Total Synthesis of Cacalol†

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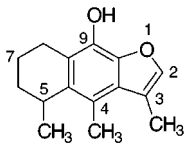
Psacalium decompositum[1] is a shrub native to northern Mexico, and decoctions of the plant have been used as a treatment for diabetes.[2] As part of an ongoing effort to develop novel antihyperglycemic agents for non-insulin-dependent diabetes,[3] the components of the root extracts of *P. decompositum* were recently isolated and evaluated for activity.[4] Among the isolated components was the sesquiterpene cacalol.[5] The furotetralin ring structure of cacalol seemed to afford reasonable opportunity for analogue development, and as part of a medicinal chemistry effort, a total synthesis of cacalol was undertaken.



1: Cacalol

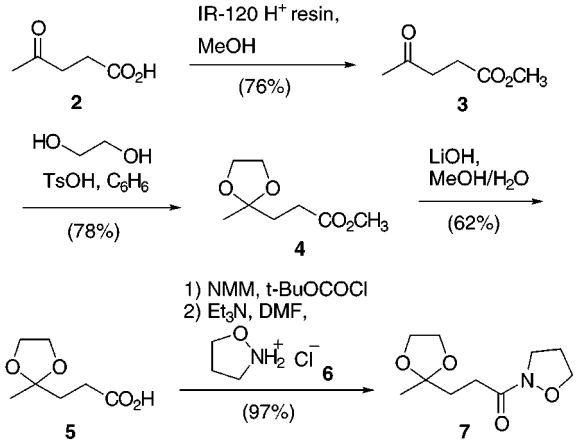
Results and Discussion

Several previous syntheses of cacalol have been reported;[6] however, these syntheses suffered from low-yielding steps or procedures which were not reproducible in our lab. These approaches to the tetralin ring system used a Friedel−Crafts alkylation strategy. In attempting to reproduce these published procedures, the reactions were extremely exothermic and gave intractable mixtures or mixtures of isomeric products. Furthermore, it became clear that larger scale reactions required to produce the amount of material needed would constitute a hazard, and consequently we abandoned this approach.

Our straightforward approach constructs the 15-carbon furotetralin ring system in 11 steps starting with 2-bromo-4-methylphenol (**8**). An alkylation/cyclization strategy is employed to install both the furyl and cyclohexyl rings. We envisioned using radical or palladium-catalyzed methodology to construct the benzofuran ring system of cacalol. Although both methods have been used extensively to synthesize benzofurans originating from simple phenols and 1,3-dihydroxybenzenes, both methods have shown limited use in constructing benzofurans from catechol building blocks.[7]

First, the synthesis of tetralin intermediate **13** required isoxazolidide **7**. Esterification of levulinic acid (**2**) afforded methyl levulinate (**3**), which was then treated with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene to give the ketal **4** (Scheme 1).[8] Careful hydrolysis of the

Scheme 1



ester followed by mixed anhydride formation and exposure to isoxazolidine hydrochloride (**6**) gave isoxazolidide **7**.[9]

Next, dimethyl sulfate etherification of 2-bromo-4-methyl phenol (**8**) followed by lithium−halogen exchange using *tert*-butyllithium and condensation with isoxazolidide **7** afforded the methylanisole **10** (Scheme 2).[10] It is noteworthy that attempted lithiation with *n*-butyl- or *sec*-butyllithium resulted only in the recovery of unreacted **9** and **7**. Benzylic decarbonylation of **10** catalyzed with 10% Pd−C in EtOH and *p*-toluenesulfonic acid was accompanied by deprotection to afford pentanone **11** in 77% yield. Reduction to the pentanol and cyclization in P_2O_5−$MeSO_3H$[11] completed the tetralin ring system, **13**, in high yield.

† Dedicated to Professor Henry Rapoport on the occasion of his 80th birthday.

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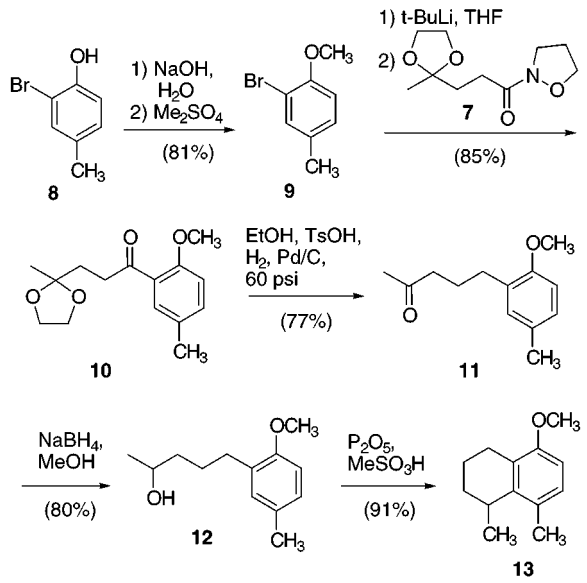
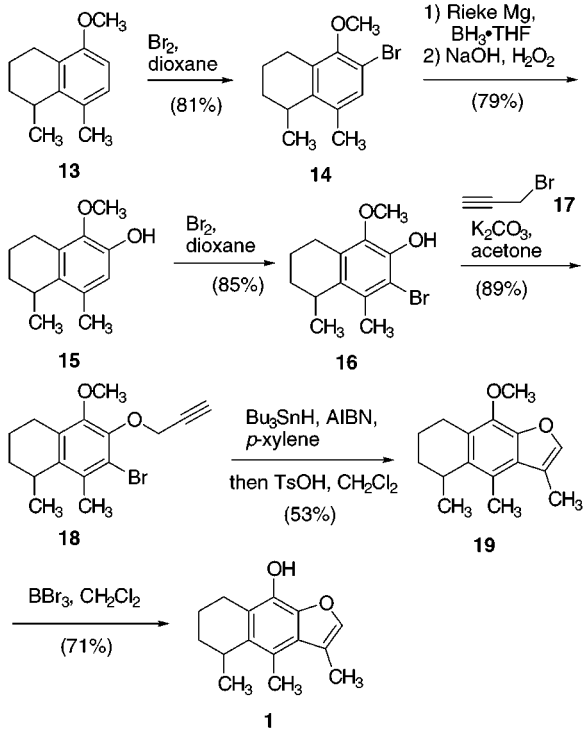
Scheme 2



The furyl ring was fused to tetralin **13** as shown in Scheme 3. Regioselective bromination of tetralin **13** using

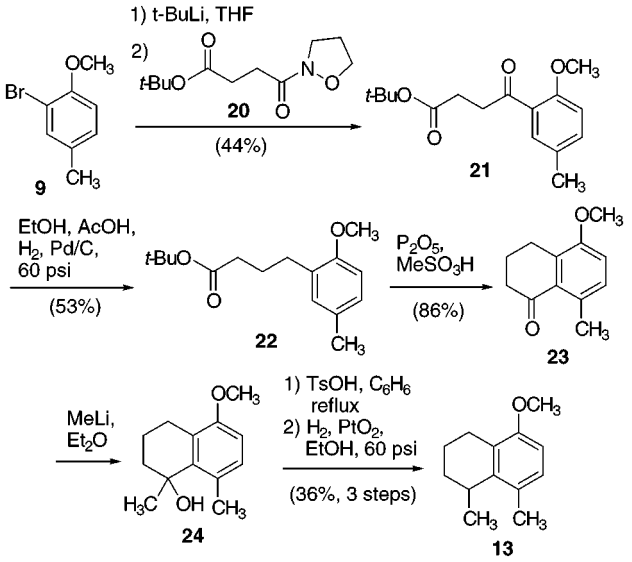
Scheme 3



bromine in dioxane afforded bromotetralin **14**.[12] Attempts to form the aryl Grignard using magnesium shavings were unsuccessful; however, the use of Rieke magnesium ameliorated the problem. Transmetalation with BH_3·THF and oxidation with alkaline hydrogen peroxide then afforded tetralol **15**.[13] Bromination as before followed by alkylation with propargyl bromide afforded the cyclization precursor **18**. Radical cyclization using Bu_3SnH and AIBN in *p*-xylene completed the furotetralin ring system but gave a mixture of exo- and endocyclic double-bond isomers.[14] The exo isomer could be isomerized to the desired endo by exposure to *p*-toluenesulfonic acid in CH_2Cl_2. Demethylation with BBr_3 in CH_2Cl_2 afforded cacalol (**1**) in 7% overall yield from phenol **8**.

Several alternative strategies were simultaneously studied during the course of our synthesis. Acylation of bromoaniline **9** with isoxazolidide **20**[15] followed by benzylic decarbonylation[16] gave butyrate **22** (Scheme 4).

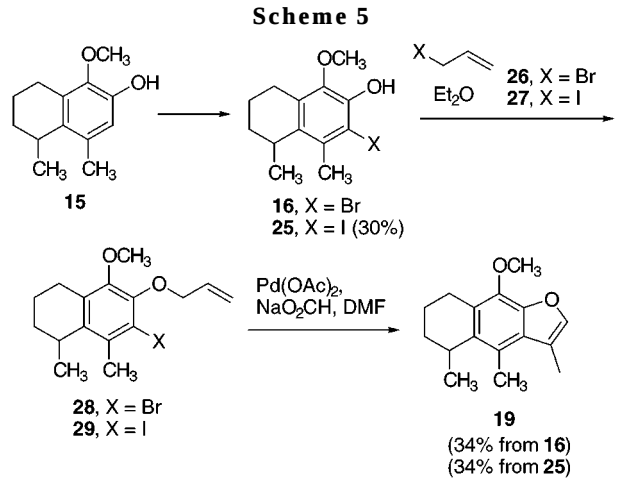
Scheme 4



Cyclization as before produced the α-tetralone **23** in 86% yield. Addition of methyllithium followed by dehydration to the intermediate alkene and hydrogenation with PtO_2 in ethanol afforded tetralin **13**.[6a]

A second successful approach to the formation of the furan was also examined (Scheme 5). Hydroxytetralin **15**

Scheme 5



could be halogenated, either brominated (**16**) or iodinated (**25**), and alkylated with either allylbromide (**26**) or

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allyliodide (**27**). $Pd(OAc)_2$-catalyzed cyclization[17] afforded the furotetralin **19**. In this case, only the endo double-bond isomer was isolated.

As shown above, we have presented the total synthesis of cacalol along with tangent approaches to the tetralin ring system and two methods for the incorporation of the furan moiety. Both approaches to the tetralin ring system provide regiochemically pure product free of isolation difficulty. Although the approach shown in Scheme 2 offers the best overall yield of tetralin **13**, the approach shown in Scheme 4 offers the possibility for an asymmetric synthesis of cacalol via intermediate **23**. Incorporation of the furan onto tetralin **15** was achieved using two well-known approaches that have not been widely reported for the construction of benzofurans from catechol building blocks.

Experimental Section

General Methods. THF was distilled from sodium/benzophenone. Moisture- and air-sensitive reactions were performed under a nitrogen atmosphere. Analytical TLC was performed on E. Merck silica gel 60 F254 precoated plates (250 μm thickness). Plates were analyzed by either UV light or by staining with a solution of phosphomolybdic acid (PMA) in EtOH. Flash chromatography was performed on E. Merck silica gel 60 (230−400 mesh) using nitrogen pressure. Combustion microanalysis was performed at the University of California, Berkeley. ^{1}H and ^{13}C NMR were recorded at 400 and 100 MHz respectively, with NMR shifts being expressed in ppm downfield from TMS. NMR coupling constants (J) are reported in hertz. Mass spectrometry was performed on a Kratos MS 50 spectrometer. Melting points are uncorrected.

1-[4-(Ethylenedioxy)pentanoyl]isoxazolidine (7). A solution of pentanoic acid **5** (18.98 g, 0.12 mol) in dry THF (250 mL) was stirred at −20 °C as *N*-methylmorpholine (13.0 mL, 0.12 mol) was added, followed by isobutyl chloroformate (15.5 mL, 0.12 mol). After 5 min, a slurry of isoxazolidine hydrochloride[9] (14.3 g, 0.13 mol) and Et_3N (18.5 mL, 0.13 mol) in dry DMF (190 mL) was added. The reaction mixture was stirred for 30 min, warmed to room temperature, and stirred for an additional 2 h. The reaction mixture was quenched with 1 M NaH_2PO_4 and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. Purification of the material on a silica gel column using EtOAc as eluant afforded 24.72 g (97%) of **7** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.94 (m, 6H), 3.70 (dd, J = 7.4, 7.4, 2H), 2.53 (dd, J = 8.0, 8.0, 2H), 2.30 (m, 2H), 2.01 (dd, J = 8.0, 8.0, 2H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.52, 109.36, 69.08, 64.62, 43.12, 33.23, 27.51, 27.44, 23.82. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.57; H, 7.99; N, 6.65.

2-[(4-Ethylenedioxy)pentanoyl]-4-methylanisole (10). A solution of anisole **9** (20.26 g, 0.10 mol) in dry THF (400 mL) was stirred at −78 °C as a 1.2 M solution of *tert*-butyllithium (140 mL, 0.17 mol) was added dropwise. After 1 h, a solution of isoxazolidide **7** (14.59 g, 0.07 mol) in THF (100 mL) was added using a cannula. The reaction mixture was allowed to warm to room temperature. After 20 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. Purification of the material on a silica gel column using EtOAc−hexanes (3:7) as eluant afforded 12.14 g (68%) of methylanisole **10** as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.46 (d, J = 2.4, 1H), 7.25 (dd, J = 8.5, 2.4, 1H), 6.85 (d, J = 8.5, 1H), 3.93 (m, 4H), 3.87 (s, 3H), 3.06 (dd, J = 7.7, 7.7, 2H), 2.30 (s, 3H), 2.08 (dd, J = 7.7, 7.7, 2H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.42, 156.36, 133.49, 130.47, 129.94, 111.59, 109.71, 64.67, 55.61, 38.55, 33.45, 24.00, 20.19. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.36; H, 7.65.

5-(2-Methoxy-5-methyl)phenyl-2-pentanone (11). A solution of methylanisole **10** (0.97 g, 3.7 mmol) and *p*-toluenesulfonic acid (0.16 g, 0.84 mmol) with 10% Pd−C (0.91 g) in ethanol (45 mL) was agitated for 3 h under 50−60 psi of hydrogen. The reaction mixture was filtered through Celite, and the solvent was removed by rotary evaporation. Purification of the material on a silica gel column using EtOAc−hexanes (3:7) as eluant afforded 0.58 g (77%) of pentanone **11** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.97 (d, J = 8.1, 1H), 6.94 (s, 1H), 6.74 (d, J = 8.3, 1H), 3.79 (s, 3H), 2.45 (dd, J = 7.5, 7.5, 2H), 2.45 (dd, J = 7.4, 7.4, 2H), 2.28 (s, 3H), 2.13 (s, 3H), 1.87 (dddd, J = 7.5, 7.5, 7.5, 7.5, 2H); ^{13}C NMR ($CDCl_3$) δ 209.23, 155.34, 130.73, 129.66, 129.47, 127.32, 110.18, 55.33, 43.24, 29.79, 29.34, 24.00, 20.43. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.59; H, 8.87.

5-(2-Methoxy-5-methyl)phenyl-2-pentanol (12). A solution of pentanone **11** (8.25 g, 0.04 mol) in absolute MeOH (450 mL) was stirred at room temperature as powdered $NaBH_4$ (2.29 g, 0.06 mol) was added. After 1 h, the reaction mixture was poured into brine, and the pH was lowered to 5 with 1 M HCl. The solution was then extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. Purification of the material on a silica gel column using EtOAc−hexanes (3:7) as eluant afforded 6.64 g (80%) of pentanol **12** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.96 (m, 2H), 6.75 (d, J = 8.1, 1H), 3.85 (tq, J = 6.1, 6.1, 1H), 3.80 (s, 3H), 2.61 (m, 2H), 2.28 (s, 3H), 1.75−1.45 (m, 4H), 1.20 (d, J = 6.1, 3H); ^{13}C NMR ($CDCl_3$) δ 155.25, 130.59, 130.49, 129.45, 127.10, 110.20, 67.98, 55.39, 39.00, 29.94, 26.14, 23.36, 20.45. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.66; H, 9.84.

5-Methoxy-1,8-dimethyltetralin (13). A solution of P_2O_5 (17.18 g, 60.5 mmol) in methanesulfonic acid (110 mL) was stirred at room temperature as pentanol **12** (6.30 g, 30.2 mmol) was added. The reaction mixture was stirred for 2 h, poured into water, and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and filtered, and the solvent was removed by rotary evaporation. Purification of the material on a silica gel column using hexanes as eluant afforded 5.25 g (91%) of tetralin **13** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.98 (d, J = 8.3, 1H), 6.62 (d, J = 8.3, 1H), 3.81 (s, 3H), 3.07 (m, 1H), 2.88 (dd, J = 18.1, 5.3, 1H), 2.48 (ddd, J = 18.1, 10.6, 7.5, 1H), 2.29 (s, 3H), 1.92−1.74 (m, 4H), 1.21 (d, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$) δ 155.59, 141.76, 127.64, 127.54, 124.99, 106.66, 55.19, 29.59, 29.33, 23.14, 20.58, 18.30, 16.65. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.00; H, 9.76.

6-Bromo-5-methoxy-1,8-dimethyltetralin (14). A solution of tetralin **13** (2.3 g, 12.1 mmol) in dry ether (50 mL) was added to a solution of dioxane dibromide (3.2 g, 12.9 mmol) in ether (40 mL) at −15 °C. The reaction mixture was stirred for 20 min and then allowed to warm to room temperature overnight. The reaction mixture was poured into brine and extracted with ether. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. Purification of the material on a silica gel column using hexanes as eluant afforded 2.62 g (81%) of bromotetralin **14** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.19 (s, 1H), 3.79 (s, 3H), 3.03−2.95 (m, 2H), 2.61 (ddd, J = 18.0, 10.4, 7.2, 1H), 2.26 (s, 3H), 1.85−1.73 (m, 4H), 1.16 (d, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$) δ 152.87, 141.66, 133.31, 131.77, 131.61, 113.25, 59.77, 29.48, 29.28, 24.07, 20.63, 18.31, 16.80. Anal. Calcd for $C_{13}H_{17}BrO$: C, 58.01; H, 6.37. Found: C, 58.25; H, 6.43.

6-Hydroxy-5-methoxy-1,8-dimethyltetralin (15). A solution of tetralin **14** (0.48 g, 1.8 mmol) in dry THF (5.0 mL) was stirred at room temperature as a 5% w/v suspension of Rieke Mg in THF (2.10 mL, 4.3 mmol) was added, followed by a 1 M solution of BH_3·THF (2.30 mL, 2.3 mmol). The mixture was refluxed for 1 h and cooled to room temperature, and water was then carefully added dropwise until H_2 gas evolution ceased. Next, a 1 M aqueous solution of NaOH was added (10 mL, 10.0 mmol), followed by 30% H_2O_2 (1.0 mL, 8.8 mmol). After 62 h, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. Purification of the material on a silica gel column using EtOAc−hexanes (2:8) as eluant afforded 0.29 g (79%) of tetralol **15** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.66 (s, 1H), 5.35 (s, 1H), 3.76 (s, 3H), 3.02 (m, 1H), 2.93 (m, 1H), 2.59 (ddd, J = 17.6, 10.4,

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6.4, 1H), 2.26 (s, 3H), 1.90−1.74 (m, 4H), 1.16 (d, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$) δ 145.77, 142.64, 133.17, 132.56, 129.63, 115.00, 60.17, 30.03, 28.87, 23.61, 21.09, 18.69, 16.93. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.46; H, 8.96.

7-Bromo-6-hydroxy-5-methoxy-1,8-dimethyltetralin (16). A solution of bromine (0.03 mL, 0.58 mmol) in dioxane (4.0 mL) was stirred at 0 °C for 15 min after which a solution of tetralol **15** (0.10 g, 0.48 mmol) in dioxane (1.0 mL) was added. After 5 h, the solvent was removed by rotary evaporation. Purification of the material on a silica gel column using EtOAc−hexanes (2:8) as eluant afforded 0.12 g (85%) of tetralol **16** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.65 (s, 1H), 3.80 (s, 3H), 3.11 (m, 1H), 2.92 (m, 1H), 2.54 (ddd, J = 18.0, 10.4, 7.6, 1H), 2.37 (s, 3H), 1.79 (m, 4H), 1.15 (d, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$) δ 143.45, 142.98, 133.92, 131.27, 129.32, 111.25, 60.05, 30.11, 29.96, 23.52, 21.32, 18.68, 16.77. Anal. Calcd for $C_{13}H_{17}BrO_2$: C, 54.75; H, 6.01. Found: C, 54.76; H, 6.08.

7-Bromo-5-methoxy-6-propargyloxy-1,8-dimethyltetralin (18). A solution of tetralol **16** (0.85 g, 3.0 mmol) in dry acetone (30 mL) was stirred at room temperature as K_2CO_3 (2.10 g, 15.2 mmol) was added, followed by an 80% w/w solution of propargyl bromide in toluene (0.67 g, 4.5 mmol). The reaction mixture was refluxed for 2 h, cooled to room temperature, and filtered through Celite. The filtrate was concentrated, and the residue was dissolved in CH_2Cl_2. The solution was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. Purification of the material on a silica gel column using EtOAc−hexanes (1:9) as eluant afforded 0.86 g (89%) of tetralin **18** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.68 (dd, J = 2.4, 0.8, 2H), 3.85 (s, 3H), 3.11 (m, 1H), 2.89 (m, 1H), 2.55 (dd, J = 2.4, 2.4, 1H), 2.49 (ddd, J = 18.0, 9.0, 9.0, 1H), 2.38 (s, 3H), 1.80 (m, 4H), 1.16 (d, J = 6.9, 3H); ^{13}C NMR ($CDCl_3$) δ 149.46, 145.66, 138.82, 131.67, 130.05, 118.79, 79.10, 75.13, 60.13, 30.27, 29.89, 29.68, 23.49, 21.03, 18.80, 16.66. Anal. Calcd for $C_{16}H_{19}BrO_2$: C, 59.45, H; 5.93. Found: C, 59.44; H, 5.95.

9-Methoxycacalol (19). A solution of tetralin **18** (0.51 g, 1.6 mmol) in dry *p*-xylene (16 mL) was stirred at room temperature as tributyltin hydride (0.50 mL, 1.9 mmol) was added, followed by 2,2′-azobisisobutyronitrile (0.51 g, 0.03 mmol). The reaction mixture was then heated to reflux for 2 h. Solvent was then removed from the reaction mixture by rotary evaporation. The residual oil was then chromatographed on a silica gel column using EtOAc−hexanes (1:19) as eluant to give a coeluting mixture of exo and endo double-bond isomers.

The mixture of double-bond isomers was then dissolved in CH_2Cl_2 (25 mL) and stirred at room temperature as *p*-toluenesulfonic acid (0.15 g, 0.8 mmol) was added. After 1 h, the solvent was removed from the mixture by rotary evaporation. Purification of the material on a silica gel column using EtOAc−hexanes (1:19) as eluant afforded 0.20 g (53%) of methoxycacalol **19** as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 1H), 4.06 (s, 3H), 3.25 (m, 1H), 3.05 (m, 1H), 2.64 (ddd, J = 18.0, 10.8, 7.2, 1H), 2.56 (s, 3H), 2.40 (s, 3H), 1.83 (m, 4H), 1.20 (d, J = 7.1, 3H); ^{13}C NMR ($CDCl_3$) δ 145.31, 140.91, 140.41, 135.52, 127.25, 124.29, 123.05, 116.48, 60.05, 30.18, 28.99, 23.53, 21.51, 16.97, 14.03, 11.41. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.30; H, 8.36.

Cacalol (1). A solution of methoxycacalol **19** (0.090 g, 0.4 mmol) in dry CH_2Cl_2 (4.0 mL) was stirred at −78 °C as a 1.0 M solution of BBr_3 in CH_2Cl_2 (0.41 mL, 0.4 mmol) was added dropwise. The reaction mixture was allowed to slowly warm to room temperature. After 4 h, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. Purification of the material on a silica gel column using EtOAc−hexanes (1:9) as eluant afforded 0.060 g (71%) of cacalol (**1**) as a clear, colorless oil, which could be recrystallized from hexanes to give white crystals, mp 87 °C (lit.[18] 89−91 °C): ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 1H), 4.98 (s, 1H), 3.25 (m, 1H), 3.00 (m, 1H), 2.63 (ddd, J = 17.6, 11.2, 7.3, 1H), 2.53 (s, 3H), 2.39 (s, 3H), 1.95−1.75 (m, 4H), 1.20 (d, J = 6.9, 3H); ^{13}C NMR ($CDCl_3$) δ 142.12, 140.85, 136.29, 135.57, 126.13, 120.21, 118.65, 117.12, 30.08, 28.93, 22.90, 21.35, 16.63, 13.80, 11.30. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.18; H, 7.90.

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Supporting Information Available: Experimental procedures for compounds **3**−**5** and **9**, and ^{1}H NMR spectra of compounds **3**−**5**, **9**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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