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A Concise Synthesis of (±)-Cacalol

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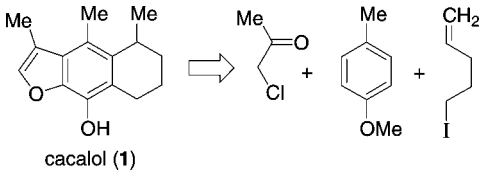


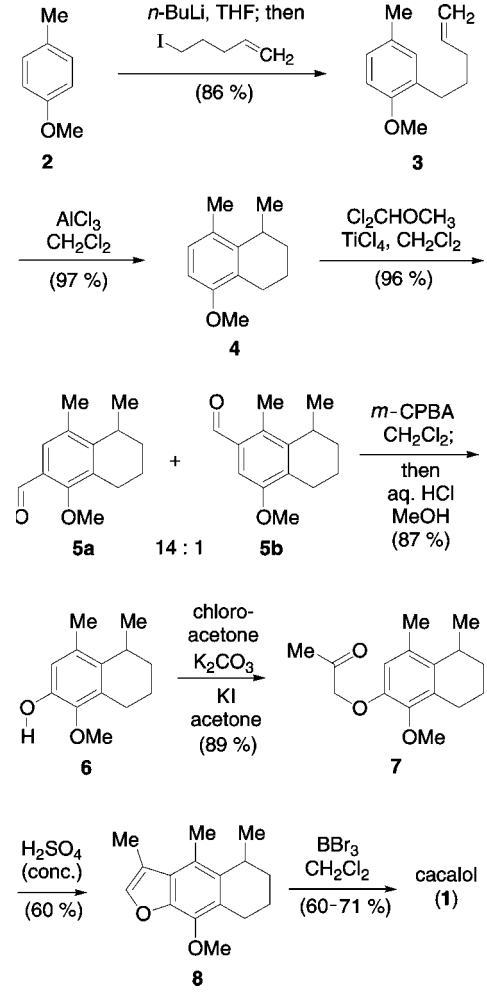
cacalol (**1**)

A simple synthesis of the natural product cacalol has been developed that proceeds in seven steps and 21−25% overall yield. *Ortho*-lithiation of 4-methylanisole and alkylation with 5-iodo-1-pentene, followed by intramolecular Friedel−Crafts alkylation, gave 5-methoxy-1,8-dimethyltetralin. This compound was then formylated in the 6-position. Baeyer−Villiger oxidation and hydrolysis of the resulting formate gave 6-hydroxy-5-methoxy-1,8-dimethyltetralin. Alkylation of the phenolic hydroxyl group with chloroacetone followed by cyclodehydration gave cacalol methyl ether. Deprotection of this aryl methyl ether yielded cacalol.

Cacalol (**1**) is a sesquiterpene natural product isolated from the roots of the shrub *Psacalium decompositum* in northern Mexico.[1] It has antihyperglycemic,[2a] anti-inflammatory,[2b] antimicrobial,[2b] and antioxidant[2c] activities, which have made it an attractive target for synthesis. A number of syntheses of this molecule have been reported.[3a–f] The method described herein offers a number of improvements in synthetic efficiency, providing a shorter, higher yielding route to **1**.

The synthesis of **1** is described in Scheme 1. It began with *ortho*-lithiation[4a,b] of 4-methylanisole (**2**) by *n*-butyllithium in THF. This anion was alkylated with 5-iodo-1-pentene[5] to give the alkene **3**. This molecule was then cyclized in an intramolecular Friedel−Crafts alkylation by treatment with aluminum chloride in methylene chloride to give the tetralin **4**. Compound **4** has been a key intermediate in several previous syntheses of cacalol. These routes have required four or more steps from commercially available starting materials and proceeded in overall yields of between 39% and 80%.[3a,c,d] The annulation of **2** described here provides a new route to **4** that proceeds in two steps and 83% overall yield.

SCHEME 1. Synthesis of Cacalol



A two-step procedure next installed a hydroxyl group in the 6-position of tetralin **4**. Formylation of **4** with α,α-dichloromethyl methyl ether and titanium tetrachloride[6] at 0 °C gave a 96% combined yield of the regioisomeric aldehydes **5a** and **5b** in a 14:1 mixture as determined by ^{1}H NMR and GCMS analyses. Aldehydes **5a** and **5b** had the same mobility on silica gel and were inseparable by flash chromatography at this point.

The mixture of aldehydes **5a** and **5b** was subjected to Baeyer−Villiger oxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA) in methylene chloride. Workup with aqueous HCl and methanol hydrolyzed the resulting mixture of aryl formates to

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give a mixture of regioisomeric phenols, which were easily separated by flash chromatography on silica gel. Thus, the hydroxytetralin **6** was produced. In previous syntheses that proceeded through intermediate **4**, oxygenation to **6** was accomplished by first brominating **4** selectively *ortho* to the methoxy group.[3a,c,d] The resulting aryl bromide was then converted to an aryl anion that was quenched with a variety of electrophiles including nitrobenzene,[3d] borane·THF,[3c] or dimethylformamide[3a] to either install the oxygen directly or generate it in one additional step.

The phenol **6** was alkylated on oxygen with chloroacetone using anhydrous potassium carbonate and potassium iodide in acetone, which gave the ketone **7**. Cyclodehydration of **7** in concentrated sulfuric acid then gave cacalol methyl ether (**8**). A similar alkylation/cyclodehydration strategy has been used previously to construct the furan ring of two cacalol analogs.[7] The approach was also attempted in a previous synthesis of **1**. However, the cyclodehydration step was reported to be unsuccessful in that study.[3e]

Finally, cleavage of the methyl aryl ether of **8** using boron tribromide in methylene chloride according to a literature method gave cacalol.[3b,c] In one literature preparation, (±)-cacalol is reported to be a crystalline solid.[3c] However, others report that the product does not crystallize even after chromatographic purification,[3d–f] which was also true in this study. Derivatization of cacalol as its acetate is commonly used to generate a crystalline product.[3b,d–f]

In summary, a new synthesis of **1** has been developed which proceeded from **2** in seven steps and 21−25% overall yield. Key features include a two-step annulation of **2** to give **4**, a two-step oxygenation of **4** to give **6**, and a two-step annulation of **6** to give **8**.

Experimental Section

2-(4-Pentenyl)-4-methylanisole (3). A round-bottom flask was charged with 4-methylanisole (3.414 g, 27.95 mmol) and THF (37 mL) and cooled to 0 °C under an argon atmosphere. A freshly titrated 1.6 M solution of *n*-butyllithium in hexane (23.3 mL, 37.2 mmol, 1.3 equiv) was added dropwise, with stirring. After 15 min, the yellow solution was warmed to rt and was stirred for an additional 3 h. The solution was cooled to 0 °C, and a solution of 5-iodo-1-pentene (7.122 g, 36.34 mmol, 1.3 equiv) in THF (24 mL) was added dropwise, with stirring. After 1 h at 0 °C, the reaction was warmed to rt and stirred 48 h. It was quenched with water (30 mL) and the resulting mixture extracted twice with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and filtered, and volatile components were evaporated under reduced pressure. The crude product was purified by flash chromatography (silica gel, pentane) giving the product as a clear colorless liquid (4.57 g, 86%): TLC R_f 0.17 (hexane); IR (thin film, cm^{-1}) 3075, 2998, 2926, 2859, 2833, 1640, 1612, 1504, 1464, 1441, 1251, 1229, 1038, 910, 804; ^{1}H NMR ($CDCl_3$, δ ppm) 6.98−6.92 (m, 2 H), 6.73 (d, J = 7.7 Hz, 1 H), 5.85 (ddt, J = 16.8, 10.1, 6.7 Hz, 1 H), 5.07−4.92 (m, 2 H), 3.78 (s, 3 H), 2.57 (t, J = 7.6 Hz, 2 H), 2.26 (s, 3 H), 2.14−2.05 (m, 2 H), 1.71−1.60 (m, 2 H); ^{13}C NMR (CD_3OD, δ ppm) 155.5, 138.7, 130.4, 130.2, 129.0, 127.0, 113.7, 110.0, 54.5, 33.5, 29.6, 29.3, 19.6; EI MS m/z 190 (M^+, 39), 148 (58), 135 (100), 105 (85). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.00; H, 9.44.

5-Methoxy-1,8-dimethyltetralin (4).[3a,c,d] Alkene **3** (4.568 g, 24.00 mmol) was dissolved in dichloromethane (240 mL) and cooled to 0 °C under an argon atmosphere. Aluminum chloride (3.521 g, 26.41 mmol, 1.1 equiv) was added at once, with stirring. After 15 min, the cooling bath was removed and the mixture warmed to rt. A cherry red solution formed, and stirring was continued for 4 h. The solution was then cooled to 0 °C, and 1.6 N HCl was added with vigorous stirring, giving a pale yellow emulsion. The mixture was warmed to rt and extracted with ether (275 mL). The organic layer was washed with satd aq $NaHCO_3$, washed with brine, dried over $MgSO_4$, and filtered and solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane) giving the product as a clear colorless liquid (4.449 g, 97%): TLC Rf 0.25 (100:1 hexane/ether); IR (thin film, cm^{-1}) 2930, 2869, 2832, 1587, 1477, 1439, 1301, 1253, 1242, 1089, 1055, 796; ^{1}H NMR ($CDCl_3$, δ ppm) 6.96 (d, J = 8.2 Hz, 1 H), 6.60 (d, J = 8.2 Hz, 1 H), 3.79 (s, 3 H), 3.10−3.00 (m, 1 H), 2.91−2.81 (m, 1 H), 2.52−2.37 (m, 1 H), 2.27 (s, 3 H), 1.96−1.71 (m, 4 H), 1.19 (d, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 156.0, 142.0, 127.95, 127.85, 125.3, 106.9, 55.4, 30.0, 29.8, 23.6, 20.9, 18.7, 17.1; EI MS m/z 190 (M^+, 59), 175 (100). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.21; H, 9.57.

5-Methoxy-1,8-dimethyltetralin-6-carboxaldehyde (5a).[3a] Tetralin **4** (1.745 g, 9.172 mmol) was dissolved in dichloromethane (18.3 mL) and cooled to 0 °C under an argon atmosphere. A 1 M solution of titanium tetrachloride in CH_2Cl_2 (18.30 mL, 18.30 mmol, 2 equiv) was added dropwise, with stirring, followed by α,α-dichloromethyl methyl ether (1.65 mL, 18.30 mmol, 2 equiv) dropwise, with stirring.[6] After 30 min at 0 °C, the inky black solution was warmed to rt and stirred for 1 h. The dark solution was poured into a separatory funnel filled with 10 g of ice and shaken thoroughly. The layers were separated, and the aqueous phase was diluted with water (10 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with water and satd aq $NaHCO_3$, diluted with ether (75 mL), and washed with brine. The solution was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude product as a dark oil. Purification by flash chromatography (silica gel, 20:1 hexane/EtOAc) gave a clear colorless liquid, which was an inseparable mixture of product **5a** and regioisomeric aldehyde **5b** in a 14:1 ratio (1.929 g, 90% **5a**, 6% **5b**): TLC R_f 0.30 (8:1 hexane/EtOAc); IR (thin film, cm^{-1}) 2935, 2869, 1685, 1600, 1456, 1411, 1388, 1223, 1049, 998; ^{1}H NMR ($CDCl_3$, δ ppm) 10.37 (s, 1/14 × 1 H, **5b**), 10.28 (s, 1 H, **5a**), 7.45 (s, 1 H, **5a**), 7.15 (s, 1/14 × 1 H, **5b**), 3.83 (s, 3H), 3.14−2.88 (m, 2 H), 2.66−2.47 (m, 1 H), 2.30 (s, 3 H), 1.90−1.70 (m, 4 H), 1.17 (d, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 190.2, 160.0, 150.3, 132.4, 130.7, 127.2, 126.1, 63.2, 30.1, 29.5, 23.0, 20.6, 18.6, 16.8; EI MS m/z 218 (M^+, 81), 203 (100). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.18; H, 8.44.

5-Methoxy-1,8-dimethyltetralin-6-ol (6).[3a,c,d] A 14:1 mixture of aldehydes **5a** and **5b** (1.082 g, 4.956 mmol) was dissolved in CH_2Cl_2, and 100% *m*-chloroperoxybenzoic acid (1.026 g, 5.947 mmol, 1.2 equiv) was added, with stirring. The resulting solution was refluxed for 7 h and then cooled to rt. Methanol (10 mL) was added followed by concd aq HCl (10 mL), and the mixture was stirred rapidly for 16 h at rt as a red color developed. The CH_2Cl_2 layer was then separated and washed with aq $Na_2S_2O_3$ and satd aq $NaHCO_3$ twice and then dried over $MgSO_4$. Filtration and evaporation under reduced pressure gave a yellow oil. At this point, it was straightforward to separate the desired phenol **6** from the regioisomeric phenol produced from reaction of **5b**. Flash chromatography (silica gel, 10:1 hexane/EtOAc) gave pure phenol **6** as a clear colorless liquid, which slowly solidified to a white solid (0.832 g, 87%): TLC R_f 0.24 (hexane/EtOAc); mp 43−45 °C; IR (thin film, cm^{-1}) 3415 br, 2930, 2869, 1593, 1478, 1319, 1248, 1180, 1120, 995, 909, 734; ^{1}H NMR ($CDCl_3$, δ ppm) 6.66 (s, 1 H), 5.7−5.1 (br s, 1 H), 3.76 (s, 3 H), 3.06−2.88 (m, 2 H), 2.66−2.48 (m, 1 H), 2.25 (s, 3 H), 1.90−1.71 (m, 4 H), 1.16 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 145.9, 142.8, 133.3, 132.7, 129.8, 115.2, 60.3, 30.2, 29.0, 23.7, 21.2, 18.8, 17.1; EI MS m/z 206 (M^+, 37),

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191 (100), 159 (31), 131 (19). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 76.03; H, 8.87.

1-(5-Methoxy-1,8-dimethyltetralin-6-yloxy)propan-2-one (7). Phenol **6** (0.832 g, 4.03 mmol) was dissolved in acetone (25 mL), and chloroacetone (0.67 mL, 8.4 mmol, 2.1 equiv) was added. The solution was placed under an atmosphere of argon, and KI (1.392 g, 8.39 mmol, 2.1 equiv) was added, followed by anhydrous K_2CO_3 (1.159 g, 8.39 mmol, 2.1 equiv). The mixture was stirred vigorously for 20 h at rt. Volatile components were evaporated under reduced pressure, and the resulting residue was partitioned between water and CH_2Cl_2. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with 5% aq $Na_2S_2O_3$ solution, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to give a yellow oil. Purification by flash chromatography (silica gel, 8:1 hexane/EtOAc) gave ketone **7** as a pale yellow oil (0.943 g, 89%): TLC R_f 0.16 (8:1 hexane/EtOAc); IR (neat, cm^{-1}) 2930, 2870, 1722, 1484, 1315, 1128; ^1H NMR ($CDCl_3$, δ ppm) 6.46 (s, 1 H), 4.52 (s, 2 H), 3.81 (s, 3 H), 3.04−2.88 (m, 2 H), 2.54 (ddd, J = 18.0, 10.8, 8.1 Hz, 1 H), 2.30, s, 3 H), 2.24 (s, 3 H), 1.86−1.64 (m, 4 H), 1.13 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 206.3, 148.0, 145.2, 135.2, 131.6, 131.2, 114.1, 74.2, 60.0, 29.9, 29.1, 26.7, 23.6, 20.9, 18.9, 16.9; EI MS m/z 262 (M^+, 68), 247 (100). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.45; H, 8.53.

Cacalol Methyl Ether (8).[3b–d] Ketone **7** (59.0 mg, 0.225 mmol) was placed in a 5 mL point bottom flask and cooled to 0 °C. Concentrated sulfuric acid at 0 °C (1 mL) was added dropwise to **7** with magnetic stirring. The dark red mixture was stirred at 0 °C for 1 h. Ice was added with shaking, which gave a milky-white emulsion. The mixture was extracted three times with ether, and the combined fractions were washed successively with water, satd aq $NaHCO_3$, and brine and dried over $MgSO_4$. The mixture was filtered and solvent evaporated under reduced pressure giving an oil. Purification by flash chromatography (silica gel, 40:1 hexane/ether) gave **8** as a white crystalline solid (32.8 mg, 60%): TLC R_f 0.35 (20:1 hexane/EtOAc); mp 66−67 °C; IR (neat, cm^{-1}) 2957, 2935, 2859, 1468, 1445, 1337, 1111, 1066, 1000; ^1H NMR ($CDCl_3$, δ ppm) 7.26 (s, 1 H), 4.06 (s, 3 H), 3.31−3.18 (m, 1 H), 3.11−2.99 (m, 1 H), 2.72−2.57 (m, 1 H), 2.56 (s, 3 H), 2.35 (d, J = 1.0 Hz, 3 H), 1.94−1.74 (m, 4 H), 1.20 (d, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 145.2, 141.0, 140.5, 135.6, 127.4, 124.4, 123.1, 116.6, 60.1, 30.3, 29.1, 23.7, 21.6, 17.1, 14.1, 11.5; EI MS m/z 244 (M^+, 83), 229 (100). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.62; H, 8.30.

Cacalol (1). Compound **8** was treated with boron tribromide giving **1** as a clear colorless oil, as described in the literature (60−71%):[3b–d] TLC R_f 0.22 (10:1 hexane/EtOAc); IR (neat, cm^{-1}) 3500, 2930, 2886, 1629, 1452, 1406, 1223, 1112, 908, 734; ^1H NMR ($CDCl_3$, δ ppm) 7.24−7.22 (m, 1 H), 4.95 (br s, 1 H), 3.29−3.17 (m, 1 H), 3.03−2.92 (m, 1 H), 2.61 (ddd, J = 17.8, 10.1, 7.9 Hz, 1 H), 2.51 (s, 3 H), 2.36 (d, J = 1.0 Hz, 3 H), 1.95−1.72 (m, 4 H), 1.18 (d, J = 7.2, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 142.2, 140.9, 136.4, 135.6, 126.2, 120.3, 118.7, 117.2, 30.2, 29.0, 23.0, 21.4, 16.7, 13.9, 11.4; EI MS m/z 230 (M^+, 58), 215 (100).

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Supporting Information Available: General experimental methods, copies of ^1H and ^{13}C NMR spectra, as well as chromatograms and MS spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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