Synthesis and Biological Activity of Geranyloxy Compounds

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Disk assays on the compounds (10 and 12) showed both to have antifungal activity against the dermatophytic fungus *Trichophyton mentagrophytes* ATCC 28185, (1 and 3 mm inhibition zones at 60 μg/disc), but not against the Gram-positive bacterium *B. subtilis* or the Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* or fungi *Cladosporium resinae* and *Candida albicans*. However, the compound (13) did not show against antifungal activity. The geranyloxy compounds (10, 12, and 13) were cytotoxic to P388 murine leukaemia cells ATCC CCL 46 P388D1, (IC_{50} >6,250 ng/mL at 7.5 μg/disc). These results suggest that The geranyloxy compounds possesses antimicrobial and antitumor activities.

Key words : *Trichophyton mentagrophytes*, Antifungal activity

Introduction

Prenylated benzyl ethers are characteristic of *Trichocolea*, having been identified in many *Trichocolea species* from different parts of the world[1-3]. Liverworts of the genus *Trichocolea* are a treasury of isoprenyl phenyl ethers. *Trichocolea hatcheri* Hodgs, which grows throughout New Zealnd, is distinguished from *T. mollissima* by its smaller size, dark green color, and prostrate habit[4]. A chemical abstracts search of *Trichocolea* revealed that only *T. tomentella*[1,5,6], *T. lanata*[1], *T. mollisima*[1,7], *T. hatcheri*[3], and *T. pluma*[8] have been studied for their chemical constituents. Methyl-4-(geranyloxy)-3-hydroxybenzoate (10) tested for its growth inhibitory effects against tumor cell lines(KB, SK-MEL-3) using the MTT method. It showed growth inhibition activity against *Staphylococcus epidermidis* (MIC, 1,000 μg/ml)[9]. In this study, the synthesis and antifungal activity of geranyl phenyl ethers have investigated.

Materials and Methods

1. General experimental procedures

All solvents were distilled before use. Removal of solvents from chromatography fractions were removed by rotary evaporation at temperature up to 40℃. Initial fractionation of crude plant extract using reverse phase column chromatography was performed with octadecyl-functionalized silica gel (C-18 Aldrich) as the adsorbent. Further column fractionation was performed using Davisil silica 60 Å (35-70 μ m silica gel, Allth) as adsorbent. TLC was carried out using Merck DC-plastikfolien Kieselgel 60 F_{254} visualized first with a UV lamp, then by dipping in a vanillin solution (1% vanillin, 1% H_2SO_4 in EtOH) followed by heating. Microanalyses were performed by Marianne Dick and Bob McAllister (Campbel Microanalytical Laboratory, Chemistry Department, University of Otago). MS, UV and IR spetra were recorded on Krato MS-80, Shimadzu UV 240, and Perkin-Elmer 1600 FT-IR instruments respectively. NMR spectra, of $CDCl_3$ solutions at 25℃, were recorded at 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR on a Varian VXR-300 spectrometer. Chemical shifts are given in parts per million on the δ scale referenced to the solvent peak $CHCl_3$ at 7.25 ppm and $CDCl_3$ at 77.08 ppm and are referenced to TMS at 0.00 ppm.

2. Synthesis of 3-methyl-2-butenoyl chloride (2)[2,10]

3-Methyl-2-butenoic acid (1, 14.48 g, 144 mmol) in a flame dried flask under nitrogen, was heated under reflux for 2 hours in thionyl chloride (54.90 g, 460 mmol). On completion of reaction, as shown by IR, the crude product was distilled (100℃/24 mmHg), to give a clear oil (2, 16.72 g, 98%). ^{1}H-NMR Spectrum is identical with those reported previously for the synthetic product. Also, the ^{13}C-NMR spectrum is

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identical with the reported one.

3. Synthesis of 8-chloro-2,6-dimethyl-2,6-octadiene-4-one (3)

3-Methyl-2-butenoyl chloride (2, 4.76 g, 40.17 mmol) in dry CH_2Cl_2 (20 ml) was added to tin (IV) chloride (9.301 g, 35.70 ml) in CH_2Cl_2 (20 ml) with vigorous stirring in a flame dried flask under nitrogen. The temperature was reduced to -78℃, and isoprene (3.53 g, 51.88 mmol) in CH_2Cl_2 (60 ml) was added dropwise over 2 hrs, and the mixture left to stir at -78℃ for a further 0.5 hours. Dried pyridine (15 ml) was added and the mixture stirred for 10 min, then poured into ether (200 ml) and left to stand for 10 min. The pale yellow solid was filtered and washed with ether (100 ml). The filtrate was washed with water (4 x 500 ml), and the water fractions reextracted with ether (200 ml). The combined organic fractions were washed with saturated sodium chloride solution (3 x 500 ml), dried with anhydrous magnesium sulfate, filtered, and evaporated to dryness, Separation by flash chromatography (elution with ethyl acetate - hexane, 5 : 95) yielded 8-chloro-2,6-dimethyl -2,6-octadiene-4-one (3, 6.07 g, 81%). 8-chloro-2,6-dimethyl-2,6-octadiene-4-one (3) was shown to be identical with authentic sample on the basis of comparison of the spectral data (TLC, ^{1}H and ^{13}C-NMR)[2].

4. Synthesis of 8-chloro-2,6-dimethyl-2,6-octadiene-4-ol (4)

8-chloro-2,6-dimethyl-2,6-octadiene-4-one (3, 140 mg, 0.75 mmol) was dissolved in dry tetrahydrofuran (0.25 ml). Absolute ethanol (2.5 ml) was added to the solution. The mixture was cooled to -40℃, and $NaBH_4$ (56.5 mg, 1.5 mmol) was added. The reaction mixture was stirred for 15 min at -40℃, allowed to warm to -10℃, and quenched by the addition of water (50 ml). Ether (25 ml) was added, the organic layer was evaporated to dryness. Separation by flash chromatography (elution with ethyl acetate - hexane, 25 : 75) yielded 8-chloro-2,6-dimethyl-2,6-octadiene-4-ol (4, 45 mg, 32%)[10]. TLC; Rf 0.22 (blue with anisolaldehyde/H_2SO_4); ^{1}H-NMR ($CDCl_3$), δ 1.70 (3H, s, H-10), 1.73 (3H, s, H-8), 1.79 (3H, s, H-9), 2.23 (2H, m, H-4), 4.10 (2H, d, J= 8 Hz, H-1), 4.50 (1H, m, H-5), 5.17 (1H, brd, J=8.0 Hz, H-6), 5.55 (1H, brt, J=8.0 Hz, H-2); ^{13}C-NMR ($CDCl_3$), δ 18.2 (C-10), 22.6 (C-9), 25.7 (C-8), 40.6 (C-1), 47.6 (C-4), 66.5 (C-5), 123.5 (C-6), 127.3 (C-2), 135.3 (C-3), 139.2 (C-7).

5. Synthesis of 6, 7, and 8 (8)[11]

3,4-dihydroxybenzoic acid (5, 3.08 g, 20.0 mmol) in dry acetone (10 ml)was mixed with anhydrous sodium hydrogen carbonate (2.52 g, 30.0 mmol) and dimethyl sulfate (2.78 g, 22.0 ml) and was heated gently under reflux. On completion of the reaction, as shown by TLC, the solvent was removed under reduced pressure, the reside stirred with cold water and chloroform, the separated ester was filtered, washed and dried. The residue was chromatographed on flash chromatography (20% EtOAC / Hex. to afford methyl-4-methoxy-3-hydroxybenzoate (6, 2.88 g, 39.6%); TLC R_f 0.44 (UV, 40% EtOAC /Hex. 2 times); IR (film), 3409, 2952, 1719, 1700, 1592, 1514, 1413, 1285, 1221, 1128, 1025, 989, 891, 763 cm^{-1}.; ^{1}H-NMR ($CDCl_3$), δ 7.54 (1H, ddd, J=6.6 Hz, H-6), 7.49 (1H, dd, J=7.2 Hz, H-2), 6.82 (1H, dd, J=19.8 Hz, H-5), 3.82 (3H, s, CH3), 3.81 (3H, s, CH_3); ^{13}C-NMR ($CDCl_3$), 51.7 (C-8), 55.7 (C-9), 109.9 (C-5), 115.5 (C-2), 122.5 (C-1), 122.8 (C-6), 145.1 (C-3), 150.6 (C-4), 166.9 (C-7). Methyl-3,4-dimethoxybenzoate (7); Yield (0.2%); TLC R_f 0.52 (UV, 40% EtOAC / Hex. 2 times), IR (Nujol), 1775, 1594, 1519, 1464, 1414, 1377, 1291, 1271, 1228, 1187, 1137, 1107, 1035, 1018, 991, 889, 870, 815, 762, 725 cm^{-1}.; ^{1}H-NMR ($CDCl_3$), δ 7.61 (1H, dd, J=8.2 Hz, H-6), 7.52 (1H, d, J=2 Hz, H-5), 6.86 (1H, d, J=9 Hz, H-2), 3.90 (2 x 3H, s, CH3), 3.87 (3H, s, CH3),; ^{13}C-NMR ($CDCl_3$), δ 51.9 (C-8), 55.9 (C-9, C-10), 110.2 (C-5), 111.9 (C-2), 122.6 (C-1), 123.5 (C-6), 148.5 (C-4), 152.9 (C-3), 166.7 (C-7). Methyl-3,4-dihydroxybenzoate (8, 3.69 g); Yield (55%); TLC R_f 0.25 (UV, 40% EtOAC / Hex. 2 times), mp. 124-126 oC, IR (Nujol), 3466, 1684, 1610, 1533, 1456, 1377, 1129, 1185, 1090, 984, 910, 764, 721 cm^{-1}.; ^{1}H-NMR ($CDCl_3$), δ 7.61 (1H, brs, H-6), 7.57 (1H, d, J=2 Hz, H-2), 6.92 (1H, d, J=8 Hz, H-5), 5.88 (1H, brs, 4-OH), 5.78 (1H, brs, 3-OH), 3.89 (3H, s, CH3); ^{13}C-NMR ($CDCl_3$), δ 52.1 (C-8),114.8 (C-5), 116.5 (C-2), 123.8 (C-1), 124.6 (C-6), 140.4 (C-4), 148.6 (C-3), 167.1 (C-7).

6. Synthesis of methyl-3-methoxy-4-hydroxybenzoate (9)

3-Methyl-4-hydroxybenzoic acid (5, 10.61 g, 63 mmol), and sodium bicarbonate (8.10 g, 96 mmol) in acetone (50 ml) was heated under reflux with dimethyl sulphate (8.73 g, 69 mmol) for 48 hrs. On completion of the reaction, as shown by TLC, solvent was removed under reduced pressure, to give a brown oil. Ice cold water (50 ml) was added and vigorously stirred for two hours to give a pale solid (9, 9.20 g, %) which was collected by filtration. Methyl-3- methoxy-4-hydroxy-benzoate (9) was shown to be identical with authentic sample on the basis of comparison of the spectral data (TLC, ^{1}H and ^{13}C-NMR)[2].

7. Synthesis of methyl-4-[{(2E)-3,7-dimethyl-2,6-octadienyl}oxy] -3-hydroxy- benzoate (10)

Methyl-3,4-dihydroxybenzoate (8, 278 mg, 1.65 mmol); geranyl bromide (434 mg, 2.00 mmol); NaH (60%, 66 mg, 1.65 mmol) in dry DMF (2 mL); 0℃; 17 hrs; flash chromatography (5% ethyl acetate - hexane) gave 10 (220 mg, 44%). Also

isolated was methyl-3,4-di-[{(2E)-3,7-dimethyl-2,6-octadienyl} oxy]-benzoate (11, 130 mg, 18%). Compounds (10, 11) were identified by comparing its spectral data (TLC, MS, NMR and IR) with those published or by directly comparing it with an anthentic sample[3].

8. Synthesis of methyl-4-[{(2E)-3,7-dimethyl-5-hydroxy-2,6-octadienyl}oxy]-3- methoxybenzoate (12)

Methyl vanillate (9, 88 mg, 0.48 mmol); 8-chloro-2,6-dimethyl-2,6-octadien-4-ol (4, 110 mg, 0.58 mmol); NaH (60%, 19.2 mg, 0.48 mmol) in dry DMF (0.5 mL); 20℃; 26 hrs. Flash chromatography (5% ethyl acetate - hexane) gave 12 (125 mg, 78%); colorless oil; TLC R_f 0.13 (blue with anisaldehyde - H_2SO_4); anal. C 68.26%, H 7.64%, cald for $C_{19}H_{26}O_5$, C 68.26%, H 7.78%. Compounds (12) was identified by comparing its spectral data (TLC, MS, NMR and IR) with those published or by directly comparing it with an anthentic sample[3].

9. Synthesis of methyl-4-[{(2E)-3,7-dimethyl-5-oxo-2,6-octadienyl} oxy]-3- methoxybenzoate (13)

Pyridinium chlorochromate-alumina[12] (1,402 mg, 1.14 mmol) was added to solution of 13 (127 mg, 0.38 mmol) in dry hexane (10 mL). After stirring for 24 hrs, the mixture was filtered and washed with Et_20 (3 X 10 ml). The combined Et_20 solutions were evaporated. Flash chromatography (elution with ethyl acetate - hexane 5 : 95) yielded 13 (37.8 mg, 30%). Compound (13) was identified by comparing its spectral data (TLC, MS, NMR and IR) with those published or by directly comparing it with an anthentic sample[3].

10. Disk diffusion assays.

The microorganisms used were: *Bacillus subtilis* (ATCC 19659), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Cladosporium resinae* (ATCC 52833), *Candida albicans* (ATCC 14053) and *Trichophyton mentagraphytes* (ATCC 28185) were performed by Gill Ellis at the Chemistry Department, University of Canterbury, Christchruch[13]. Solutions of samples for assay were dried onto 6 mm filter paper disks, which were then placed onto seeded agar Petri dishes and incubated. Activity was observed as a zone of inhibition around the disk, with its width recorded from the edge of the disk in mm. HM and SM refer to the observed margin surrounding the zone of inhibition. (H= hazy, S= sharp).

Results and Discussion

For the synthesis of methyl-4-[{(2E)-3,7-dimethyl-2,6-octadienyl}oxy]-3- hydroxybenzoate (10) (Fig. 1) we followed a modification of the method descirbed by Baek[3], which mainly consists of condensing methyl-3,4-dihydroxybenzoate (7) with geranyl bromide in the presence of sodium hydride in dry dimethylformamide. Here we described the preparation of 13, along with syntheses of two less-oxidized geranyl ethers, 13 and methyl-4-[{(2E)-3,7-dimethyl-2,6-octadienyl}oxy]-3-methoxybenzoate (12) which we have isolated from *T. tomentella* (Ehrh.) Dum[1]. and *T. hatcheri* Hodgs.[14], respectively. The key intermediate in the synthesis of 13 is a geranyl halide that has appropriate functionality at C-5 and is suitable for alkylating methyl vanillate (9). The inexpensive and commercially available 3-methyl-2-butenoic acid (1) is readily converted into its acid chloride by reaction with excess thionyl chloride[15]. This compound (1) has been converted previously into 8-chloro-2,6- dimethyl-2,6-octadiene-4-one (3). This compound (3) was reduced to 8-chloro-2,6-dimethyl-2,6-octadiene-4-ol (4). 8-chloro-2,6-dimethyl-2,6-octadiene-4-ol (4) could be reacted satisfactorily with methyl vallate (9) to yield the methyl-4-[{(2E)-3,7-dimethyl-5-hydroxy-2,6-octadienyl}oxy] -3-methoxy benzoate(12), which, upon oxidation by pyridinium chlorochromate-alumina[12], formed the desired natural product 13 in about 30% yield (Fig. 1). The details on the syntheses will be published elsewhere.

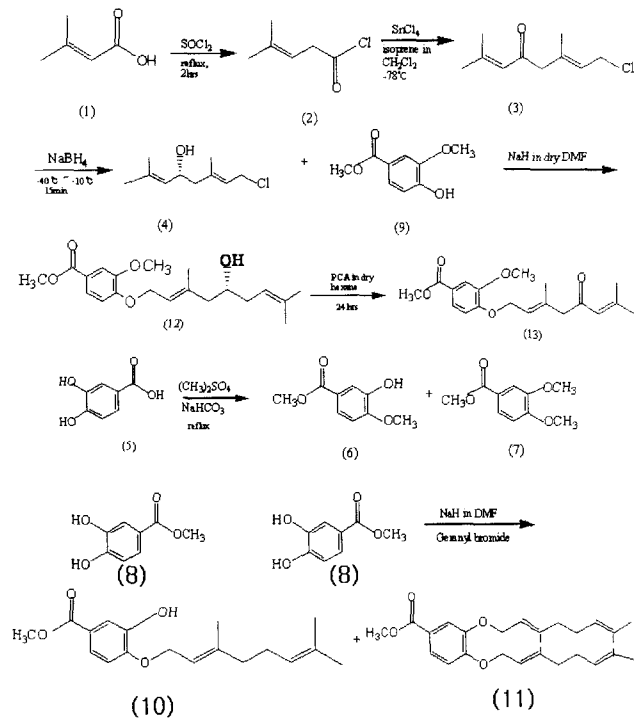

Fig. 1. Synthesis of geranyloxy compounds

Methyl-4-[{(2E)-3,7-dimethyl-2,6-octadienyl}oxy]-3-hydroxybenzoate (10) which isolated from *T. hatcheri* is

cytotoxic to P388 murine leukaemia cells ATCC CCL 46 P388D1 (IC_{50} > 6,250 ng/mL at 7.5 μg/disc) and BSC monkey kidney cells (25% activity, at 15 μg/disc). As indicated in Table 1, disk assays on the compounds (10 and 12) showed both to have activity against the dermatophytic fungus *Trichophyton mentagrophytes* ATCC 28185, (1 and 3 mm inhibition zones at 60 μg/disc), but not against the Gram-positive bacterium *B. subtilis* or the Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* or fungi *Cladosporium resinae* and *Candida albicans*. However, the compound (13) did not show against antimicrobial activity. Methyl-4-(5'-hydroxygeranyloxy)-3-methoxybenzoate (12) is stronger antifungal activity than methyl-4-(geranyloxy)-3-hydroxybenzoate (10) against the dermatophytic fungus *Trichophyton mentagrophytes*. We supposed that the enhancement of antifungal activity of 5'-hydroxy-geranyl group of (12) was stronger than the phenolic OH of (10). The critical features that distinguish this compound (12) are the linking of the 5'-hydroxy-geranyl group to the aromatic ring via an ether linkage. The activities are expressed by the diameter of the developed inhibition zones and compared with those of the widely antibious chloramphenicol, gentamycin and nystatin (Tables 1 and 2)[1,3].

Table I. Biological activity of geranyloxy compounds.

Tested sample	Cytotoxicity					
	BSC[a]	*Herpes simplex virus*[b]		*Polio virus*[b]		
10	+	+		+		
12	+	+		+		
13	+	+		+		
	Antimicrobial activity[c]					
	B.subtilis	*T.mentagrophytes*	*E.coli*	*C.resinae*	*P.aerug*	*C.albicans*
10	-	HM 1	-	-	-	-
12	-	HM 3	-	-	-	-
13	-	-	-	-	-	-
Chloramphenicol	SM 13	0	0	0	0	0
Nystatin	0	SM 7	0	0	0	SM 12
Gentamycin	0	0	SM 10	0	SM 10	0
	P388 Cytotoxicity					
Mitomycin C		53[d]				
10		> 6,250[e]				
12		> 6,250[e]				
13		> 6,250[e]				

[a]% of well showing cytotoxic effects. @0.5 mg/mL, 15 μg/disc: +: 25% activity. [b]Cytotoxicity in antiviral assays. @0.5 mg/mL, 15 μg/disc: Zone of cytotoxic activity: +: 25% activity. [c]Width of zone of inhibition in mm: 60 μg/disc: -: not detected, 0: not determined. Chloramphenicol: 30 mcg/disc, Gentamycin: 30 mcg/disc, Nystatin: 100 unit/disc. HM: Hazy margin, SM: Sharp margin, numbers refer to zone of inhibition (mm). [d]Toxicity of sample to P388 murine leukaemia cells ATCC CCL 46 P388D1 in ng/ml at 0.075 μg/disc. P388 : Concentration of the sample required to inhibit cell growth to 50% of a solvent control. [e]Toxicity of sample to P388 murine leukaemia cells ATCC CCL 46 P388D1 in ng/mL at 7.5 μg/disc.

Fig. 2 showed the weak potent cytotoxic activity of synthetic geranyl phenyl ethers against murine leukaemia cells ATCC CCL 46 P388D1. but *Trichocolea hatcheri* ethanol extract showed a dose-dependent inhibition of murine leukaemia cell ATCC CCL 46 P388D1 (150 μg/disc). The cytotoxicity of this ethanol extract were in a dose-dependent manner over the absorbance range of 1.989 to 4.097. The cytotoxic activity of these compounds (10 and 12) was in a dose-dependent inhibition of cell proliferation (30 μg/disc). The compound (10) was rapidly increased when its absorbance was raised from 3.796 to 4.097, but the compound (13) were a little changeable in the MTT assay when its absorbance was raised from control to 4.097. All of these compounds showed a little dose-dependent increase of cell antiproliferation after treatment with these compounds against murine leukaemia cells ATCC CCL 46 P388D1 (7.5 μg/disc).

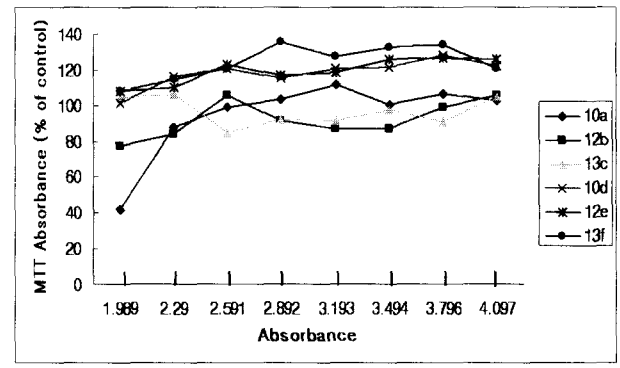

Fig. 2. *In vitro* cytotoxic effect of *Trichocolea hatcheri* ethanol extract and the compounds by the MTT method. These materials were serially diluted in RPMI-1640 with 10% FBS and mixed with equal volume of murine leukaemia cells ATCC CCL 46 P388D1. [a]Toxicity of Trichocolea hatcheri ethanol extract to P388 murine leukaemia cells ATCC CCL 46 P388D1 in ng/ml at 150 μg/disc. [b]Toxicity of compound to P388 murine leukaemia cells ATCC CCL 46 P388D1 in ng/mL at 30 μg/disc. [c]Toxicity of compound to P388 murine leukaemia cells ATCC CCL 46 P388D1 in ng/mL at 7.5 μg/disc. P388 : Concentration of the sample required to inhibit cell growth to 50% of a solvent control. The colorimetric method was performed as described in material and methods. Data are means of results obtained from three sets of experiments.

Table 2. List of microorganisms used for antimicrobial susceptibility test.

Gram-positive bacterium	
Bacillus subtilis	ATCC 19659
Gram-negative bacteria	
Escherichia coli	ATCC 25922
Pseudomonas aeruginosa	ATCC 27853
Fungi	
Cladosporium resinae	ATCC 52833
Candida albicans	ATCC 14053
Trichophyton mentagrophytes	ATCC 28185

Conclusion

In summary, disk assays on the compounds (10 and 12) showed both to have antifungal activity against the

dermatophytic fungus *Trichophyton mentagrophytes* ATCC 28185, (1 and 3 mm inhibition zones at 60 μg/disc), but not against the Gram-positive bacterium *B. subtilis* or the Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* or fungi *Cladosporium resinae* and *Candida albicans*. However, the compound (13) did not show against antifungal activity.

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