Stereoselective Synthesis of (+)-Avarol, (+)-Avarone, and Some Nonracemic Analogues

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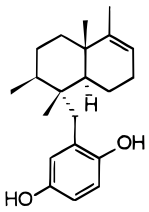
Synthesis of the rearranged drimane sesquiterpenoids (+)-avarol and (+)-avarone from Wieland−Miescher ketone is described. This synthetic sequence provides convenient access to the natural enantiomers and, based on comparison of the optical rotation of synthetic avarol dimethyl ether with literature data, affords material of significantly higher optical rotation than a natural source. Similar synthetic strategies have been used to obtain several related compounds, including a decalin bearing an exocyclic olefin and a highly substituted cyclohexane, that can be viewed as hybrids of the trans-fused avarol and cis-fused arenarol skeletons.

Over the past two decades, dozens of natural products with quinone or hydroquinone systems appended to a sesquiterpene or diterpene skeleton have been isolated from marine sponges.[1] Among the more well-known members of this family are the drimane derivatives avarol (**1**) and avarone (**2**). Avarol and avarone were first



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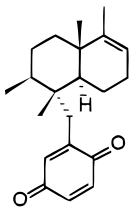

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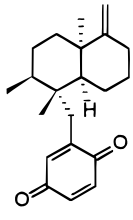
isolated from the Mediterranean sponge *Dysidea avara* and assigned structures in 1974,[2] later assigned absolute stereochemistry on the basis of CD experiments,[3] and finally confirmed in stereochemistry by diffraction analysis of a simple derivative.[4] While early studies indicated modest activity for avarol and avarone as antibiotic and antileukemic agents,[5] subsequent research that reported significant antiviral activity against HIV-I greatly stimulated interest in these compounds.[6] Unfortunately, *in vivo* antiviral activity has not been confirmed by later assays, and recent papers suggest that the initial reports of significant antiviral activity were overly optimistic.[7,8] While the pharmaceutical potential of avarol and avarone is far from clear, a number of avarol derivatives[9] and related compounds[10] have shown interesting activity in enzyme assays measuring inhibition of the various functions of HIV-I reverse transcriptase.

Despite their interesting structures and the continued biological interest, there has been little published work on synthesis of avarol or avarone. The only total synthesis appeared in 1982, when Sarma and Chattopadhyay reported their preparation of racemic avarol.[11] Recently, there has been a surge of interest in preparation of related compounds, including our total synthesis of the cis-fused (±)-arenarone (**3**)[12] and independent syntheses of (−)-ilimaquinone (**4**)[13] and (±)-mamanuthaquinone (**5**).[14] In this report we present our synthesis of (+)-avarol (**1**) and (+)-avarone (**2**), the first synthesis of either as the natural enantiomer, along with preparations of several analogues.



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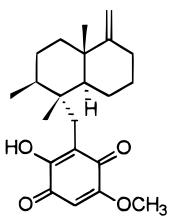

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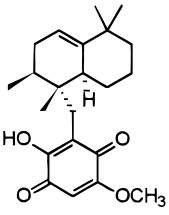

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To obtain the natural avarol/avarone enantiomers, it was attractive to employ the methylated Wieland−Meischer ketone derivative **8** because this compound has been prepared in optically active form.[15] However, given that the L-phenylalanine mediated Robinson annulation leading directly from 2-methyl-1,3-cyclohexanedione and ethyl vinyl ketone to compound **8** is reported in modest yield (60%) and limited ee (75−90%), we chose instead to begin with Wieland−Miescher ketone (**6**) itself to take advantage of the higher chemical yield and ee (96%)

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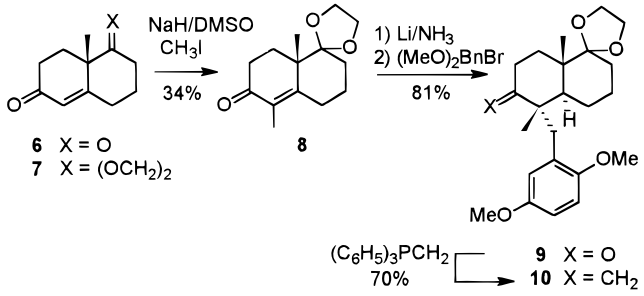
known for its preparation.[16] Despite a low yield in the methylation step, this approach proved to be advantageous from the standpoint of optical purity. After protection of the Wieland−Miescher ketone through reaction with ethylene glycol, the enone ketal **7** was treated with NaH/DMSO[17] followed by addition of methyl iodide in order to obtain compound **8** in optically pure form. Reduction of enone **8** by treatment with Li/NH_3, followed by trapping the intermediate enolate through reaction with 2,5-dimethoxybenzyl bromide, gave the expected product **9** as a single isomer. The Wittig reaction of ketone **9** and methylene triphenylphosphorane gave the exocyclic olefin **10** in 70% yield.

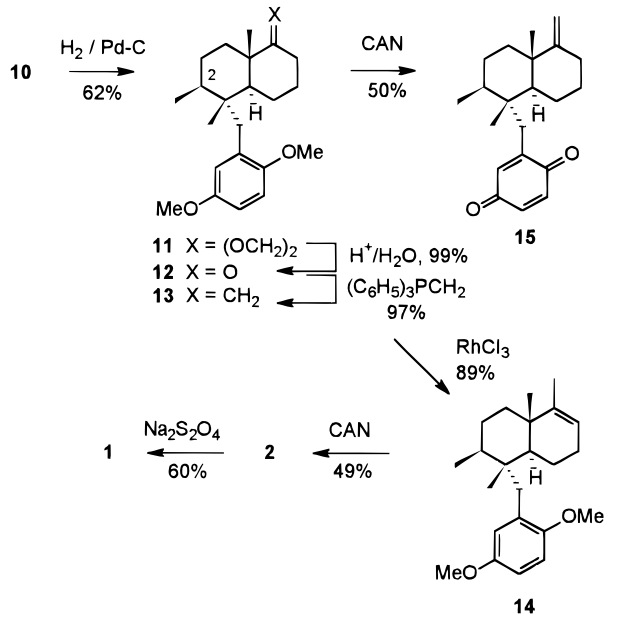


Catalytic hydrogenation of olefin **10** over Pd−C gave a mixture of the desired product **11** (62%) and its C-2 epimer (27%, avarol numbering). After separation of the diastereomers, the major product was treated with aqueous acid to remove the ketal, and the resulting ketone **12** was treated with methylene triphenylphosphorane to provide the exocyclic olefin **13** in very good yield. Treatment of olefin **13** with $RhCl_3$ in ethanol, in a fashion similar to that reported by Sarma,[11] resulted in isomerization of the exocyclic olefin to the more stable endocyclic olefin in good yield, providing the known dimethyl avarol **14**.

The synthetic sequence to compound **14** was conducted twice, initially with a sample of ketone **6** of about 80% ee, and subsequently with material of greater than 96% ee. From the more optically pure ketone **6**, we obtained the methylated intermediate **8** in high enantiomeric excess and ultimately obtained compound **14** in high optical purity ($[\alpha]_D = +8.9°$ ($CHCl_3$, $c = 1.1$) vs a literature[3] value of $[\alpha]_D = +5.2°$ ($CHCl_3$, $c = 1.7$)). Because the synthesis beginning with material of approximately 80% ee produced compound **14** with a proportionally lower rotation, it is likely that the reported preparation of compound **14** via methylation of natural avarol did not provide optically pure material.

Completion of the (+)-avarone synthesis was accomplished by oxidation of the dimethyl ether **14** with ceric ammonium nitrate (CAN),[13,14] and (+)-avarol itself was then obtained by sodium dithionite reduction of the quinone **2**. Both of the synthetic materials gave spectroscopic data identical to that reported for the natural products, confirming the identity of the synthetic products.

A recent publication[18] established that arenarone (**3**) and avarone (**2**) share the same absolute configuration at three of their four stereogenic centers. Thus these two natural products differ only in that avarone incorporates a trans-fused decalin while arenarone is cis-fused, and



in that avarone contains an endocyclic olefin while arenarone bears an exocyclic olefin. In anticipation of bioassays comparing the activity of avarone and arenarone, we prepared a new compound that can be viewed as a hybrid of the two natural products, the "exo" avarone **15**. Compound **15** was readily available by treatment of compound **13** with CAN to accomplish deprotection of the methyl ethers and formation of the quinone system.

The similarity between the structures of avarone (**2**) and arenarone (**3**) also inspired interest in related monocyclic analogues designed to simplify both the trans- and cis-fused decalin systems to a common, highly substituted, cyclohexane derivative. From this perspective (Scheme 1), hypothetical deletion of C-7 and C-8 of avarone allowed identification of the cyclohexane **16** as a prime target. In a retrosynthetic sense, compound **16** can be dissected to a methyl ketone or ketal at the C-4 position of a methylenecyclohexane (**17**). This exocyclic olefin could be viewed as a derivative of an enone such as compound **18**, through a sequence involving conjugate addition and alkylation of the resulting enolate. Finally, it was anticipated that enone **18** would be readily available by straightforward Horner−Wadsworth−Emmons condensation of the nonracemic phosphonate **19** with formaldehyde. Because the nonracemic β-keto phosphonate **19** has recently been prepared from the known, prochiral 4,4-disubstituted cyclohexanone **20** via a diastereoselective vinyl phosphate rearrangement,[19] phosphonate **19** represents a convenient starting material for this sequence.

To obtain the monocyclic avarol analogue best reflecting the natural avarol stereochemistry, the 4*S* enantiomer of compound **19** was employed to begin the synthetic sequence. Treatment of phosphonate **19** with K_2CO_3 and formaldehyde in aqueous dioxane afforded the expected α-methylene ketone **21** in good yield. When this enone was treated with lithium metal in liquid ammonia, and the resulting enolate was quenched by addition of 2,5-dimethoxybenzyl bromide, regiospecific alkylation was achieved. The major product was assigned structure **22** based on the assumption that with the bulky ketal moiety in an equatorial orientation the stereochemistry

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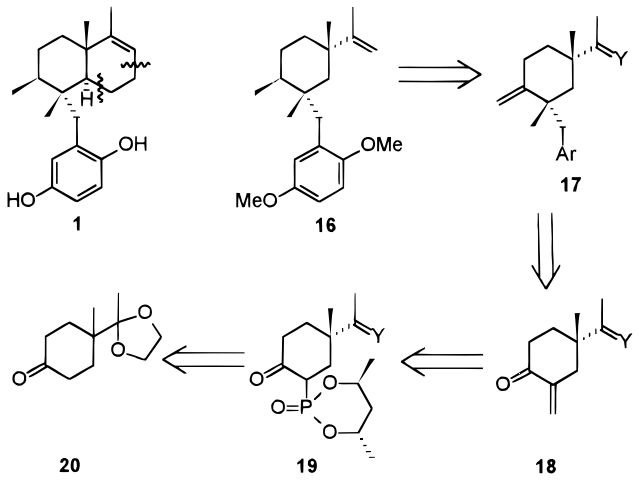
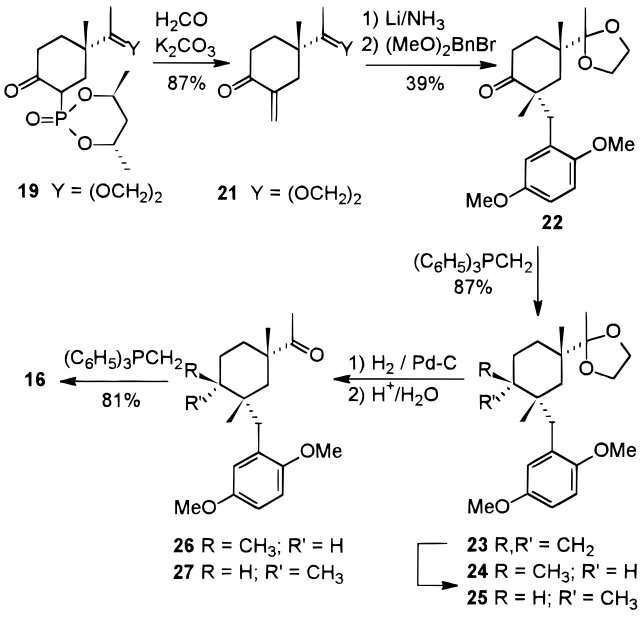
Scheme 1



of this alkylation would be controlled by the axial methyl group and parallel that known for the trans-fused decalin **9**. This product was isolated in modest yield primarily because it was accompanied by a significant amount of the corresponding diketone formed by hydrolysis of the ketal upon workup.



Olefination of ketone **22** through a Wittig reaction with methylene triphenylphosphorane in refluxing THF gave compound **23** in good yield (87%). Hydrogenation of this exocyclic olefin over Pd−C gave two diastereomers, compounds **24** and **25**, in a ratio of ca. 2:1, respectively, as measured by direct GC and HPLC analyses of the reaction mixture. The two isomers were not readily separable by flash column chromatography, but after deprotection of the ketals the corresponding ketones (**26** and **27**) were separated. The major component was expected to be compound **26** which has the desired avarol-like stereochemistry at C-1, based on the assumption that the two larger substituents, the ketal and benzyl groups, take equatorial positions in compound **23,** and that catalytic hydrogenation is favored from the less sterically congested face of compound **23**. Finally, the carbonyl group of ketone **26** was converted to an olefin via Wittig methylenation to give the desired dimethyl avarol analogue **16** in 81% yield.

In conclusion, the natural products (+)-avarone and (+)-avarol have been prepared via a stereocontrolled sequence from Wieland−Miescher ketone. The observed rotations for the synthetic compounds are significantly higher than those reported for the natural products. Further experiments with natural avarol and avarone's enantiomeric purity on their biological activity. Parallel bioassays with nonracemic analogues, such as compounds **15** and **16**, may help establish the importance of the trans- and cis-fused decalin systems to the activity associated with avarol and arenarol.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone, while triethylamine was distilled from CaH_2. All nonaqueous reactions were conducted in oven-dried glassware, under an atmosphere of nitrogen, and with magnetic stirring. Flash chromatography was carried out on Baker silica gel with 40 μm average particle diameter. Melting points are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter. NMR spectra (^{1}H at 300 MHz and ^{13}C at 75 MHz) were recorded with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^{1}H) or $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards. Both low and high resolution mass spectra were obtained at an ionization potential of 70 eV; only selected ions are reported here. High resolution mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

(4a*S*)-(+)-5-(1,3-Dioxolan-2-yl)-1,4a*β*-dimethyl-4,4a,7,8-tetrahydro-2,5-(3*H*,6*H*)-naphthalenedione (8). A dispersion of NaH (0.31 g, 13.0 mmol) in 20 mL of DMSO was stirred at 65 °C under N_2 until the solution became clear. After the solution was allowed to cool to rt, a solution of ketal **7** (2.77 g, 12.5 mmol in 10 mL of DMSO), derived from optically active Wieland−Miescher ketone prepared as previously described,[20] was added dropwise to the reaction flask. After 1.5 h, a solution of CH_3I (2.13 g, 15.0 mmol in 40 mL DMSO) was added over a period of 3 h, and the reaction was stirred at rt for an additional 5 h. The reaction was quenched by addition of saturated NH_4Cl, and the aqueous layer was extracted three times with ether (50 mL each). The combined organic layer was washed five times with water (50 mL each) and three times with brine (30 mL each) and dried over Na_2SO_4. After concentration in *vacuo*, the residue was purified by flash column chromatography (60% hexanes, 40% EtOAc) to give compound **8** (0.99 g, 34%) as a white solid with ^{1}H NMR data identical to the reported partial spectrum:[17] $[\alpha]_D = +114°$ ($CHCl_3$, $c = 1.1$), lit.[17] $[\alpha]_D = +110°$ (CH_3OH, $c = 0.5$); ^{1}H NMR δ 4.02−3.90 (m, 4), 2.77−2.70 (br, m, 1), 2.52−2.34 (m, 2), 2.29−2.10 (m, 2), 1.95−1.73 (m, 2), 1.79 (d, $J = 1.4$ Hz, 3), 1.70−1.55 (br, m, 3), 1.34 (s, 3), ^{13}C NMR δ 198.5, 160.0, 130.0, 112.7, 65.2, 64.9, 45.2, 33.6, 29.6, 26.4, 26.3, 21.3, 20.8, 11.3; EIMS *m*/*z* (rel intensity) 236 (M^+, 7), 121 (3), 107 (4), 100 (13), 99 (100), 55 (31).

(1*S*,4a*S*)-(+)-*trans*-1α-[(2,5-Dimethoxyphenyl)methyl]-1*β*,4a*β*-dimethyl-5-(2-methyl-1,3-dioxolan-2-yl)-hexahydro-2,5(3*H*,6*H*)-naphthalenedione (9). To lithium (0.07 g, 10.0 mmol) in liquid ammonia (100 mL) at −78 °C in a flask fitted with a Dewar condenser was added dropwise a solution of compound **8** (0.90 g, 3.8 mmol in 10 mL of THF). The cooling bath was withdrawn, and the reaction was allowed to warm to reflux and maintained at that temperature for 1 h. 2,5-Dimethoxybenzyl bromide (3.5 g, 15.2 mmol in 5 mL of THF) was added as rapidly as possible, and an additional 30 mL of THF was added. After 2 h at reflux, the Dewar condenser was

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replaced by a water condenser, and the NH_3 was allowed to evaporate. The reaction was quenched by addition of saturated NH_4Cl, and the aqueous layer was extracted three times with ether (50 mL each). The combined organic layer was dried over Na_2SO_4 and concentrated in *vacuo*. Flash column chromatography (40% hexanes, 60% ethyl acetate) gave compound **9** (1.19 g, 81%) as an oil: $[\alpha]_D = +24.6°$ ($CHCl_3$, c = 1.0); ^{1}H NMR δ 6.72−6.71 (m, 2), 6.50 (s, 1), 3.94−3.75 (m, 4), 3.73 (s, 3), 3.70 (s, 3), 2.90 (d, J = 13.3 Hz, 1), 2.80 (d, J = 13.3 Hz, 1), 2.57−2.47 (m, 1), 2.36−2.22 (m, 2), 1.95−1.85 (m, 1), 1.77−1.44 (br, m, 7), 1.04 (s, 6); ^{13}C NMR δ 217.0, 152.9, 152.3, 127.4, 117.8, 112.7, 112.3, 110.8, 65.0, 64.6, 55.6, 55.3, 51.8, 45.0, 42.1, 39.6, 35.2, 29.9, 28.3, 22.8, 22.7, 20.9, 17.2; EIMS m/z (rel intensity) 388 (M^+, 8), 237 (6), 210 (6), 151 (100), 121 (19), 99 (58), 85 (12), 55(14); HRMS calcd for $C_{23}H_{32}O_5$ 388.2250, found 338.2271. Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 71.01; H, 8.31.

(1*S*,4a*S*)-(+)-*trans*-1α-[(2,5-Dimethoxyphenyl)methyl]-1*β*,4a*β*-dimethyl-5-(2-methyl-1,3-dioxolan-2-yl)-2-methyleneoctahydro-5(6*H*)-naphthalenone (10). To a suspension of methyltriphenylphosphonium bromide (4.20 g, 12.0 mmol) in anhydrous 1,4-dioxane (50 mL) was added n-BuLi (6.9 mL, 11.0 mmol, 1.6 M in hexane) over 5 min. The resulting orange suspension was stirred at rt for 60 min, compound **9** (0.66 g, 1.7 mmol) in 5 mL of 1,4-dioxane was added, and the reaction was heated at reflux for 24 h. After the reaction was quenched by addition of water (20 mL) and concentrated in *vacuo*, the residue was purified by flash column chromatography (90% hexanes, 10% ethyl acetate) to give olefin **10** (0.46 g, 70%) as an oil: $[\alpha]_D = +101°$ ($CHCl_3$, c = 1.04); ^{1}H NMR δ 6.70−6.60 (m, 3), 4.74 (br, 1), 4.27(br, 1), 4.00−3.84 (m, 4), 3.73 (s, 3), 3.70 (s, 3), 2.77 (d, J = 13.1 Hz, 1), 2.59 (d, J = 13.1 Hz, 1), 2.35−2.27 (m, 1), 2.17−1.95 (m, 3), 1.74−1.40 (br, m, 6), 1.30−1.15 (m, 1), 1.05 (s, 3), 0.91 (s, 3); ^{13}C NMR δ 153.9, 152.8, 152.4, 128.4, 118.7, 113.6, 111.4, 110.6, 107.3, 64.9, 64.5, 55.7, 55.6, 46.3, 43.5, 42.9, 39.9, 32.0, 29.8, 26.9, 23.0, 22.9, 20.8, 20.3; EIMS m/z (rel intensity) 386 (M^+, 3), 324 (2), 235 (13), 189 (1), 151 (16), 121 (12), 99 (100), 91 (9), 55 (14); HRMS calcd for $C_{24}H_{34}O_4$ 386.2457, found 386.2457. Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.56; H, 8.87. Found: C, 74.41; H, 8.84.

(1*S*,2*S*,4a*S*)-(−)-*trans*-1α-[(2,5-Dimethoxyphenyl)methyl]-5-(2-methyl-1,3-dioxolan-2-yl)-octahydro-1*β*,2*β*,4a*β*-trimethyl-5(6*H*)-naphthalenone (11). Olefin **10** (0.41 g, 1.05 mmol), 10% Pd−C (0.68 g) in triethylamine (10 mL), and methanol (2 drops) was stirred at rt under 1 atm of hydrogen for 12 h. The reaction was filtered through Celite, and the filtrate was concentrated in *vacuo*. The residue was purified by flash column chromatography (90% hexanes, 10% ethyl acetate) to give compound **11** (0.25 g, 62%): ^{1}H NMR δ 6.77−6.66 (m, 3), 3.87−3.67 (m, 4), 3.78 (s, 3), 3.73 (s, 3), 2.63 (s, 2), 1.94 (d, J = 13.6 Hz, 1), 1.71−1.59 (m, 3), 1.51−1.43 (m, 2), 1.39−1.22 (br, m, 6), 1.05 (s, 3), 0.94 (d, J = 5.6 Hz, 3), 0.8 (s, 3); ^{13}C NMR δ 152.9, 152.7, 128.9, 118.3, 113.4, 111.9, 110.9, 65.1, 64.8, 55.8, 55.4, 43.7, 43.2, 41.5, 37.2, 36.1, 30.7, 29.6, 27.3, 22.8, 21.8, 17.5 (2), 16.8; EIMS m/z (rel intensity) 388 (M^+, 6), 237 (43), 175 (27), 152 (90), 99 (100), 55 (28); HRMS calcd for $C_{24}H_{36}O_4$ 388.2613, found 388.2585. Anal. calcd for $C_{24}H_{36}O_4$: C, 74.18; H, 9.34. Found: C, 74.24; H, 9.29.

(1*S*,2*S*,4a*S*)-(−)-*trans*-1α-[(2,5-Dimethoxyphenyl)methyl]-octahydro-1*β*,2*β*,4a*β*-trimethyl-5(6*H*)-naphthalenone (12). Ketal **11** (400 mg, 10 mmol) in THF (8 mL) and aqueous HCl (5%, 2 mL) was stirred at rt for 2 h. The reaction was quenched by addition of solid Na_2CO_3, and THF was removed in *vacuo*. The remaining aqueous layer was extracted three times with ether (20 mL each). The combined organic layer was dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by flash column chromatography (80% hexanes, 20% ethyl acetate) to give compound **12** as a white solid (350 mg, 99%) with ^{1}H NMR data identical to the partial spectrum reported for racemic material:[11] $[\alpha]_D = -42.3°$ ($CHCl_3$, c = 1.04); mp 105 °C; ^{1}H NMR δ 6.74−6.61 (m, 3), 3.73 (s, 3), 3.70 (s, 3), 2.73 (d, J = 14.0 Hz, 1), 2.63 (d, J = 14.0 Hz, 1), 2.63−2.51 (m, 1), 2.24−2.04 (br, m, 3), 1.81−1.67 (m, 1), 1.59−1.37 (m, 6), 1.14 (s, 3), 1.11 (m, 1), 1.05 (d, J = 5.8 Hz, 3), 0.90 (s, 3); ^{13}C NMR δ 216.2, 152.7, 152.6, 127.9, 119.0, 111.0, 110.8, 55.5, 55.3, 49.3, 47.6, 42.3, 37.5, 37.2, 35.6, 32.3, 26.8, 25.6, 21.9, 18.9, 18.0, 17.3.

(1*S*,2*S*,4a*S*)-(−)-*trans*-Decahydro-1α-[(2,5-dimethoxyphenyl)methyl]-5-methylene-1*β*,2*β*,4a*β*-trimethylnaphthalene (13). To a suspension of methyltriphenylphosphonium bromide (0.66 g, 1.84 mmol) in anhydrous 1,4-dioxane (10 mL) was added n-BuLi (1.1 mL, 1.60 mmol, 1.6 M in hexane) over 2 min. The resulting orange suspension was stirred at rt for 1 h. Ketone **12** (0.11 g, 0.31 mmol) in 2 mL of 1,4-dioxane was then added to the phosphorane solution, and the reaction was heated at reflux for 3 h. The reaction was quenched by addition of water (5 mL) and concentrated in vacuo. The residue was purified by flash column chromatography (80% hexanes, 20% ethyl acetate) to give compound **13** (0.10 g, 97%) as a white solid: $[\alpha]_D = -34°$ ($CHCl_3$ c = 1.4); mp 80 °C; ^{1}H NMR δ 6.74−6.63 (m, 3), 4.40 (s, 1), 4.37 (s, 1), 3.74 (s, 3), 3.70 (s, 3), 2.66 (d, J = 14.0 Hz, 1), 2.58 (d, J = 14.0 Hz, 1), 2.39−2.28 (m, 1), 2.10 (br, 1), 2.06 (br, 1), 1.93−1.88 (br, m, 1), 1.60−1.27 (br, m, 7), 1.05 (s, 3), 1.05−0.95 (m, 1), 1.00 (d, J = 5.8 Hz, 3), 0.84 (s, 3); ^{13}C NMR δ 160.2, 152.9, 152.7, 128.6, 118.7, 111.2, 110.7, 102.6, 55.6, 55.3, 48.1, 42.1, 40.2, 37.1, 36.5, 36.2, 33.1, 28.3, 27.7, 23.1, 20.6, 17.7, 17.5; EIMS m/z (rel intensity) 342 (M^+, 12), 191 (10), 177 (7), 152 (100), 121 (29), 109 (16), 95 (68), 55 (14); HRMS calcd for $C_{23}H_{34}O_2$ 342.2559, found 342.2559.

(1*S*,2*S*,4a*S*)-(+)-*trans*-1α-[(2,5-Dimethoxyphenyl)methyl]-1,2,3,4,4a,8a,7,8-octahydro-1*β*,2*β*,4a*β*,5-tetramethylnaphthalene (14, dimethyl ether avarol). A mixture of compound **13** (76 mg, 0.22 mmol) and $Rh_3Cl\cdot H_2O$ (5 mg) in 5 mL of ethanol was heated at reflux for 20 h. After concentration of the solution, the residue was purified by flash column chromatography (80% hexanes, 20% ethyl acetate) to give compound **14** (68 mg, 89%) as a white solid: $[\alpha]_D = +8.9°$ ($CHCl_3$, c = 1.1); mp 78 °C (lit.[3] mp 80−81 °C); both ^{1}H NMR and ^{13}C NMR spectra were identical to literature data for material derived from the natural product; EIMS m/z (rel intensity) 342 (M^+, 2), 191 (2), 190 (2), 152 (57), 151 (44), 121 (11), 120 (14), 95 (81), 94 (100), 55 (8).

Avarone (2). A mixture of compound **14** (26 mg, 0.08 mmol) and $(NH_4)_2Ce(NO_3)_6$ (83 mg, 0.15 mmol) in CH_3CN (4 mL) and water (2 mL) was stirred at rt for 3 days. The reaction was then concentrated in *vacuo* and purified by flash column chromatography (90% hexanes, 10% ethyl acetate) to give compound **2** (12 mg, 49%) as a yellow oil with ^{1}H NMR data identical to that reported for natural product;[2] ^{13}C NMR δ 187.4, 187.3, 147.4, 144.1, 137.2, 136.2, 136.0, 120.5, 47.0, 42.7, 38.5, 37.0, 36.1, 35.4, 27.4, 26.4, 20.0, 19.3, 18.0, 17.7, 16.7.

Avarol (1). To a solution of avarone (**2**, 5 mg, 0.016 mmol) in THF (2 mL) and water (0.7 mL) was added solid $Na_2S_2O_3$ at rt, and the reaction mixture was stirred for 10 min. After concentration of the solution, the residue was purified by flash column chromatography (10% hexanes, 90% ethyl acetate) to give avarol **1** (3 mg, 60%): ^{1}H NMR, identical to that reported for natural product;[2] EIMS m/z (rel intensity) 314 (M^+, 0.5), 189 (2), 107 (43), 95 (100), 55 (24); HRMS calcd for $C_{21}H_{30}O_2$ 314.2245, found 314.2265.

Exo-avarone (15). A mixture of compound **13** (45 mg, 0.13 mmol) and $(NH_4)_2Ce(NO_3)_6$ (288 mg, 0.53 mmol) in CH_3CN (6 mL) and water (2 mL) was stirred at rt for 3 days. The reaction was then concentrated in *vacuo* and purified by flash column chromatography (90% hexanes, 10% ethyl acetate) to give compound **15** (20.3 mg, 50%) as a yellow oil: ^{1}H NMR δ 6.77−6.68 (m, 2), 6.64 (br, 1), 4.46 (s, 1), 4.44 (s, 1), 2.58 (d, J = 13.5 Hz, 1), 2.40 (d, J = 13.5 Hz, 1), 2.32−2.25 (m, 1), 2.12−2.06 (m, 1), 1.92−1.82 (m, 2), 1.57−1.40 (m, 6), 1.25−1.10 (m, 2), 1.05 (s, 3), 0.94 (d, J = 6.5 Hz, 3), 0.86 (s, 3); ^{13}C NMR δ 187.4, 187.2, 159.6, 147.2, 137.2, 136.1, 136.0, 103.2, 49.3, 43.1, 40.3, 37.2, 36.8, 35.3, 32.9, 28.1, 27.5, 22.7, 20.6, 17.7, 16.8; EIMS m/z (rel intensity) 312 (M^+, 0.3), 192 (4), 191 (23), 175 (4), 135 (10), 121 (16), 109 (23), 95 (100), 79 (18), 67 (12), 55 (13); HRMS calcd for $C_{21}H_{28}O_2$ 312.2089, found 312.2095.

(4*S*)-(+)-4-Methyl-4-(2-methyl-1,3-dioxolan-2-yl)-2-methylenecyclohexanone (21). A mixture of β-keto phosphonate **19** (0.79 g, 2.3 mmol), K_2CO_3 (0.32 g, 2.3 mmol), and paraformaldehyde (0.21 g, 7.0 mmol) in 1,4-dioxane (10 mL)

and water (3 drops) was stirred at rt for 12 h. After the reaction mixture was filtered through Celite, the filtrate was concentrated in *vacuo* and the residue was purified by flash column chromatography (80% hexanes, 20% ethyl acetate) to give compound **21** as an oil (0.42 g, 87%): $[\alpha]_D = +7.3°$ ($CHCl_3$, c = 2.4); ^{1}H NMR δ 5.90 (s, 1), 5.15 (s, 1), 4.02−3.86 (m, 4), 2.73 (d, J = 15.0 Hz, 1), 2.62−2.52 (m, 1), 2.49−2.33 (m, 2), 2.12−2.04 (m, 1), 1.75−1.65 (m, 1), 1.30 (s, 3), 1.08 (s, 3). ^{13}C NMR δ 201.6, 143.3, 121.3, 113.5, 65.0, 64.8, 41.5, 38.5, 36.2, 29.5, 20.5, 19.0; EIMS m/z (rel intensity) 210 (M^+, 0.1), 195 (4), 88 (6), 87 (100), 79 (3), 67 (4), 55 (5); HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1233.

(2*R*,4*S*)-(+)-2-[(2,5-Dimethoxyphenyl)methyl]-2,4-dimethyl-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexanone (22). To lithium (0.05 g, 6.9 mmol) in liquid ammonia (40 mL) at −78 °C in a flask fitted with Dewar condenser was added dropwise a solution of compound **21** (0.416 g, 1.98 mmol) in 5 mL of THF. The dry ice bath was withdrawn, and the reaction was allowed to warm to reflux and maintained at that temperature for 1 h. 2,5-Dimethoxybenzyl bromide (3.22 g, 14.0 mmol in 10 mL of THF) was then added as rapidly as possible, and 10 mL of THF was also added. After refluxing for 2 h, the Dewar condenser was replaced by a water condenser, and the NH_3 was allowed to evaporate. The reaction was quenched by addition of saturated NH_4Cl, and the aqueous layer was extracted three times with ether (20 mL each). The combined organic layer was dried over Na_2SO_4, and concentrated in *vacuo*. Flash column chromatography (80% hexanes, 20% ethyl acetate) gave compound **22** (0.28 g, 39%) as a colorless oil: $[\alpha]_D = +39.4°$ ($CHCl_3$, c = 1.0); ^{1}H NMR δ 6.76−6.68 (m, 3), 3.98−3.85 (m, 4), 3.73 (s, 3), 3.71 (s, 3), 3.00 (d, J = 13.3 Hz, 1), 2.76 (d, J = 13.3 Hz, 1), 2.48−2.42 (m, 2), 2.24 (d, J = 14.3 Hz, 1), 2.12−2.02 (m, 1), 1.64−1.55 (m, 1), 1.38 (dd, J = 14.3, 1.9 Hz, 1), 1.21 (s, 3), 1.18 (s, 3), 1.11 (s, 3); ^{13}C NMR δ 217.0, 152.9, 152.3, 127.7, 118.3, 114.3, 111.9, 111.0, 64.9, 64.8, 55.6, 55.5, 47.8, 41.5, 40.9, 39.7, 35.8, 29.2, 26.3, 22.6, 18.8; EIMS m/z (rel intensity) 362 (M^+, 5), 151 (61), 121 (14), 91 (6), 87 (100), 77 (4), 55 (5); HRMS calcd for $C_{21}H_{30}O_5$ 362.2093, found 362.2094.

(2*R*,4*S*)-(+)-2-[(2,5-Dimethoxyphenyl)methyl]-2,4-dimethyl-4-[2-methyl-1,3-dioxolan-2-yl]-1-methylenecyclohexane (23). To a suspension of methyltriphenylphosphonium bromide (0.73 g, 0.48 mmol in 5 mL of THF) was added n-BuLi (0.28 mL, 0.45 mmol, 1.6 M in hexane) over 5 min. The resulting orange suspension was stirred at rt for 60 min. Ketone **22** (30 mg, 0.08 mmol) in 1 mL of THF was added to the phosphorane solution, and the reaction was heated at reflux for 18 h. After the reaction was quenched by addition of water (5 mL), the THF was removed in *vacuo*, the aqueous layer was extracted with ether (3 × 5 mL), and the organic layer was concentrated in *vacuo*. The residue was purified by flash column chromatography (90% hexanes, 10% ethyl acetate) to give compound **23** (25 mg, 87%) as an oil: $[\alpha]_D = +41.2°$ ($CHCl_3$, c = 2.0); ^{1}H NMR δ 6.78−6.59 (m, 3), 4.79 (s, 1), 4.72 (s, 1), 3.96−3.83 (m, 4), 3.75 (s, 3), 3.73 (s, 3), 2.89 (d, J = 12.7 Hz, 1), 2.73 (d, J = 12.7 Hz, 1), 2.48−2.38 (m, 1), 2.28−2.20 (m, 1), 1.90 (d, J = 13.6 Hz, 1), 1.74−1.64 (m, 1), 1.47−1.42 (m, 1), 1.19 (br, 1), 1.17 (s, 3), 1.14 (s, 3), 1.07 (s, 3); ^{13}C NMR δ 156.0, 152.8, 152.8, 129.0, 119.0, 114.6, 111.5, 111.2, 106.2, 65.1, 64.9, 55.7, 55.7, 42.7, 42.3, 42.2, 40.1, 32.2, 30.0, 27.3, 22.0, 19.1; EIMS m/z (rel intensity) 360 (M^+, 2), 345 (1), 298 (2), 209 (3), 195 (2), 151 (17), 121 (20), 87 (100), 43 (20); HRMS calcd for $C_{22}H_{32}O_4$ 360.2301, found 360.2306. Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.16; H, 8.97.

(1*S*,2*R*,4*S*)-(+)-2-[(2,5-Dimethoxyphenyl)methyl]-4-(1-ketoethyl)-1,2,4-trimethylcyclohexane (26) and Its (1*R*) Isomer (27). A mixture of compound **23** (0.14 g, 0.39 mmol), 10% Pd−C (0.25 g), triethylamine (5 mL), and methanol (1 drop) was stirred at rt under 1 atm hydrogen for 12 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated in *vacuo*. The residue was dissolved in a solution of THF/5% HCl (4 mL/1 mL) and stirred at rt for 2 h, and the reaction solution was neutralized by addition of solid Na_2CO_3. After concentration of the filtrate in *vacuo*, the residue was purified by flash column chromatography (80% hexanes, 20% ethyl acetate) to give compound **26** (55 mg, 45%) and compound **27** (40 mg, 32%), both as oils. For compound **26**: $[\alpha]_D = +26.3°$ ($CHCl_3$, c = 2.1); ^{1}H NMR δ 6.77−6.65 (m, 3), 3.75 (s, 3), 3.73 (s, 3), 2.72 (d, J = 12.9 Hz, 1), 2.40 (d, J = 12.9 Hz, 1), 2.06 (s, 3), 1.58−1.38 (br, m, 7), 1.10 (s, 3), 0.94 (d, J = 6.8 Hz, 3), 0.93 (s, 3); ^{13}C NMR δ 214.2, 152.7, 152.6, 128.5, 118.7, 111.2, 111.1, 55.6, 55.5, 47.7, 43.7, 41.8, 38.4, 37.2, 31.8, 27.1, 24.4, 22.9, 21.8, 15.9; EIMS m/z (rel intensity) 318 (M^+, 28), 167 (37), 152 (100), 151 (38), 123 (32), 109 (44), 91 (17), 85 (16), 59 (14); HRMS calcd for $C_{20}H_{30}O_3$ 318.2195, found 318.2181.

For the minor isomer **27**: $[\alpha]_D = +48.5°$ ($CHCl_3$, c = 1.6); ^{1}H NMR δ 6.89 (d, J = 2.8 Hz, 1), 6.74−6.66 (m, 2), 3.78 (s, 3), 3.74 (s, 3), 2.62 (d, J = 13.4 Hz, 1), 2.30 (dd, J = 14.3, 1.7 Hz, 1), 2.22 (s, 3), 2.20 (d, J = 13.8 Hz, 1), 1.63−1.50 (m, 2), 1.38−1.32 (m, 1), 1.22−1.10 (m, 3), 1.08 (s, 3), 0.92 (d, J = 6.9 Hz, 3), 0.79 (s, 3); ^{13}C NMR δ 214.5, 153.0, 152.4, 130.1, 118.1, 111.0, 110.9, 55.6, 55.6, 48.0, 46.6, 41.9, 37.7, 33.0, 33.0, 28.1, 27.8, 26.8, 25.3, 15.7; EIMS m/z (rel intensity) 318 (M^+, 28), 167 (74), 152 (100), 123 (52), 121 (42), 109 (59), 91 (25), 85 (20), 77 (17), 59 (21); HRMS calcd for $C_{20}H_{30}O_3$ 318.2195, found 318.2193.

(1*S*,2*R*,4*S*)-(+)-2-[(2,5-Dimethoxyphenyl)methyl]-4-(propylen-2-yl)-1,2,4-trimethylcyclohexane (16). To a suspension of methyltriphenylphosphonium bromide (0.19 g, 0.55 mmol) in anhydrous 1,4-dioxane (5 mL) was added n-BuLi (0.31 mL, 0.5 mmol, 1.6 M in hexane) over 1 min. The resulting orange suspension was stirred at rt for 60 min. Ketone **26** (29 mg, 0.09 mmol) in 1 mL of 1,4-dioxane was added to the phosphorane solution, and the reaction was heated at reflux for 48 h. The reaction was quenched by addition of water (5 mL), and THF was removed in *vacuo*. After the aqueous layer was extracted with ether (3 × 5 mL), the combined organic layer was concentrated in *vacuo*, and the residue was purified by flash column chromatography (90% hexanes, 10% ethyl acetate) to give compound **16** (23 mg, 81%) as an oil: $[\alpha]_D = +18.4°$ ($CHCl_3$, c = 1.0); ^{1}H NMR δ 6.77−6.68 (m, 3), 4.62 (s, 1), 4.58 (s, 1), 3.75 (s, 3), 3.73 (s, 3), 2.78 (d, J = 12.8 Hz, 1), 2.37 (d, J = 12.8 Hz, 1), 1.68 (s, 3), 1.51−1.32 (br, m, 7), 0.99 (s, 3), 0.95 (d, J = 6.2 Hz, 3), 0.93 (s, 3); ^{13}C NMR δ 156.7, 152.7, 152.7, 129.0, 118.7, 111.1, 110.9, 106.5, 55.6, 55.5, 46.5, 42.5, 38.6, 38.5, 38.4, 35.4, 28.0, 24.8, 21.4, 19.3, 16.2; EIMS m/z (rel intensity) 316 (M^+, 4), 152 (100), 151 (30), 121 (19), 109 (79), 95 (85), 91 (19), 81 (18), 69 (29), 55(37), 41 (27); HRMS calcd for $C_{21}H_{32}O_2$ 316.2402, found 316.2418.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **13**, **15**, **16**, **21**, **22**, **26**, and **27** (14 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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