2.1 Hz, 1 H), 7.13 (d, J = 2.1 Hz, 1 H), 6.95 (d, J = 8.4 Hz, 1 H), 6.04 (m, 1 H), 5.14 (dd, J = 17.4, 9.9 Hz, 2 H), 3.79 (s, 3 H), 3.42 (d, J = 6.9 Hz, 2 H); ^{13}C NMR δ 155.4, 137.7, 131.6, 131.5, 128.3, 127.7, 115.4, 111.0, 55.7, 39.3; IR (neat) 3005, 2980, 2950, 2923, 2872, 1480, 1228, 1192, 1173, 1069, 1002 cm^{-1}; HRMS calcd for $C_{20}H_{22}O_2$ 294.1619$_7$, found 294.1623.

Magnolol (1) from Dimethyl Ether 38. A solution of 68 mg 0.23 mmol) of **38** in 1 mL of CH_2Cl_2 was treated by dropwise addition of 0.5 mL (1 M in CH_2Cl_2, 0.5 mmol) of BBr_3 at −78 °C with stirring. After 1 h, the mixture was warmed to 0 °C, and 2 mL of water was added. The aqueous phase was extracted with three 3-mL portions of CH_2Cl_2. The combined organic layers were washed with brine, and the solvent was evaporated. Flash chromatography of the crude product (hexane−EtOAc, 90:10) afforded 46 mg (75%) of **1**, whose spectral properties were identical to those of magnolol prepared from **36**.

(3*S*,4*S*)-4-Isopropyl-3-(2-(methoxymethoxy)-5-(3-(methoxymethoxy)propyl)phenyl)-1-methyl-1-cyclohexene (39). The procedure for bis-MOM ether formation was similar to that used for **25**. From 304 mg (1.06 mmol) of phenol alcohol **30** was obtained 318 mg (80%) of diether **39** as a clear oil after purification by flash chromatography (hexane−EtOAc, 90:10): ^{1}H NMR δ 6.95 (m, 3 H), 5.18 (s, 1 H), 5.16 (s, 2 H), 4.64 (s, 2 H), 3.78 (m, 1 H), 3.55 (t, J = 6.3 Hz, 2 H), 3.48 (s, 3 H), 3.38 (s, 3 H), 2.64 (t, J = 7.5 Hz, 2 H), 2.03 (m, 1 H), 1.88 (t, J = 6.6 Hz, 2 H), 1.71 (s, 6 H), 1.54 (m, 1 H), 1.43 (m, 1 H), 0.89 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 153.4, 135.1, 134.9, 134.1, 129.1, 126.4, 125.3, 113.7, 96.5, 94.7, 67.1, 55.9, 55.1, 46.0, 37.7, 31.7, 31.6, 29.8, 27.6, 23.6, 21.6, 17.4; IR (neat) 1552, 1505, 1492, 1445, 1379, 1352, 1233, 1146, 1113, 1066, 1033 cm^{-1}; HRMS calcd for $C_{23}H_{36}O_4$ 376.2613$_4$, found 376.2607.

(3*S*,4*S*)-3-(5′-Allyl-2,2′-bis(methoxymethoxy)-5-(3-(methoxymethoxy)propyl)-3,3′-biphenylyl)-1-methyl-1-cyclohexene (41). A solution of *tert*-butyllithium in hexane (0.39 mL of a 1.7 M solution, 0.67 mmol) was added to 168 mg (0.447 mmol) of precursor **39** in 0.5 mL of anhyd THF at −78 °C. After 2 h, the solution was warmed to −10 °C and transferred *via* cannula to 0.45 mL (0.447 mmol of a 1.0 M solution in ether) of anhyd zinc chloride at rt. The mixture was stirred for 1.5 h. The palladium catalyst was prepared in a separate flask by treating 10 mg (0.015 mmol) of $PdCl_2(PPh_3)_2$ in 0.5 mL of THF with 0.03 mL (0.03 mmol) of DIBALH (1 M solution in hexane). To this catalyst solution was added 91 mg (0.298 mmol) of aryl iodide **34** in 1 mL of THF and the supernatant solution of the arylzinc chloride **40** prepared above. The

reaction mixture was stirred for 16 h at rt and quenched with 5 mL of saturated ammonium chloride solution. The aqueous layer was extracted with three 10-mL portions of ether, and the combined extract was washed once with brine and dried over sodium sulfate. After removal of the solvent *in* vacuo, the crude product was purified by chromatography (hexane–EtOAc, 90:10) to give 61 mg (37%) of **41** as a clear oil: ^{1}H NMR δ 7.10 (m, 3 H), 6.98 (s, 1 H), 6.92 (s, 1 H), 5.95 (tdd, J = 16.5, 10.3, 6.5 Hz, 1 H), 5.24 (s, 1 H), 5.03 (m, 3 H), 4.63 (m, 3 H), 4.47 (m, 1 H), 3.71 (m, 1 H), 3.55 (t, J = 7.5 Hz, 2 H), 3.36 (s, 9 H), 3.02 (s, 2 H), 2.66 (t, J = 7.2 Hz, 2 H), 2.09 (m, 2 H), 1.88 (m, 3 H), 1.70 (s, 3 H), 1.59 (m, 2 H), 1.47 (m, 2 H), 0.86 (d, J = 6.9 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 153.2, 139.2, 137.7, 135.2, 133.9, 133.4, 132.0, 131.6, 130.8, 130.3, 130.2, 128.5, 128.1, 126.1, 115.6, 115.5, 99.4, 96.5, 95.2, 67.2, 56.8, 55.8, 53.4, 39.4, 38.6, 31.9, 31.4, 30.6, 27.7, 23.5, 22.3, 21.6, 16.9; IR (neat) 1640, 1598, 1485, 1443, 1274, 1231, 1154, 1048, 1013 cm^{-1}; HRMS calcd for $C_{34}H_{48}O_6$ 552.3451, found 552.3462.

(3*S*,4*S*)-3-(5′-Allyl-2,2′-dihydroxy-5-(3-hydroxypropyl)-3,3′-biphenylyl)-4-isopropyl-1-methyl-1-cyclohexene (42). The same procedure used for removal of the MOM groups from **28** was employed. From 40 mg (0.072 mmol) of **41** there was obtained 22 mg (73%) of **42** as a clear oil after purification by flash chromatography (hexane–EtOAc, 80:20): ^{1}H NMR δ 7.22 (s, 1 H), 7.12 (s, 2 H), 6.98 (m, 2 H), 6.11 (s, 1 H), 5.99 (m, 2 H), 5.48 (s, 1 H), 5.06 (m, 1 H), 3.68 (t, J = 6.3 Hz, 2 H), 3.50 (m, 1 H), 3.76 (d, J = 6.6 Hz, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 1.87 (m, 2 H), 1.74 (s, 3 H), 1.59 (m, 2 H), 1.42 (m, 1 H), 1.25 (m, 1 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 151.7, 150.3, 149.0, 137.7, 134.2, 132.7, 131.1, 130.9, 130.7, 129.5, 124.1, 117.1, 116.5, 115.9, 115.6, 44.4, 39.4, 39.3, 34.6, 34.5, 31.3, 30.3, 27.5, 23.7, 21.7, 21.6, 16.5; IR (neat) 3335 (br), 1632, 1598, 1499, 1465, 1359, 1219, 1159, 1126, 1033, 758 cm^{-1}; HRMS calcd for $C_{28}H_{36}O_3$ 420.2664, found 420.2662.

(−)-Monoterpenylmagnolol (3). To a stirred solution of 8 mg (0.019 mmol) of biaryl **42** and 7.5 mg (0.025 mmol) of *N*-PSP in 0.5 mL of anhyd THF was added 0.01 mL (0.037 mmol) of tributylphosphine at rt. After being stirred for 5 h, the mixture was passed through a short column of silica gel and the solvent was removed *in vacuo*. The entire product was dissolved in 0.5 mL of THF, and 0.05 mL of a 30% hydrogen peroxide solution was added. After being stirred at rt for 12 h, the mixture was quenched with 1 mL of 1 M $Na_2S_2O_4$. The mixture was extracted with three 5-mL portions of ether. The combined extract was washed with brine and dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude product was purified by chromatography (hexane–EtOAc, 90:10) to afford 5.4 mg (70%) of monoterpenylmagnolol (**3**) as a clear oil: $[\alpha]^{25}_D$ = −129.1 (c = 0.004, $CHCl_3$) [lit.[2b] $[\alpha]^{25}_D$ = −138.0 (c = 1.03, $CHCl_3$)]; ^{1}H NMR δ 7.11 (dd, J = 7.9, 2.5 Hz, 1 H), 7.08 (d, J = 2.0 Hz, 1 H), 6.96 (d, J = 8.3 Hz, 1 H), 6.92 (d, J = 2.5 Hz, 1 H), 6.09 (s, 1 H), 5.97 (tdd, J = 16.7, 9.9, 6.9 Hz, 4 H), 5.84 (s, 1 H), 5.50 (s, 1 H), 5.11 (m, 1 H), 5.09 (m, 1 H), 3.48 (m, 1 H), 3.37 (d, J = 6.9 Hz, 2 H), 3.35 (d, J = 6.9 Hz, 2 H), 2.10 (broad s, 2 H), 1.75 (s, 3 H), 1.62 (m, 1 H), 1.60 (m, 1 H), 1.40 (m, 2 H), 0.89 (d, J = 6.5 Hz, 3 H), 0.85 (d, J = 6.5 Hz, 3 H); ^{13}C NMR δ 151.7, 149.2, 139.0, 137.8, 137.7, 137.6, 132.7, 132.5, 131.1, 129.6, 129.7, 125.1, 124.9, 124.1, 117.1, 115.7, 115.6, 44.3, 42.3, 39.5, 39.4, 30.3, 27.4, 23.7, 21.7, 21.6, 16.4; IR ($CHCl_3$) 3298 (br), 1645, 1612, 1505, 1459, 1425, 1379, 1252, 1139, 1113, 1040 cm^{-1}; EIMS m/z (rel intensity) 404 (5), 403 (5), 402 (M^+,16), 359 (2), 337 (2), 334 (3), 332 (2), 319 (2), 318 (3), 317 (10); HRMS calcd for $C_{28}H_{34}O_2$ 402.2558$_6$, found 402.2567 (lit.[2b] ^{1}H NMR δ 7.11 (dd, J = 8.1, 2.2 Hz, 1 H), 7.08 (d, J = 2.2 Hz, 1 H), 6.95 (d, J = 2.2 Hz, 1 H), 6.92 (d, J = 2.2 Hz, 1 H), 6.89 (d, J = 8.1 Hz, 1 H), 6.09 (s, 1 OH), 5.98 (tdd, J = 16.9, 10.1, 6.7 Hz, 2 H), 5.97 (tdd, J = 16.9, 10.1, 6.7 Hz, 2 H), 5.87 (s, 1 OH), 5.48 (broad s, 1 H), 5.10 (m, 1 H), 5.08 (m, 1 H), 3.49 (broad d, 1 H), 3.35 (d, J = 4.9 Hz, 2 H), 3.34 (d, J = 4.9 Hz, 2 H), 2.09 (broad s, 2 H), 1.74 (broad s, 3 H), 1.61 (m, 1 H), 1.60 (m, 1 H), 1.41 (m, 2 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 151.46, 149.20, 138.52, 137.68, 137.63, 132.67, 132.41, 131.28, 129.58, 129.49, 125.21, 125.02, 124.19, 116.97, 115.59, 44.42, 42.16, 39.41, 30.25, 27.43, 23.65, 21.60, 16.53; IR ($CHCl_3$) 3300, 1615, 1650 cm^{-1}).

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Supplementary Material Available: A listing of the EI mass spectral data of compounds **9**–**11**, **13**, **14**, **17**, **19**, **25**, **27**–**32**, **34**, **36**–**39**, **41**, **42**. Experimental procedures for the preparations of **15**, **16**, **10a**, **11a**, **20**, **21**, **23**, **24**, **19** (alternate route), **23-OH**, **32-OH**, and **33** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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