A formal total synthesis of (±) –cacalol

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A formal total synthesis of Cacalol is described. Synthesis of methyl tetralin **8** has been achieved from the 5–methoxy-1-tetralone **2.** The conversion of **8** into tetralol **11** has been accomplished in three steps (bromination, formylation and oxidation).

Keywords: cacalol, bromination, formylation, metallation

Cacalol is a sesquiterpene isolated[1] from the root of *Cacalia decomposita A Gray* for which the structure **1** has been proposed on the basis of its chemical and spectroscopic evidences.[2-4] In view of its important biological activities[5,6] and in continuation of our earlier work[7] on terpene compounds, we decided to examine a simple route for the synthesis of cacalol whose synthesis has been accomplished by other workers.[8-11] Our efforts have focussed on the transformation of the commercially available 5–methoxy-1-tetralone **2** into cacalol **1**.

We now report the results of our investigations,[12] which led to a formal total synthesis of cacalol **1**.

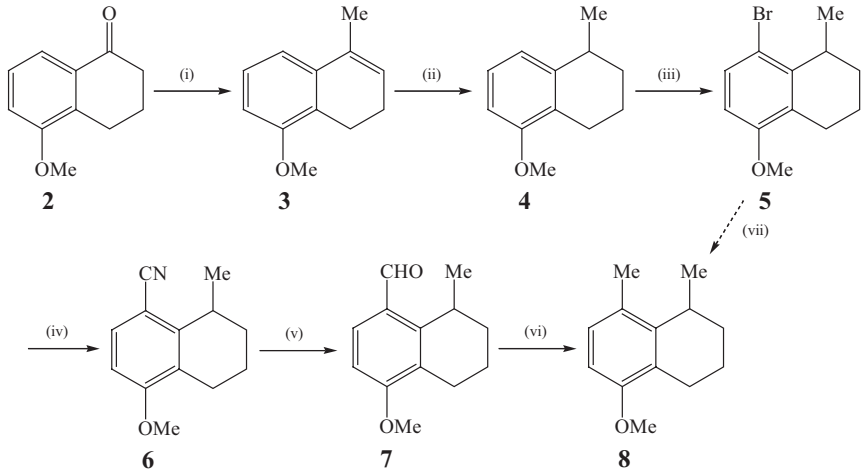
Results and discussions

Treatment of tetralone **2** (Scheme 1) with methylmagnesium bromide followed by acid hydrolysis afforded the already reported[7,13] dihydronaphthalene **3** which on catalytic hydrogenation over PtO_2 in ethanol furnished the known tetralin **4**.[14] Bromination[15] of **4** with ammonium bromide and hydrogen peroxide in acetic acid yielded the bromotetralin **5** in high yield. In agreement with the structure the ^{1}H NMR spectrum of this compound exhibited a clean signal at δ 6.59 and 7.36 (d, J = 8.69, C-8) which indicated that bromination occurred exclusively at C-8. Heating the bromotetralin **5** with cuprous cyanide in tetrahydrofuran[16] led to the formation of cyanotetralin **6** which on reduction with diisobutylaluminium hydride (DIBAL) in tetrahydrofuran gave aldehyde **7**. It showed absorption at 1683 cm^{-1} for carbonyl group in its IR spectrum and the expected signals at δ 10.16 (s, 1H, CHO) in its NMR spectrum. The aldehyde **7** was converted smoothly into the desired methyltetralin **8** by catalytic hydrogenation on Pd/C (10%) in ethyl acetate. The spectral properties were quite similar with those reported[11] for this compound.

The synthesis of methyltetralin **8** was also accomplished by a direct metallation procedure.[11] Thus bromotetralin **5** in tetrahydrofuran was treated with *n*-BuLi in hexane to generate the anion which on treatment with methyl iodide yielded methyltetralin **8** in 97% yield (Scheme 1) whose spectral data were very similar with those reported.[11] This metallation procedure not only shortened (two steps) the reaction sequence but also considerably improved the yield.

Having obtained the compound **8** in high yield, efforts to effect its conversion to tetraol **11** (Scheme 2) were initiated. Bromination of **8** with already mentioned procedure[15] yielded the bromo compound **9**. This was treated with *n*-BuLi in hexane to form the anion and then condensed with dimethylformamide to obtain the aldehyde **10** in 84% yield as evidenced by spectroscopic data. The metallation procedure again proved helpful in shortening (one step) the reaction sequence. Oxidative rearrangement of aldehyde **10** to tetraol **11** (overall yield 57%) was accomplished by treatment with hydrogen peroxide in acidic methanol[17].

Its spectral data were in complete agreement with the proposed structure and were quite similar with those reported.[11] for this tetraol **11**. The three steps conversion of 11 to cacalol **1** has already been reported and thus our alternative approach constitutes a formal total synthesis of cacalol.



Reagents: (i) MeMgBr;Et_2O (ii)H_2, Pd/C, EtOH; (iii) NH_4Br, H_2O_2 , AcOH; (iv) CuCN, THF; (v) DIBAL; (vi) H_2 , Pd/C, AcOEt; (vii) n-BuLi, MeI.

Scheme 1

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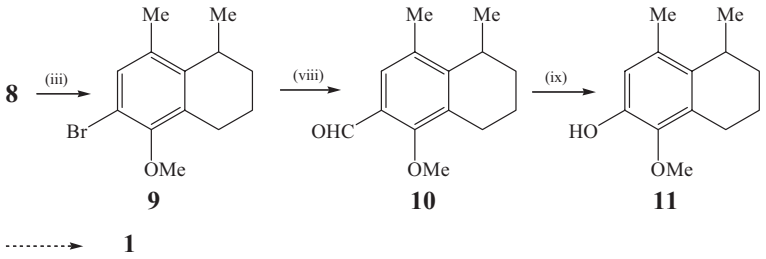

Reagents: (iii) NH_4Br, H_2O_2, AcOH; (viii) DMF, n-BuLi; (ix) H_2O_2,H_2SO_4, MeOH.

Scheme 2

In summary we have developed an efficient, shorter (five steps) and considerably higher yielding (57% overall) synthesis of tetraol **11** starting from the commercially available 5–methoxy-1-tetralone.

Experimental

Unless otherwise stated, IR spectra were taken on a Nicolet FT spectrophotometer Varian A-90 and Bruker AM 300 MHz spectrometers were employed for the determination of ^1H and ^{13}C NMR spectra, with tetramethylsilane (TMS) as internal reference and deuteriochloroform as solvent. Mass spectra were run on Kratos MS25RFA and on gas chromatography Hewlett Packard 5890 Quadrupolar 5972 Series S. The expression work up indicates that the solution is diluted with water, extracted with ether, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Column chromatography was performed on silica gel (Merck, grade 60, 70–230 mesh). The spectra and analytical data of all compounds have been reported in this section. Microanalyses were carried out at the Chemistry Department, IVIC, Caracas.

1–Methyl-5–methoxytetralin (**4**): A solution of dihydronaphthalene **3** (711 mg, 4.08 mmol) in ethanol (20 ml) was stirred for with Pd/C (10%) (400 mg) at room temperature under an atmosphere of hydrogen. Removal of catalyst and solvent left an oil which on chromatographic purification (hexane) yielded tetralin **4** (685 mg, 95%) as a colourless liquid; ^1H NMR: δ1.31 (d, 3H, Me, J = 7.1 Hz), 1.92–2.54 (m, 4H), 2.68 (m, 2H), 2.93 (m, 1H), 3.84 (s, 3H, OMe), 6.69 (d, ArH, J = 8.1 Hz), 6.87 (d, ArH, J = 7.7 Hz), 7.14 (t, ArH, J = 7.9 Hz); ^{13}C NMR: 157.04, 143.47, 125.68, 120.37 (C7, C10), 106.61, 55.18 (OMe), 32.5, 30.83, 23.55, 22.80 (Me), 19.53; *m/z* 176 (M^+), 161 (M^+–Me). Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 82.03; H, 9.29.

1–Methyl-5–methoxy-8–bromotetralin (**5**): To a flask containing tetralin **4** (1.01 g, 5.58 mmol) and a solution of ammonium bromide (0.71 g, 7.21 mmol) was added dropwise hydrogen peroxide (3 ml, 35%) and the contents were allowed to stir at room temperature for 2.5 h. The reaction was monitored by thin layer chromatography (TLC). The reaction mixture was treated with saturated sodium bicarbonate solution and extracted with dichloromethane. The extracts were washed with brine, dried and evaporated to give the bromotetralin **5** (1.39 g, 96%) as pale yellow oil; ν_{max} 1295 cm^{-1} (Br); ^1H NMR: δ1.27 (d, 3H, Me, J = 6.9 Hz), 1.73–1.91 (m, 4H), 2.45 (m, 1H), 2.86 (m, 1H), 3.22 (m, 1H), 3.81 (s, 3H, OMe), 6.59 (d, 1H, ArH, J = 8.69 Hz), 7.36 (d, 1H, ArH, J = 8.69 Hz); ^{13}C NMR: δ156.58, 141.91, 129.98, 127.69, 115.89, 108.45, 55.33 (OMe), 32.33, 29.13, 23.24, 20.41 (Me), 16.71; *m/z* 254 (M^+), 239 (M^+–Me), 175 (M^+–Br), 160 (M^+–Br–Me), 129 (M^+–Br–OMe–Me). Anal. Calcd. for $C_{12}H_{15}OBr$: C, 56.69; H, 5.91. Found: C, 56.97; H, 6.09.

1–Methyl-5–methoxy-8-cyanotetralin (**6**): To a solution of bromotetralin **5** (1.31 g, 5.12 mmol) in anhydrous dimethylformamide (10 ml) was added copper cyanide (0.91 g, 10.16 mmol) and heated to reflux under a nitrogen atmosphere for 4 h. The reaction mixture was cooled to 100°C, treated with hydrochloric acid containing aqueous ferric chloride (10%, 15 ml) and stirred for an additional 20 min. After cooling to room temperature the reaction mixture was diluted with water and extracted with chloroform several times. The combined extracts were washed, dried, and evaporated and the residual oil was chromatographed (hexane: ether 8:2) to yield cyanotetralin **6** (0.91 g, 87%), m.p. 87°C; ν_{max} 2217 cm^{-1} (CN); ^1H NMR: δ1.31 (d, 3H, Me, J = 7.09 Hz), 1.71–1.85 (m, 4H), 2.37 (m, 1H), 2.78 (m, 1H), 3.25 (m, 1H), 3.85 (s, 3H, OMe), 6.67 (d, 1H, ArH, J = 8.51 Hz), 7.45 (d, 1H, ArH, J = 8.50); ^{13}C NMR: δ160.50, 147.09, 132.22, 126.69, 118.97 (CN), 107.10, 103.99, 55.47, 31.07, 28.68, 22.72, 21.88 (Me), 16.44; MS: *m/z* 201 (M^+), 186 (M^+–Me). Anal. Calcd. for $C_{13}H_{15}ON$: C, 77.61; H, 7.46. Found: C, 77.32; H, 7.31.

1–Methyl-5–methoxy-8-formyltetralin (**7**): To a solution of cyanotetralin (0.41 g, 1.96 mmol) in dry toluene (15 ml) was added diisobutylaluminium hydride (DIBAL-H, 1M, 4 ml, 4 mmol) in toluene. The reaction mixture was stirred at room temperature overnight, and then quenched with water and hydrochloric acid (2M) until pH = 1. The solution was diluted with water and extracted with dichloromethane. The combined extracts were washed, dried and evaporated. The residual oil was chromatographed (hexane: ether 8:2) to give formyl tetralone **7** (0.35 g, 87%) as pale brown oil; ν_{max} 1683 cm^{-1} (CHO); ^1H NMR: δ1.28 (d, 3H, Me, J = 7.02 Hz), 1.76–1.89 (m, 4H), 2.47 (m, 1H), 2.86 (m, 1H), 3.87 (m, 1H), 3.91 (s, 3H, OMe), 6.80 (d, ArH, J = 8.55 Hz), 7.73 (d, ArH, J = 8.55 Hz), 10.16 (s, 1H, CHO); ^{13}C NMR: δ191.22 (CHO), 161.73, 146.63, 132.79, 126.52, 125.81, 106.73, 55.44, (OMe), 28.83, 27.64, 23.56 (Me), 23.09, 16.37; MS: *m/z* 204 (M^+), 189 (M^+–Me), 175 (M^+–CHO), 161 (M^+–CHO–Me). Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.72; H, 8.12.

1,8-Dimethyl-8–methoxytetralin (**8**): *Method A*: The formyl tetralin **7** (0.51 g, 2.5 mmol) was hydrogenated over palladium charcoal (10%, 0.22 g) under atmospheric pressure at room temperature. After 14 h when absorption had ceased, the catalyst was filtered off and the filtrate evaporated to give a viscous oil which on chromatographic purification (hexane) afforded dimethyl tetralin **8** (0.41 g, 89%) as a colourless oil; ν_{max} 1301 cm^{-1}; ^1H NMR: δ1.29 (d, 3H, Me, J = 7.01 Hz), 1.83–1.94 (m, 4H), 2.37 (s, 3H, Me), 2.56 (ddd, 1H, J = 18.32, 10.47, 7.75 Hz), 2.96 (dd, 1H, J = 18.22, 5.77 Hz), 3.14 (m, 1H), 3.88 (s, 3H, OMe), 6.69 (d, ArH, J = 8.24 Hz), 7.05 (1H, d = 8.24 Hz); ^{13}C NMR: δ155.62, 141.75, 127.62, 127.57, 124.99, 106.67, 55.17 (OMe), 29.63, 29.37, 23.18, 20.61 (Me), 18.32 (Me), 16.70; MS: 190 (M^+), 175 (M^+–Me), 160 (M^+-2Me). Anal. Calcd. for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.28; H, 9.68

Method B: To a solution of bromotetralin **5** (1.21 g, 4.6 mmol) dissolved in dry tetrahydrofuran (20 ml) at –78°C under nitrogen was added dropwise a solution of *n*-butyllithium (6.3 ml, 6.3 mmol), allowed to stir for 5 min. and added slowly methyl iodide (1 ml, 1.5 mmol). The reaction mixture was stirred for further 20 min, allowed to attain room temperature, stirred for an additional 2 h. and then diluted with water (5 ml). The reaction solution was extracted with dichloromethane. The organic layer was washed, dried and evaporated. Purification of the residue over silica gel (eluant hexane) afforded dimethyl tetralin **8** (0.87 g, 97%) whose identity was confirmed by comparison its spectroscopic properties (IR, ^1H NMR, ^{13}C NMR) and by tlc measurements with a sample prepared by the Method A.

1,8-Dimethyl-5–methoxy-6–bromotetralin (**9**): To a flask containing 1,8-dimethyl-5–Methoxytetralin **8** (0.81 g, 4.2 mmol) and a solution of ammonium bromide (0.56 g, 7.0 mmol) was added dropwise hydrogen peroxide (3 ml, 35%) and the contents were allowed to stir at room temperature for 4 h. The reaction was monitored by thin layer chromatography (TLC). The reaction mixture was treated with saturated sodium bicarbonate solution and extracted with dichloromethane. The extracts were washed with brine dried and evaporated to give a brown oil which on chromatographic purification (hexane: ether 9:1) yielded bromotetralin **9** (1.11 g, 98%) as a colourless oil, ν_{max} 1301 cm^{-1}; ^1H NMR: δ1.14 (d, 3H, Me, J = 7.01 Hz), 1.71–1.84 (m, 4H), 2.24 (s, 3H, Me), 2.61 (m, 1H), 2.95 (m, 1H), 2.99 (m, 1H), 3.76 (s, 3H, OMe), 7.16 (s, 1H); ^{13}C NMR: δ152.86, 141.62, 133.25, 131.73, 131.59, 113.21, 59.72 (OMe), 29.45, 29.25, 24.03, 20.58 (Me), 18.25 (Me), 16.78; MS: *m/z* 268 (M^+), 252 (M^+–15), 188 (M^+–Br), 173 (M^+–Me–Br), 158 M^+–Br–2Me). Anal. Calcd. for $C_{13}H_{17}OBr$: C, 58.21; H, 6.35. Found: C, 58.49; H, 6.53.

1,8-Dimethyl-5–methoxy-6-formyltetralin (**10**): To a solution of bromotetralin **9** (0.88 g, 3.28 mmol) dissolved in dry tetrahydrofuran (15 ml) at –78°C under nitrogen was added (over 2 min) 1.4 M solution of *n*-butyllitium (8 ml, 11.2 mmol), stirred for 10 min and then added dropwise (3 min) dimethylformamide (1 ml, 11.75 mmol). The reaction mixture was allowed to attain room temperature, diluted with water and extracted with dichloromethane. The organic extract was washed, dried and evaporated to leave a dark red oil which on chromatographic purification (hexane: ether 7 : 3) afforded formyltetralin **10** (0.61 g, 84%) as pale red oil; ν_{max} 1684 cm^{-1}; (CHO); ^{1}H NMR: δ1.16 (d, 3H, Me, J = 7.02 Hz), 1.73–1.84 (m, 4H), 2.30 (s, 3H, ArMe), 2.51 (m, 1H), 2.95 (m, 1H), 3.07 (m, 1H), 3.82 (s, 3H, OMe), 7.45 (s, ArH), 10.27 (s, 1H, CHO); ^{13}C NMR: δ190.19 (CHO), 159.85, 150.22, 132.33, 130.60, 127.08, 63.08 (OMe), 29.99, 29.33, 22.85, 20.44 (Me), 18.51 (Me), 16.33; *m/z* 218 (M^+), 174 (M^+–CHO–Me). Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.31; H, 8.48.

1,8-Dimethyl-5–methoxy-6-hidroxytetralin (**11**): To a solution of the formyl tetralin **10** (0.42 g, 1.93 mmol) in dry methanol (10 ml) was added 35% of hydrogen peroxide (0.20 ml, 6.1 mmol), and conc. sulfuric acid (01 ml) and stirred for 24 h at room temperature. To the reaction solution was added slowly a solution of sodium bicarbonate (5 ml, 10%) and extracted with ether. The organic extract was washed, dried and evaporated. The residue was chromatographed (hexane: ether 7:3) yielded hydroxytetralin **11** (0.31 g, 82%) as colourless oil; ν_{max} 3409 cm^{-1} (OH); ^{1}H NMR: δ1.21 (d, 3H, Me, J = 7.01 Hz), 1.78–1.90 (m, 4H), 2.29 (s, 3H, Me), 2.63 (m, 1H), 3.01 (m, 2H), 3.80 (s, 3H, OMe), 5.69 (Br, s, 1H, OH), 6.71 (s, ArH); ^{13}C NMR: δ145.81, 142.69, 133.12, 132.49, 129.65, 115.22, 60.10 (OMe), 30.04, 28.88, 23.60, 21.07 (Me), 18.65 (Me), 16.95; *m/z* 206 (M^+), 191 (M^+–Me). Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.91; H, 8.96.

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