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Studies on the Synthesis of Naphthoquinoids

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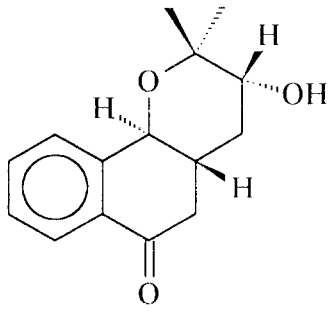
Four derivatives of 6-oxo-3,4,4a,5-tetrahydro-3-hydroxy-2,2-dimethylnaphtho-1,2-pyran (1), known as bactericidal, bacteriostatic, fungicidal, fungistatic agents, were synthesized to investigate the effect of substituents on the aromatic ring.

Key words : (+)-6-Oxo-3,4,4a,5-tetrahydro-3-hydroxy-2,2-dimethylnaphtho-1,2-pyran, *Lippia sidoides*, Bactericidal, Bacteriostatic, Fungicidal, Fungistatic

INTRODUCTION

(+)-6-Oxo-3,4,4a,5-tetrahydro-3-hydroxy-2,2-dimethylnaphtho-1,2-pyran (1) which was first isolated from the essential oil of *Lippia sidoides* Cham (Macambira *et al.* 1986), has been known to show bactericidal, bacteriostatic, fungicidal and fungistatic activities against *Staphylococcus aureus* and other microorganisms.

Four derivatives of 6-oxo-3,4,4a,5-tetrahydro-3-hydroxy-2,2-dimethylnaphtho-1,2-pyran (2-5) were synthesized, in order to investigate the effect of substituents on the aromatic ring of this compound on bactericidal, bacteriostatic, fungicidal and fungistatic activities



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MATERIALS AND METHODS

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F 254 plates from EM reagents and visualized with 254-nm UV light or ceric sulfate-ammoniummolybdate-sulfuric acid spray. Flash column chromatography was carried out on silica gel 60 (E. M. Merck, particle size 0.040~0.063 mm, 230~400 mesh ASTM). The ^1H spectra were recorded on a Brucker AC 80 (80 MHz) and/or Varian Gemini 200 (200 MHz) NMR spectrometer using $CDCl_3$ as a solvent except where noted. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values were in Hz. IR spectra were obtained on a Perkin-Elmer Model 782 spectrometer. Mass spectra were recorded on a Shimadzu-LKB 9000 GC/MS system. The optical rotations were measured with a JASCO DIP-1000 polarimeter at RT. All mps were uncorrected. When necessary, chemicals were purified according to the reported procedure (Perrin *et al.*, 1980).

General Procedure for the Preparation of Tetralones

General procedure for the synthesis of (R)-2-prenyl-1-tetralones: In a system containing a Dean-Stark trap arranged for azeotropic removal of water, the methoxy amine and α-tetralone were dissolved in benzene and heated to reflux for 4 h. Removal of benzene in vacuo and distillation of the oily residue in Kugelrohr gave the desired product as a clear viscous oils.

An oven-dried flask equipped with a magnetic bar, a pressure-equalized addition funnel, and a rubber septum cap was charged with anhydrous THF under a nitrogen atmosphere. Freshly distilled diisopropylamine was added *via* syringe and the solution was cooled to 0°C. *n*-Butyllithium was added. The solution was stirred at 0°C for 15 min and then cooled -30°C. α-Tetralone imine of (S)-2-amino-1-methoxy-3-phenylpropane in anhydrous THF was added over 10 min

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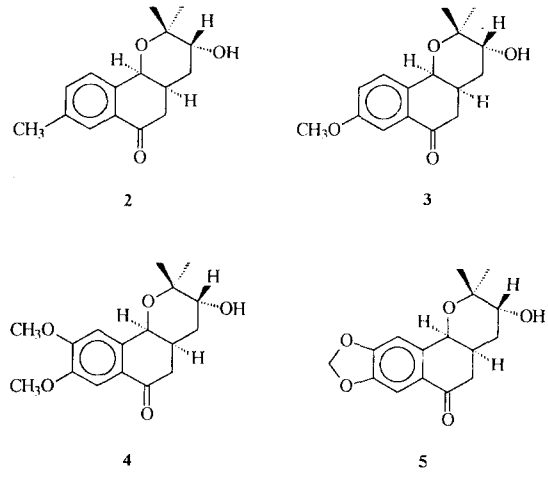

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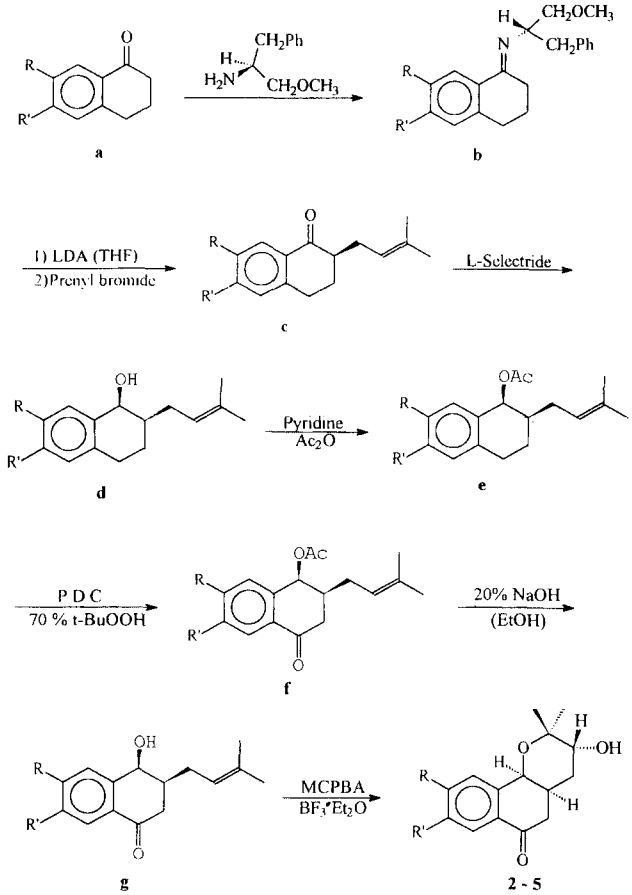
The synthetic route to these compounds is outlined in Scheme 1.



2 : R = H, R' = CH_3,
3 : R = H, R' = OCH_3,
4 : R = OCH_3, R' = OCH_3,
5 : R, R' = -OCH_2O-

Scheme 1.

and allowed to stir for 1.5 h at -15°C. The solution was then cooled to -78°C and prenyl bromide was added in a solution of anhydrous THF over a period of 10 min. The mixture was allowed to stir at -78°C for 3 h and then warmed to RT and stirred overnight. A cold saturated NaCl solution was poured into the reaction mixture. The resulting solution was extracted with ether 3 times. The combined ether extracts were washed with brine, then dried ($MgSO_4$), and concentrated in vacuo to give an amber oil. This crude imine was subjected to hydrolysis immediately. A buffer solution comprised of sodium acetate, acetic acid and water was added to the crude imine in hexane and shaken for 30 min and the aqueous layer removed and saved to recover (S)-2-amino-1-methoxy-3-phenylpropane. The aqueous layer was extraced with hexane, and the combined hexane layers were washed with 1 *N* HCl, water, 5% sodium bicarbonate, water and brine. The hexane solution was then dried ($MgSO_4$), filtered, concentrated in vacuo to afford the crude product. Chromatography of the crude product on silica gel gave the desired product.

(R)-7-Methyl-2-prenyl-1-tetralone (2c): Yield: 36.6%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.75 (m, 1 H), 6.80-7.33 (m, 2 H), 5.13 (deformed t, *J*=6.6 Hz, 1 H), 2.25 (s, 3H), 1.95-3.08 (m, 7 H), 1.63 (s, 3 H), 1.53 (s, 3 H), IR [ν_{max}, neat] 2940, 1675, 1600.

(R)-7-Methoxy-2-prenyl-1-tetralone (3c): Yield: 43.3%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.58 (m, 1 H), 7.10 (m, 2 H), 5.20 (deformed t, *J*=6.1 Hz, 1 H), 3.83 (m, 3 H), 2.90 (m, 2 H), 1.95-2.62 (m, 5 H), 1.73 (s, 3 H), 1.64 (s, 3 H), IR [ν_{max}, neat] 2940, 1670, 1600.

(R)-6,7-Dimethoxy-2-prenyl-1-tetralone (4c): Yield: 49.5%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.47 (br s, 1 H), 6.59 (br s, 1 H), 5.12 (deformed t, *J*=6.7 Hz, 1 H), 3.86 (br s, 6 H), 2.77 (m, 2 H), 2.55-1.83 (m, 5 H), 1.67 (s, 3 H), 1.63 (s, 3 H)

(R)-6,7-Methylenedioxy-2-prenyl-1-tetralone (5c): Yield: 37.8%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.46 (br s, 1 H), 6.62 (br s, 1 H), 5.98 (s, 2 H), 5.17 (deformed t, *J*=6.6 Hz, 1 H), 2.87 (m, 2 H), 2.71-1.95 (m, 4 H), 1. 73 (s, 3 H), 1.65 (s, 3 H).

General procedure for the reduction of (*R*)-2-prenyl-1-tetralones (d)

An oven-dried 100-mL flask equipped with a magnetic bar and a rubber septum cap was charged with L-selectride (1.0 mL of a 1.0 M solution in THF, 1.0 mmol) under a nitrogen atmosphere. The solution was cooled to -15°C. (*R*)-(+)-2-prenyl-1-tetralone (0.5 mmol) was added dropwise in a solution of THF (1.1 mL) via a syringe. The solution was stirred for 2 h at this temperature. NaOH (1.1 mL of a 3.0 M solution in water) was poured into the reaction mixture. The resulting solution was stirred for 10 min and then H_2O_2 solution (1.1 mL of 30% solution) was added. After stirring for 10 min, the reaction mixture was saturated with potassium carbonate and then extracted with dichloromethane. The combined dichloromethane ex-

tracts were washed with water, then dried ($MgSO_4$), and concentrated in vacuo to afford the crude product. Chromatography of the crude product on silica gel gave the desired product.

***(1S,2R)*-7-Methyl-2-prenyl-1-tetralol (2d):** Yield: 89%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.90-7.25 (m, 3 H), 5.20 (deformed t, *J*=6.5 Hz, 1 H), 4.53 (s, 1 H), 2.28 (s, 3 H), 1.90-3.08 (m, 8 H), 1.72 (s, 3 H), 1.66 (s, 3 H), IR [ν_{max} (KBr) disc] 3190, 1590, 770 cm^{-1}.

***(1S,2R)*-7-Methoxy-2-Prenyl-1-tetralol (3d):** Yield: 89.0 %, ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.72-7.10 (m, 3 H), 5.25 (deformed t, *J*=6.2 HZ, 1 H), 4.51 (s, 1 H) 3.76 (s, 3 H), 2.70 (t, *J*=5.9 Hz, 2 H), 1.55-2.35 (m, 6 H), 1.78 (s, 3 H), 1.70 (s, 3 H), IR [ν_{max} (KBr) disc] 3340, 1610 cm^{-1}.

***(1S,2R)*-6,7-Dimethoxy-2-prenyl-1-tetralol (4d):** Yield: 85.3%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.80 (s, 1 H), 6.54 (s, 1 H), 5.23 (deformed t, *J*=6.6 Hz, 1 H), 4.48 (br s, 1 H), 3.93 (s, 6 H) 2.63 (m, 2 H), 2.47-2.13 (m, 6 H), 1.84 (s, 3 H), 1.69 (s, 3 H).

***(1S,2R)*-6,7-Methylenedioxy-2-prenyl-1-tetralol (5d):** Yield: 88.0%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.80 (s, 1 H), 6.57 (s, 1 H), 5.90 (s, 2 H), 5.26 (deformed t, *J*=7.1 Hz, 1 H), 4.52 (br s, 1 H), 2.70 (m, 2 H), 2.50-1.96 (m, 5 H), 1.75 (s, 3 H), 1.69 (s, 3 H).

General procedure for acetylation of *(1S,2R)*-2-prenyl-1-tetralols (e)

A solution of *(1S,2R)*-2-prenyl-1-tetralol in anhydrous pyridine was treated with acetic anhydride. The resulting solution was stirred at RT overnight. The solution was poured into ice-H_2O and extracted with dichloromethane 3 times. The organic extracts were washed with cold 5% aq. HCl, water, saturated $NaHCO_3$ solution, water and brine two times, respectively. The organic layer was dried over anhydrous MgSO4 and condensed at reduced pressure. The residue was chromatographed on the silica gel column.

***(1S,2R)*-7-Methyl-2-prenyl-1-tetralol acetate (2e):** Yield: 88.1%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.10 (s, 1 H), 6.85 (s, 2 H), 6.05 (s, 1 H), 5.13 (deformed t, *J*=6.6 Hz, 1 H), 2.60-3.01 (m, 2 H), 2.30 (s, 3 H), 2.03 (s, 3 H), 1.65-2.20 (m, 5 H), 1.76 (s, 3 H), 1.63 (s, 3 H) IR [ν_{max} (NaCl) disc] 1720, 1590, 755 cm^{-1}.

***(1S,2R)*-7-Methoxy-2-prenyl-1-tetralol acetate (3e):** Yield: 98.5%, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.07-6.72 (m, 3 H), 6.00 (br s, 1 H), 5.17 (deformed t, *J*=7.3 Hz, 1 H), 3.75 (s, 3 H) 2.75 (m, 2 H), 2.03 (s, 3 H), 2.09-1.70 (m, 5 H), 1.73 (s, 3 H), 1.61 (s, 3 H).

***(1S,2R)*-6,7-Dimethoxy-2-prenyl-1-tetralol acetate (4e):** Yield: 87.2%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.94 (s, 1 H), 6.58 (s, 1 H), 5.94 (br s, 1 H), 5.17 (deformed t, *J*= 7.2 Hz, 1 H), 3.93 (s, 6 H), 2.75 (m, 2 H), 2.04 (s, 3 H), 2.39-1.71 (m, 5 H), 1.88 (s, 1 H), 1.69 (s, 3 H).

***(1S,2R)*-6,7-Methylenedioxy-2-prenyl-1-tetralol acetate (5e):** Yield: 82.6%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.94 (s, 1 H), 6.61 (s, 1 H), 5.99 (s, 2 H), 5.83 (br s, 1 H), 5.29 (deformed t, *J*=7.3 Hz, 1 H), 2.77 (m, 2 H), 2.54-2.01 (m, 5 H), 2.05 (s, 3 H), 1.76 (s, 3 H), 1.71 (s, 3 H).

General procedure for oxidation of *(1S,2R)*-2-prenyl-1-tetralyl acetate (f)

To a stirred solution of *(1S,2R)*-2-prenyl-1-tetralol acetate in benzene and celite was added pyridinium dichromate followed by the addition of 70% tert-butylhydroperoxide at 10°C. After 20 min at 10°C, the reaction mixture was stirred for 5 h at 25°C. Dichloromethane was added, and the reaction mixture was filtered through a pad of celite and washed twice with dichloromethane. Combined filtrate was washed with water, dried with $MgSO_4$ and concentrated in vacuo to afford the crude product. It was purified by flash chromatography to give unreacted starting material and the desired product.

***(1S,2R)*-7-Methyl-4-oxo-2-prenyl-1-tetralyl acetate (2f):** Yield: 20.2%, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94 (d, *J*=9.7 Hz, 1 H), 7.36-7.22 (m, 2 H), 6.05 (d, *J*=2.0 Hz, 1 H), 5.13 (deformed t, J=7.1 Hz, 1 H), 2.80-2.55 (m, 2 H), 2.50-2.20 (m, 2 H), 2.05 (s, 3 H), 1.89-2.20 (m, 1 H), 1.73 (s, 3 H), 1.61 (s, 3 H)

(1S,2R)-7-Methoxy-4-oxo-2-prenyl-1-tetralyl acetate (3f): Yield: 34.7%, ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, *J*=9.6 Hz, 1 H), 7.07-6.87 (m, 2 H), 6.04 (d, *J*= 2.0 Hz, 1 H), 5.14 (deformed t, *J*=7.3 Hz, 1 H), 3.86 (s, 3 H), 2.75-2.61 (m, 2 H), 2.60-2.31 (m, 2 H), 2.06 (s, 3 H), 1.89-2.29 (m, 1 H), 1.73 (s, 3 H), 1.61 (s, 3 H).

***(1S,2R)*-6,7-Dimethoxy-4-oxo-2-prenyl-1-tetralyl acetate (4f):** Yield: 22.9%, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 7.06 (s, 1 H), 5.98 (d, *J*=1.1 Hz, 1 H), 5.18 (deformed t, *J*=7.0 Hz, 1 H), 3.94 (s, 3 H), 3.93 (s, 3 H), 2.76-2.64 (m, 2 H), 2.60-2.29 (m, 2 H), 2.05 (s, 3 H), 1.89-2.29 (m, 1 H), 1.74 (s, 3 H), 1.62 (s, 3 H) IR [ν_{max} (NaCl) disc] 1725, 1605, 755 cm^{-1}.

***(1S,2R)*-6,7-Methylenedioxy-4-oxo-2-prenyl-1-tetralyl acetate (5f):** Yield: 27.8%, ^{1}H NMR (80 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 7.06 (s, 1 H), 5.99 (s, 2 H), 5.79 (d, *J*=2.1 Hz, 1 H), 5.14 (deformed t, *J*=7.1 Hz, 1 H), 2.81-2.60 (m, 2 H), 2.60-2.29 (m, 2 H), 2.05 (s, 3 H), 1.89-2.29 (m, 1 H), 1.74 (s, 3 H), 1.62 (s, 3 H).

General procedure for hydrolysis of *(1S,2R)*-4-oxo-2-prenyl-1-tetralyl acetate (g)

A solution of *(1S,2R)*-4-oxo-2-prenyl-1-tetralol acetate in methanol in 95% EtOH was stirred with K_2CO_3 for 30 min at RT before addition of ether and a saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water and saturated Na_2CO_3 solution and dried over anhydrous $MgSO_4$. Solvent was removed at

reduced pressure to give the crude product. It was purified by flash chromatography to afford (*1S,2R*)-4-oxo-2-prenyl-1-tetralol.

(*1S,2R*)-7-Methyl-4-oxo-2-prenyl-1-tetralol (2g): Yield: 52.8%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.91 (m, 1 H), 7.10-7.39 (m, 2 H), 5.10 (deformed t, *J*=7.2 Hz, 1 H), (br s, 1 H), 2.37 (s, 3 H), 1.95-3.08 (m, 7 H), 1.70 (s, 3 H), 1.60 (s, 3 H) IR [ν_{max} (NaCl) disc] 3190, 1670, 1590, 770 cm^{-1}.

(*1S,2R*)-7-Methoxy-4-oxo-2-prenyl-1-tetralol (3g): Yield: 60.9%, ^{1}H NMR (80 MHz, $CDCl_3$) δ 7.95 (d, *J*= 9.6 Hz, 1 H), 6.75-7.03 (m, 2 H), 5.17 (deformed t, *J*= 7.2 Hz, 1 H), 4.77 (br s, 1 H), 3.82 (s, 3 H), 2.50-2.80 (m, 2 H), 2.01-2.42 (m, 4 H), 1.69 (s, 3 H), 1.57 (s, 3 H) IR [ν_{max} (NaCl) disc] 3385, 1670, 1605.

(*1S,2R*)-6,7-Dimethoxy-4-oxo-2-prenyl-1-tetralol (4g): Yield: 70.8%, ^{1}H NMR (80 MHz, $CDCl_3$) δ 7.46 (s, 1 H), 6.89 (s, 1 H), 5.18 (deformed t, *J*=7.2 Hz, 1 H), 4.75 (br s, 1 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 2.76-2.46 (m, 2 H), 2.46-2.07 (m, 4 H), 1.69 (s, 3 H), 1.60 (s, 3 H).

(*1S,2R*)-6,7-Methylenedioxy-4-oxo-2-prenyl-1-tetralol (5g): Yield: 53.0%, ^{1}H NMR (80 MHz, $CDCl_3$) δ 7.49 (s, 1 H), 7.09 (s, 1 H), 5.10 (deformed t, *J*=7.2 Hz, 1 H), 4.68 (br s, 1 H), 2.79 (m, 2 H), 2.76-1.98 (m, 4 H), 1.75 (s, 3 H), 1.70 (s, 3 H) IR [ν_{max} (NaCl) disc] 3415, 2905, 1660, 1608.

General procedure for the synthesis of target compounds (2-5)

(*1S,2R*)-4-oxo-2-prenyl-1-tetralol in chloroform was treated with *m*-chloroperbenzoic acid in chloroform. Treatment of the reaction mixture with $BF_3.Et_2O$ (traces) followed by usual workup produced target compounds (2-5).

9-Methyl-6-oxo-3,4,4a,5-tetrahydro-3-hydroxy-2,2-dimethylnaphtho-1,2-pyran (2): Yield: 24%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.95 (br s, 1 H), 7.59-7.23 (m, 1 H), 4.61 (m, 1 H), 3.06 (br s, 1 H), 2.90-2.43 (m, 2 H), 2.36 (s, 3 H), 2.19-1.80 (m, 4 H), 1.30 (s, 3 H), 1.25 (s, 3 H).

9-Methoxy-6-oxo-3,4,4a,5-tetrahydro-3-hydroxy-2,2-dimethylnaphtho-1,2-pyran (3): Yield: 28.5%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.89 (br s, 1 H), 7.51-7.24 (m, 1 H), 4.59 (m, 1 H), 3.89-3.60 (br s, 1 H), 2.88-2.45 (m, 2 H), 2.15-1.77 (m, 4 H), 1.31 (s, 3 H), 1.25 (s, 3 H).

8,9-Dimethoxy-6-oxo-3,4,4a,5-tetrahydro-3-hydroxy-2,2-dimethylnaphtho-1,2-pyran (4): Yield: 29%, ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.47 (br s, 1 H), 6.96-6.76 (m, 1 H), 4.63 (m, 1 H), 3.96 (s, 3 H), 3.90 (s, 3 H), 3.08 (br s, 1 H), 2.85-2.46 (m, 2 H), 2.13-1.73 (m, 4 H), 1.29 (s, 3 H), 1.24 (s, 3 H).

8,9-Methylenedioxy-6-oxo-3,4,4a,5-tetrahydro-3-hydroxy-2,2-dimethylnaphtho-1,2-pyran (5): Yield: 26.3 %, ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.49 (br s, 1 H), 6.93-6.74 (m, 1 H), 5.98 (m 1, H), 4.68 (m, 1 H), 3.07 (br s, 1 H), 2.83-2.46 (m, 2 H), 2.11-1.69 (m, 4 H), 1.28 (s, 3 H), 1.24 (s, 3 H).

RESULTS AND DISCUSSION

All the procedures in this synthesis are identical to our previous work (Park and Lim, 1996). 2-Prenyl-1-tetralones were reduced with L-selectride (Brown and Krishnamurthy, 1972) to give cis-2-prenyl-1-tetralols. This was confirmed by the 1-H signals of these compounds which occur at δ=4.48-4.53 as a broad singlet in the ^{1}H NMR spectrum.

The target compounds (2-5) were prepared from (*1S, 2R*)-4-oxo-2-prenyl-1-tetralols according to the reported procedure (Macambira *et al.*, 1986). They are used to investigate the effect of substituents on the aromatic ring of parent compound on bactericidal, bacteriostatic, fungicidal and fungistatic activities.

ACKNOWLEDGEMENT

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