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A New Synthesis of 6,10,14,18-Tetramethyl-5,9,13,17 (E,E,E)-nonadecatetraen-2-one

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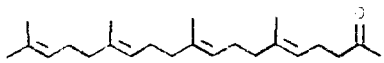
6,10,14,18-Tetramethyl-5,9,13,17(E,E,E)-nonadecatetraen-2-one was synthesized from geraniol or 6-methyl-5(E)-hepten-2-one in 6 steps, respectively. The key step in both syntheses, was the condensation of phenyl sulfone compound and allylic chloride.

Key words: 6,10,14,18-Tetramethyl-5,9,13,17(E,E,E)-nonadecatetraen-2-one, Gastric ulcer, 6-Methyl-5(E)-hepten-2-one, Geraniol

INTRODUCTION

6,10,14,18-Tetramethyl-5,9,13,17(E,E,E)-nonadecatetraen-2-one (**1**) has been used as a remedy for gastric ulcer because of its pharmacological activities such as promoting synthesis of polymeric glycoprotein and phospholipid, two main propylactic factors in gastric mucosa and gastric mucus and the improvement in the defensive function in gastric mucosa (Murakami *et al.*, 1983). It has been found that the compound is effective also in correcting abnormal GOT, GPT, caused by hepatic function disorder (Yamatsu *et al.*, 1983).



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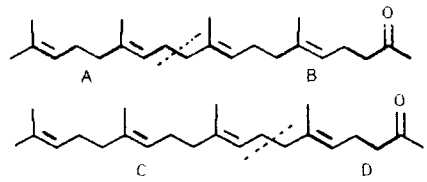
There have been many reports on the syntheses of terpene alcohols and isoprenoid ketones(Isler and Doebel 1954; Kimel *et al.*, 1957; Obol'nikova *et al.*, 1964; Corey *et al.*, 1967). In these syntheses, they were prepared by repetition of many reaction steps. Sato *et al.* (1970), synthesized isoprenoid ketones, utilizing substituted acetylenes. One drawback of Sato's synthesis was the low stereoselectivity observed in a Wittig reaction.

The target molecule was envisioned to be composed of two units, A and B or C and D as shown below. The design of our synthetic route centered upon the separate syntheses of these individual units which were assembled at appropriate stages then connected



in a convergent synthesis.

Chloride **6** and chloride **11** served as the synthetic equivalents of subunit B and subunit D, respectively. Geranyl phenyl sulfone (**3**) and farnesyl phenyl sulfone (**13**) are the functionalized derivatives of subunit A and subunit C, respectively.

Our synthetic routes to 6,10,14,18-tetramethyl-5,9,13,17(E,E,E)-nonadecatetraen-2-one from geraniol or 6-methyl-5(E)-hepten-2-one are outlined in the scheme 1 and scheme 2.

MATERIALS AND METHODS

Reactions requiring anhydrous conditions were performed with precaution 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-ammonium molybdate-sulfuric acid spray. The ^1H NMR spectra were recorded on Varian EM-360 spectrometer. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane. IR

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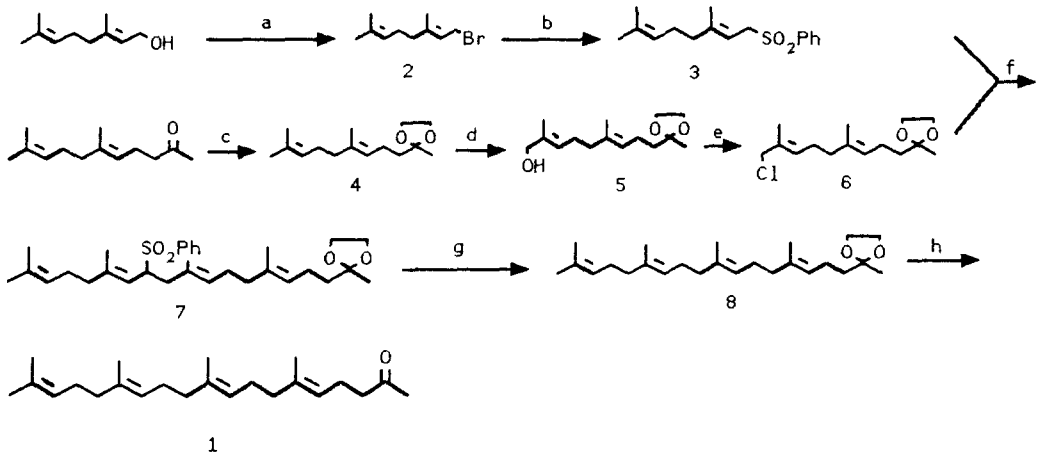
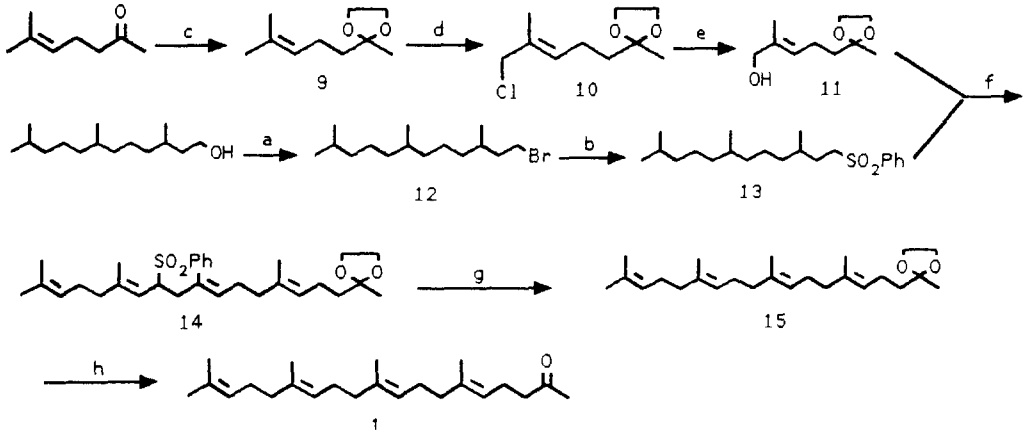


Scheme 1



Scheme 2

a. PBr_3 (hexane); b. $C_6H_5SO_2Na$ (DMF); c. $HOCH_2CH_2OH$, p-TSOH (benzene); d. t-BuOOH, SeO_2 (CH_2Cl_2); e. CH_3SO_2Cl, LiCl, 2,4,6-collidine; f. NaH (DMF); g. Na_2HPO_4, 6%-Na·Hg (MeOH); h. 50% H_3PO_4 (acetone)

spectra were obtained on Perkin-Elmer Model 337. Mass spectra were recorded on a Shimazu-LKB 9000 GC/MS system. Chemicals were purified, when necessary, according to the reported procedure (Perrin *et al.*, 1980).

Geranyl bromide (2)

To a solution of geraniol (400 mg, 2.59 mmol) in dry hexane (3 ml) was added PBr_3 (351 mg, 1.30 mmol) at 0°C under the atmosphere of nitrogen. The mixture was stirred at this temperature for 30 min, then a few drops of methanol was added. The reaction mixture was washed with cold saturated $NaHCO_3$ solution and cold brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford geranyl bromide (609 mg, 95%) as a colorless oil. Geranyl bromide obtained was used for the next reaction without purification: IR (neat, NaCl disc) 2950, 1675, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (s, 3H), 1.69 (s, 6H), 2.05 (s, 4H), 3.97 (d, J=9 Hz, 2H), 5.10 (br s, 1H), 5.42 (t, J=9 Hz, 1H).

Geranyl phenyl sulfone (3)

A solution of geranyl bromide (500 mg, 2.30 mmol) in anhydrous DMF (5 ml) was treated with benzenesulfinic acid Na salt (690 mg, 4.20 mmol), and the mixture was stirred under the atmosphere of nitrogen for 20 h. It was then diluted with water and extracted with ether (15 ml×2). The extract was washed with brine, dried over $MgSO_4$ and evaporated to give the crude product as a pale yellow oil. Chromatography of the crude product on a silica gel column (1 : 10 ethyl acetate/hexane) gave the title compound (460 mg, 72%) as a colorless oil: IR (neat, NaCl disc) 2970, 2870, 1440, 1380, 1310, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.56 (s, 3H), 1.66 (s, 3H), 1.98 (m, 4H),

3.75 (d, J=8 Hz, 2H), 4.80-5.33 (m, 2H), 7.50 (m, 3H), 7.85 (m,2H).

6,10-Dimethyl-5,9(E)-undecadien-2-one ethylene acetal (4)

In a round bottom flask swept with nitrogen was placed geranylacetone (971 mg, 5 mmol), ethylene glycol (435 mg, 7 mmol), benzene (10 ml) and several crystals of p-toluenesulfonic acid. The solution was azeotroped at reflux, in a Dean-Stark apparatus for 9 h. After cooling to RT, workup in the usual manner gave an oil. The crude product was chromatographed on silica gel with benzene to give the desired compound (1.11 g, 93%): IR (neat, NaCl disc) 2970, 2870, 1440, 1380, 1220, 1135, 1055, 950, 865 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.56 (s, 6H), 1.66 (s, 3H), 1.80-2.16 (m, 8H), 3.90 (s, 4H), 5.09 (m, 2H).

11-Hydroxy-6,10-dimethyl-5,9(E,E)-undecadien-2-one ethylene acetal (5)

A suspension of selenium dioxide (55.8 mg, 0.5 mmol) in CH_2Cl_2 was stirred with 70% t-butylhydroperoxide (287 μl, 2 mmol) for 30 min at RT in the dark. The resulting solution was cooled to 0℃, followed by the addition of 6,10-dimethyl-5,9(E)-undecadien-2-one ethylene acetal (238 mg, 1.0 mmol). The mixture was stirred for 5 h at 10℃ and then diluted with CH_2Cl_2. The organic solution was washed with water, 10% $NaHCO_3$ solution, water and brine successively. The organic layer was then dried over Na_2SO_4 and concentrated to give a pale yellow oil that was dissolved in methanol, cooled to 0℃ and treated with $NaBH_4$ (22 mg, 0.58 mmol). After stirring at RT for 30 min, the solvent was evaporated and the residue was partitioned between ether and water. Workup in the usual manner gave an oil. The crude product was chromatographed on silica gel with 1 : 3 ethyl acetate/hexane to give the allylic alcohol as a colorless oil (104 mg, 41%): IR (neat, NaCl disc) 3400, 2870, 1380, 1270, 1060, 950, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.67 (s, 6H), 1.96-2.16 (m, 8H), 3.96 (s, 4H), 3.98 (s, 2H), 4.96-5.56 (m, 2H).

11-Chloro-6,10-dimethyl-5,9(E,E)-undecadien-2-one ethylene acetal (6)

The method of Meyers (Meyers *et al.*, 1971) was followed. A Stirred mixture of 11-hydroxy-6,10-dimethyl-5,9(E,E)-undecadien-2-one ethylene acetal (254 mg, 1 mmol) and 2,4,6-collidine (133 mg, 1.1 mmol) under nitrogen was treated with lithium chloride (42 mg, 1 mmol) dissolved in a minimum amount of dry dimethylformamide. On cooling to 0℃, a suspension was formed which was treated dropwise with methanesulfonyl chloride (85 μl, 1.1 mmol). Stirring was continued at 0℃ for 1.5 h. The pale yellow reaction mixture was poured over ice-water. The aqueous layer was extracted three times with pentane and the combined extracts were washed successively with saturated copper nitrate (×3), water and brine. The organic extracts were dried over $MgSO_4$ and concentrated at RT to afford the allyl chloride (257 mg, 94%) as a pale yellow oil: IR (neat, NaCl disc) 2970, 2930, 2870, 1440, 1380, 1260, 1210, 1135, 1055, 940, 870, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.63 (s, 3H), 1.73 (s, 3H), 1.90-2.26 (m, 8H), 3.96 (s, 4H), 4.03 (s, 2H), 5.13 (m, 1H), 5.50 (m, 1H).

6,10,14,18-Tetramethyl-12-(phenylsulfonyl)-5,9,13,17(E,E,E)-nonadecatetraen-2-one ethylene acetal (7)

To a cooled (0℃) suspension of NaH (60%, 48 mg, 1 mmol) in anhydrous DMF (7 ml) was added geranyl phenyl sulfone (278 mg, 1 mmol) in anhydrous DMF (1 ml) at 0℃ under the atmosphere of nitrogen. The mixture was then stirred at RT for 30 min and treated with 11-chloro-6,10-dimethyl-5,9(E,E)-undecadien-2-one ethylene acetal (273 mg, 1 mmol) in anhydrous DMF (1 ml). After stirred at RT for 5 h, the resulting mixture was quenched with a 5% HCl solution with vigorous stirring. The reaction mixture was subjected to extractive workup with ether. Chromatography of the crude product on silica gel (1 : 4 ethyl acetate/hexane) gave the title compound 7 (313 mg, 61%) as a colorless oil: IR (neat, NaCl disc) 2970, 2870, 1440, 1380, 1310, 1220, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (s, 3H), 1.36 (s, 3H), 1.61 (s, 6H), 1.70 (s, 6H), 1.90-2.23 (m, 14H), 3.70-4.13 (m, 1H), 3.96 (s, 4H), 4.90-5.33 (m, 4H), 7.54 (m, 3H), 7.86 (m, 2 H); MS m/e (relative intensity) 514 (M^+, 1), 373 (18), 272 (100), 67 (80).

6,10,14,18-Tetramethyl-5,9,13,17(E,E,E)-nonadecatetraen-2-one ethylene acetal (8)

A mixture of compound 7 (514 mg, 1 mmol) and disodium hydrogen phosphate (568 mg, 4 mmol) was dissolved in anhydrous MeOH (50 ml). To this solution, cooled at −10℃ and kept under the atmosphere of nitrogen, was added 6% Na(Hg) (1.5 g, 4 mmol) in one portion. The resulting mixture was stirred for 20 min at −10℃, followed by quenching with a saturated NH_4Cl solution and extraction with ethyl ether. The combined extracts were washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and then concentrated under reduced pressure. The crude residue obtained was chromatographed on silica gel with 1 : 16 ethyl acetate/hexane to furnish the title compound (307 mg, 82%) as a colorless oil: IR (neat, NaCl disc) 2970, 2870, 1440, 1380, 1210, 1135, 950, 865 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.58 (s, 12H), 1.68 (s, 3H), 1.98-2.26 (m, 16H), 4.0 (s, 4H), 5.02-5.18 (m, 4H); MS m/e (relative intensity) 374 (M^+, 3), 273 (16),

205 (12), 204 (23), 137 (34), 67 (100).

6-Methyl-5(E)-hepten-2-one ethylene acetal (9)

In a round bottom flask swept with nitrogen was placed 6-methyl-5(E)-hepten-2-one (1.26 g, 10 mmol), ethylene glycol (0.87 g, 14 mmol), benzene (25 ml) and several crystals of p-toluenesulfonic acid. The solution was azeotroped at reflux in a Dean-Stark apparatus for 9 h. After cooling to RT, workup in the usual manner gave an oil. The crude product was chromatographed on silica gel with benzene to give the desired compound (1.55 g, 91%): IR (neat, NaCl disc) 2970, 1460, 1380, 1220, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.63 (s, 3H), 1.70 (s, 3H), 2.20-2.50 (m, 4H), 3.92 (s, 4H), 4.90-5.30 (m, 1H).

7-Hydroxy-6-methyl-5(E)-hepten-2-one ethylene acetal (10)

A Suspension of selenium dioxide (558 g, 5 mmol) in CH_2Cl_2 (25 ml) was stirred with 70% t-butylhydroperoxide (2.87 ml, 20 mmol) for 30 min at RT in the dark. The resulting solution was cooled to 0℃, followed by the addition of 6-methyl-5(E)-hepten-2-one ethylene acetal (1.7 g, 10 mmol). The mixture was stirred for 5 h at 10℃ and then diluted with CH_2Cl_2 (15 ml). The organic solution was washed with water, 10% $NaHCO_3$, water and brine. The organic layer was then dried (Na_2SO_4) and concentrated to give a pale yellow oil that was dissolved in methanol (25 ml), cooled to 0℃ and treated with $NaBH_4$ (220 mg, 58 mmol). After stirring at RT for 30 min, the solvent was evaporated and the residue was partitioned between ether (20 ml) and water (15 ml). Workup in the usual manner gave an oil. The crude product was chromatographed on silica gel with 1 : 4 ethyl acetate/hexane to give the allylic alcohol (1.36 g, 73%) as a colorless oil: IR (neat, NaCl disc) 3400, 2970, 2920, 2870, 1445, 1380, 1220, 1135, 1055, 950, 865 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.65 (s, 3H), 1.60 (m, 2H), 2.10 (m, 2H), 3.92 (s, 4H), 3.97 (s, 2H), 5.40 (t, J=7 Hz, 1H); MS m/e (relative intensity) 87 (56), 169 (100).

7-Chloro-6-methyl-5(E)-hepten-2-one ethylene acetal (11)

A Stirred mixture of 7-hydroxy-6-methyl-5(E)-hepten-2-one ethylene acetal (988 mg, 5.31 mmol) and 2,4,6-collidine (926 μl, 7 mmol) under nitrogen was treated with lithium chloride (550 mg, 13 mmol) dissolved in a minimum amount of dry dimethylformamide. On cooling to 0℃, a suspension was formed which was treated dropwise with methanesulfonyl chloride (565 μl, 7.31 mmol). Stirring was continued at 0℃ for 1.5 h. The pale yellow reaction mixture was poured over ice-water. The aqueous layer was extracted three times with pentane and the combined extracts were washed successively with saturated copper nitrate solution. This was continued until no further intensification of the blue copper solution occurred, indicating complete removal of s-collidine. The organic extracts were dried (Na_2SO_4) and concentrated at room temperature to afford the allylic chloride (1.01 g, 94%) as a pale yellow oil: IR (neat, NaCl disc) 2970, 2930, 2870, 1440, 1380, 1260, 1210, 1135, 1055, 940, 870, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.70 (m, 2H), 1.73 (s, 3H), 2.10 (m, 2H), 3.90 (s, 4H), 4.00 (s, 2H), 5.53 (t, J=7.5 Hz, 1H); MS m/e (relative intensity) 169 (100), 203 (2), 205 (3).

(E,E)-Farnesyl bromide (12)

To a solution of farnesol (889 mg, 4 mmol) in dry hexane (6 ml) was added PBr_3 (541 mg, 2 mmol) at 0℃ under the atmosphere of nitrogen. The mixture was stirred at this temperature for 30 min, then a few drops of methanol was added. The reaction mixture was washed with cold saturated $NaHCO_3$ solution and cold brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford farnesyl bromide (1.23 g, 98.9%) as a colorless oil. Farnesyl bromide obtained was used for the next reaction without purification: IR (neat, NaCl disc) 1665, 1455, 1380, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6 and 1.7 (s, 12H), 2.1 (br s, 8H), 3.97 (d, J=7 Hz, 2H), 5.10-5.46 (m, 3H).

(E,E)-Farnesyl phenyl sulfone (13)

A solution of (E,E)-farnesyl bromide (1.14 g, 4.0 mmol) in anhydrous DMF (11 ml) was treaed with benzenesulfinic acid Na salt (1.20 g, 7.3 mmol), and the mixture was stirred under the atmosphere of nitrogen for 20 h. It was then diluted with water (30 ml) and extracted with ether (15 ml×2). The extract was washed with brine, dried over $MgSO_4$ and evaporated to give the crude product as a pale yellow oil. Chromatography of the crude product on a silica gel column (1:10 ethyl acetate/hexane) gave the title compound (0.85 g, 61%) as a colorless oil: IR (neat, NaCl disc) 1450, 1305, 1160, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.60 (s, 3H), 1.69 (s, 6H), 2.08 (br s, 8H), 3.80 (d, J=7 Hz, 2H), 5.10 (m, 2H), 5.20 (t, J=7 Hz, 2 H), 7.50 (m, 3H), 7.85 (m, 2H); MS m/e (relative intensity) 346 (M^+, 1), 205 (100).

6,10,14,18-Tetramethyl-8-(phenylsulfonyl)-5,9,13,17(E,E,E)-nonadecatetraen-2-one ethylene acetal (14)

To a cooled (0℃) suspension of NaH (60%, 48 mg, 1 mmol) in anhydrous DMF (7 ml) was added (E,E)-farnesyl phenyl sulfone (346 mg, 1 mmol) in anhydrous DMF (1 ml) at 0℃ under the atmosphere of nitrogen. The mixture was then stirred at RT for 30 min and

treated with 7-chloro-6-methyl-5(E)-hepten-2-one ethylene acetal (205 mg, 1 mmol) in anhydrous DMF (1 ml). After stirred at RT for 5 h, the resulting mixture was quenched with a 5% HCl solution with vigorous stirring. The reaction mixture was subjected to extractive workup with ether (20 ml×3). Chromatography of the crude product on silica gel (1 : 4 ethyl acetate/hexane) gave the title compound **14** (324 mg, 63%) as a colorless oil: IR (neat, NaCl disc) 2970, 2920, 2870, 1440, 1380, 1310, 1220, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.36 (s, 3H), 1.60 (s, 6 H), 1.73 (s, 6H), 1.90-2.23 (m, 14H), 3.76-4.20 (m, 1H), 3.96 (s, 4 H), 4.90-5.33 (m, 4H), 7.55 (m, 3H), 7.86 (m, 2H); MS m/e (relative intensity) 514 (M^+, 1), 373 (21), 272 (100), 67 (80).

6,10,14,18-Tetramethyl-5,9,13,17(E,E,E)-nonadecatetraen-2-one ethylene acetal (15)

A mixture of compound **14** (514 mg, 1 mmol) and disodium hydrogen phosphate (568 mg, 4 mmol) was dissolved in anhydrous MeOH (50 ml). To this solution, cooled at −10℃ and kept under the atmosphere of nitrogen, was added 6% Na(Hg) (1.5 g, 4 mmol) in one portion. The resulting mixture was stirred for 20 min at −10℃, followed by quenching with a saturated NH_4Cl solution and extraction with ethyl ether. The combined extracts were washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and then concentrated under reduced pressure. The crude residue obtained was chromatographed on silica gel with 1 : 16 ethyl acetate/hexane to furnish the title compound (307 mg, 82%) as a colorless oil: IR (neat, NaCl disc) 2970, 2870, 1440, 1380, 1210, 1135, 950, 865 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.58 (s, 12H), 1.68 (s, 3H), 1.98-2.26 (m, 16H), 4.0 (s, 4H), 5.02-5.18 (m, 4H).

6,10,14,18-Tetramethyl-5,9,13,17(E,E,E)-nonadecatetraen-2-one (1)

To a solution of ethylene acetal **15** (420 mg, 1.03 mmol) in acetone (5 ml) was added 50% aqueous phosphoric acid (0.4 ml). The resulting solution was refluxed for 3 h, diluted with water, and subjected to extractive workup with dichloromethane (20 ml×3). Chromatography of the crude product on silica gel (2 : 98 ethyl acetate/benzene) gave geranylgeranyl acetone (365 mg, 98%) as a colorless oil: IR (neat, NaCl disc) 1690, 1660, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (s, 12H), 1.68 (s, 3H), 1.98-2.13 (m, 15H), 2.26-2.54 (m, 4H), 5.02-5.18 (m, 4H); MS m/e (relative intensity) 330 (M^+, 5), 273 (40), 272 (30), 261 (50), 67 (100).

RESULTS AND DISCUSSION

The oxidation of compound **4** and **9** with selenium dioxide in refluxing ethanol(Meinwald *et al.*, 1973) gave unsatisfactory results. A modified procedure, developed by Umbreit and Sharpless (1977), involving t-butylhydroperoxide and a catalytic or stoichiometric, amount of selenium dioxide was then employed. It was hoped that the mild reaction conditions of this modification might alleviate the complications encountered in using excess selenium dioxide and refluxing ethanol. Indeed, by treating compound **4** (2 eq) and **9** (2 eq) with selenium dioxide (0.5 eq) and 70% t-butylhydroperoxide in dichloromethane (5 h, 10℃), the allylic alcohol **5** and **10** were obtained in 41% and 73% respectively. Careful monitoring of the reaction conditions was crucial for good results, as higher temperatures and prolonged reaction times led to significant formation of the aldehyde product and less efficient conversion into the desired alcohol.

Several methods were tried to convert the hydroxyl group in compound **5** and **10**, into a leaving group appropriate for the condensation of phenyl sulfone compound **3** and **13**, respectively. Many procedures failed to give satisfactory and reproducible results. However, the difficulty was circumvented for the preparation of chloride **6** and **11**, by adopting Meyers, procedure (Collington and Meyers, 1971). The procedure involved treating a mixture of alcohol and s-collidine under nitrogen with lithium chloride and methanesulfonyl chloride at 0℃ and allowing the reaction mixture to warm to RT. The chloride **6** and **11**, owing to their unstable nature were used immediately to condensate with geranyl phenyl sulfone (**3**) and farnesyl phenyl sulfone (**13**), respectively.

By employing phenyl sulfone synthesis developed earlier (Kondo *et al.*, 1975), we were able to synthesize geranyl phenyl sulfone (**3**) and farnesyl phenyl sulfone (**13**) as shown in Scheme 1 and Scheme 2.

Incorporation of isoprene moiety was effected by the condensation of phenyl sulfone compound (**3**, **13**) and allylic chloride (**5**, **6**) to give compound **7** and compound **14**, in 61% and 63% yield, respectively.

To complete the synthesis, compound 7 and 14 were desulfonylated with 6% Na(Hg) (Trost *et al.*, 1976, 1978), and then treated with aqueous acid for the removal of ethylene acetal protecting group to give the desired compound **1** in 80.4% yield, respectively.

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