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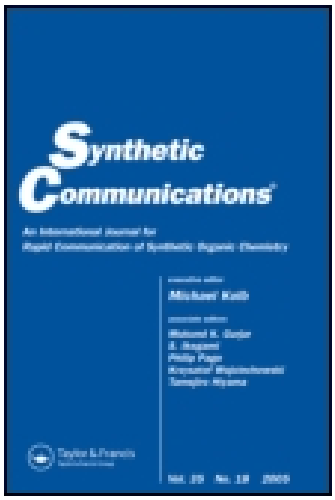

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SYNTHESIS OF NATURALLY OCCURRING DIOSPHENOLS AND HYDROXYDIOSPHENOLS

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SYNTHESIS OF NATURALLY OCCURRING DIOSPHENOLS AND HYDROXYDIOSPHENOLS

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ABSTRACT

Syntheses of diosphenol (**3**), ψ-diosphenol (**4**), 6-hydroxydiosphenol (**5**) and 6-hydroxy-ψ-diosphenol (**6**), which are constituents of the essential oil from *Barosma betulina* Bartl. (mountain buchu), are discussed.

In a recent contribution from our laboratory we communicated the synthesis of the annulated 4-alkylidenebutenolides (**1**) and (**2**) by utilizing the natural occurring diospenols (**3**) and (**4**), respectively, as starting materials.[1]

Steam distillation of the dried leaves of *Barosma betulina* Bartl. (mountain buchu), which is indigeneous to the Western Cape, affords buchu oil in 1–2% yield which contained a 53 : 47 equilibrium mixture of diosphenol (**3**) and ψ-diosphenol (**4**) as well as limonene, pulegone and menthone as major constituents.[2] Buchu oil, which is of substantial commercial value, is utilized for the creation of a well-accepted black currant

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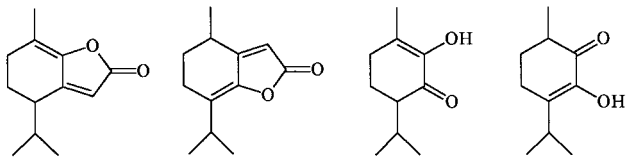
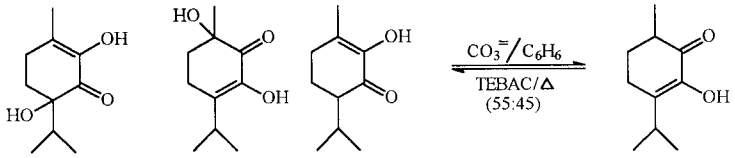


1 2 3 4

flavour and is also highly valued in the fragrance industry due to its characteristic and powerful, fresh odour.[3] Its scarcity prompted Lamparsky and co-workers[3] to undertake a detailed compositional analysis of buchu oil in order to identify the organoleptically significant constituents. These investigations resulted in the identification of 123 components which largely consisted of monoterpenes and included the hydroxydiosphenols (**5**) and (**6**).



5 6 3 4

Pure, crystalline diosphenol (**3**) can be separated from the essential oil from *B. betulina* Bartl. by fractional crystallization,[1] but no convenient method for the isolation of pure ψ-diosphenol (**4**) in useful quantities from natural sources appears to exist. Since ψ-diosphenol (**4**) was in high demand for our synthetic program[1] we decided to undertake a short investigation of viable routes towards the synthesis of (**4**). We have previously demonstrated[1] that pure diosphenol (**3**) can be partially isomerized under weakly basic conditions to yield a 55 : 45 equilibrium mixture of (**3**) and (**4**).[1] Fractional crystallization eventually produced an oily mixture of ψ-diosphenol (**4**) (86%) and diosphenol (**3**) (14%) which could be used for the synthesis of the butenolide (**2**).[1] In an effort to eliminate these tedious separation procedures we decided to investigate other more selective methods for the synthesis of (**4**). Utaka and co-workers[4] reported a procedure for the synthesis of ψ-diosphenol (**4**) via the base-catalyzed bromination of menthone (**7**), but these authors provided no convincing evidence regarding the purification and isolation of crystalline ψ-diosphenol (**4**). In our synthesis of ψ-diosphenol (**4**) the method of Utaka and co-workers[4] was largely followed but was notably improved in various aspects. Carefully controlled bromination of menthone (**7**) was

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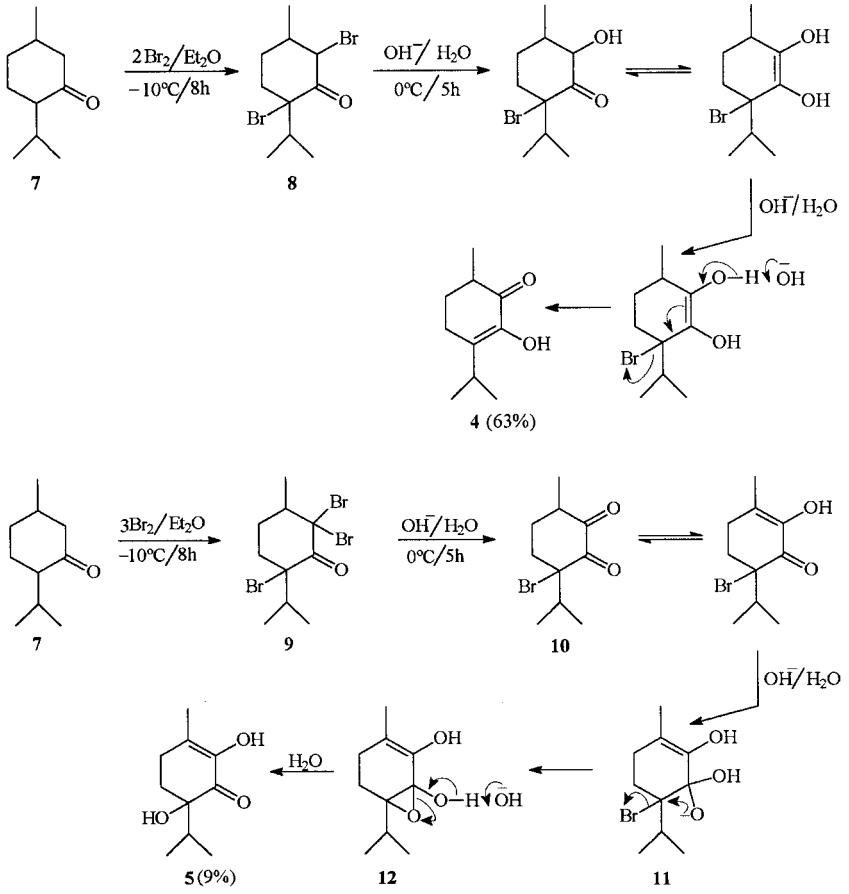

performed at low temperature to yield an intermediate, presumably α,α^1-dibromomenthone (**8**),[4] as an unstable, white solid. Immediate alkaline hydrolysis, followed by separation on a chromatotron and fractional crystallization, furnished pure ψ-diosphenol (**4**) in 63% crystallized yield (m.p. 34.5°C). Although the mother liquor comprised a 23 : 77 mixture of diosphenol (**3**) and ψ-diosphenol (**4**) in a combined yield of 16%, no additional (**4**) could be crystallized. The second eluate from the chromatodisc afforded a small quantity of 6-hydroxydiosphenol (**5**), a known constituent of buchu oil.[3] Our findings differ significantly from those published by Utaka and co-workers[4] who isolated a semi-solid reaction product in 94% yield (b.p. 93–98°C/5 mm Hg), and also did not notice the presence of (**3**) and (**5**)

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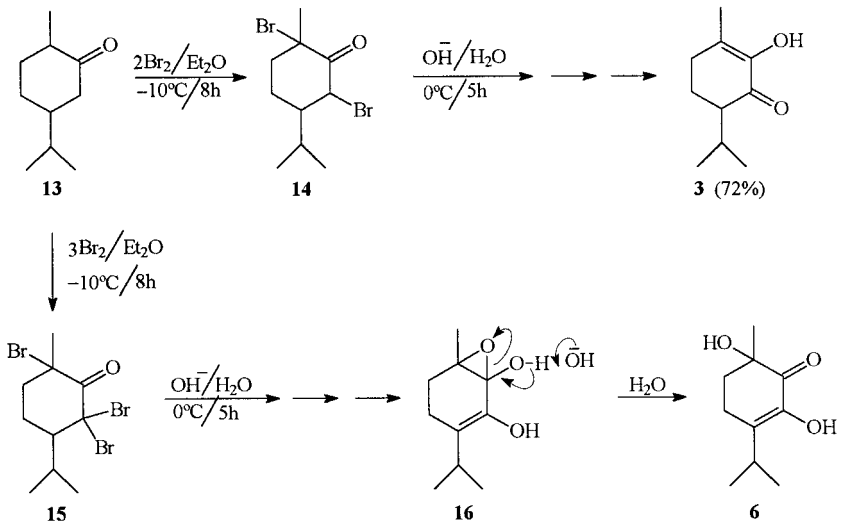
as byproducts. The formation of (**5**) under the above reaction conditions can be rationalized as the results of alkaline hydrolysis of the corresponding tribromo compound (**9**) to afford the enol epoxide (**12**) *via* the bromodiketone (**10**). Base-catalyzed opening of the epoxide ring of (**12**) may lead to the formation of the natural product (**5**).

As a result of the successful synthesis of pure, crystalline ψ-diosphenol (**4**), it was accordingly anticipated that the formation of diosphenol (**3**) could also be accomplished in an analogous fashion by utilizing carvomenthone (**13**) as starting material. Carefully controlled bromination of (**13**) followed by alkaline hydrolysis of the expected dibromoketone (**14**), indeed produced diosphenol (**3**) in good yield after crystallization from hexane. Scrutiny of the reaction mixture by tlc revealed the presence of only traces of the expected 6-hydroxy-ψ-diosphenol (**6**), which was also previously identified[3] as a constituent of natural buchu oil. Formation of (**6**) under these reaction conditions can, in analogy to the formation of the isomer (**5**), be rationalized as the result of alkaline hydrolysis of the tribromoketone (**15**) followed by base-catalyzed rearrangement of the intermediate enol epoxide (**16**).

Both the natural products (**5**) and (**6**) were structurally identified by IR, NMR and MS data[3] but no synthetic methods were reported in the chemical literature. In order to provide some support to the suggested mode of formation of 6-hydroxydiosphenol (**5**) during our synthesis of ψ-diosphenol (**4**), and in the process also establish a viable laboratory



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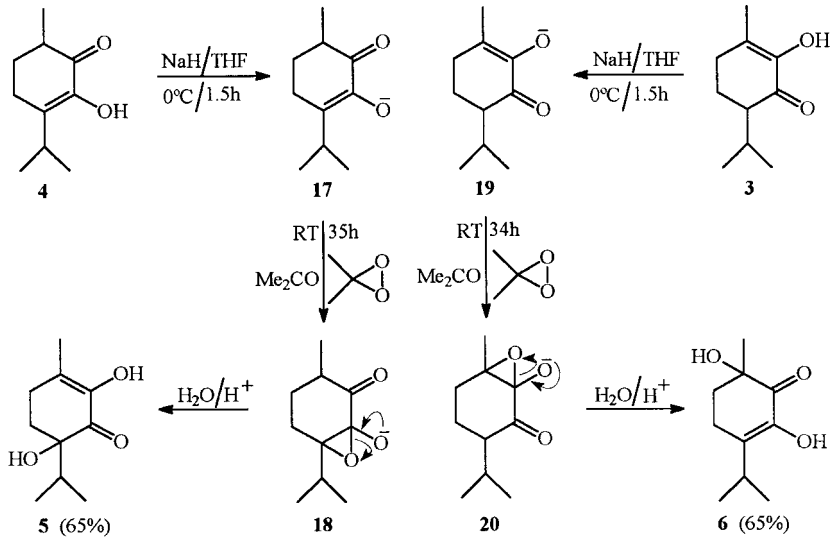
method for the synthesis of (**5**), the preparation of the intermediate enol epoxide (**12**) and its subsequent conversion to (**5**) was next investigated.

Inspired by the synthetic utility of dimethyl dioxirane[5–7] as a versatile oxidant, the epoxidation of the enolate of ψ-diosphenol (**17**) was attempted to synthesize 6-hydroxydiosphenol (**5**) via the formation of the intermediate enol epoxide (**12**) or its corresponding enolate (**18**). Rapid addition of a THF solution of the sodium enolate of ψ-diosphenol (**17**) to an excess of dimethyl dioxirane in acetone indeed produced the desired product (**5**) in an isolated yield of 65%. Similar treatment of the enolate of diosphenol (**19**) with an excess of dimethyl dioxirane gave 6-hydroxy-ψ-diosphenol (**6**) via the intramolecular nucleophilic ring opening of the intermediate epoxyenolate (**20**).



EXPERIMENTAL

All operations were standard practice performed in an argon atmosphere. NMR spectra were recorded in deuteriochloroform on a Varian VXR 300 instrument, while mass spectra were taken on a Varian MAT 311A spectrometer. COSY, HETCOR and DEPT experiments were performed to interpret more complex NMR spectra. Yields refer to isolated, recrystallized compounds, the purity and structures of which were accurately

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established by NMR, mass spectral and gas chromatographical techniques. Spectral and other physical data of reaction products are reported only in those cases where useful data could not be found in the chemical literature.

Synthesis of ψ-Diosphenol (4) from Menthone (7)[4]. Bromine (29.09 g, 181.8 mmol) was added dropwise during 8 h to a stirred solution of menthone (**7**) (14 g, 90 mmol) in ether (30 cm^3) at −10°C and stirring was maintained for an additional 30 min at this temperature. The reaction mixture was then consecutively washed with saturated, aqueous sodium chloride (50 cm^3), saturated aqueous sodium hydrogen carbonate (2 × 40 cm^3) and finally with saturated aqueous sodium chloride (40 cm^3). The unstable, semi-crystalline residue from the dried ($MgSO_4$) organic phase in THF (30 cm^3) was treated dropwise with 3.02 M aqueous sodium hydroxide (300 cm^3, 0.91 mole) during 1 h at 0°C and stirring was continued for an additional 4 h at 0°C. Evaporation of about one half of the THF yielded a light brown residual liquid which was neutralized to pH 7 by the addition of conc. hydrochloric acid (37% m/m, 110 cm^3) and extracted with ethyl acetate (3 × 100 cm^3). Evaporation of the dried ($MgSO_4$) organic extract at 40°C under reduced pressure furnished an oily, brown residue which was separated on a chromatotron (4 mm chromatodisc, Merck silica gel 60 PF254 with calcium sulphate, activated at 120°C for 5 h) with petroleum ether–ether (4 : 1) as eluent to yield two fractions: (a) a light yellow oil which was crystallized from hexane to produce pure ψ-diosphenol (**4**) (9.54 g, 63%), m.p. 34.5°C (lit.[4] b.p. 93–98°C/5 mm Hg); δ_H 1.04 (d, *J* 7.0 Hz, 3H), 1.07 (d, *J* 6.9 Hz, 3H), 1.18 (d, *J* 6.8 Hz, 3H), 1.64 (dddd, *J* 13.1, 11.9, 8.9 and 6.3 Hz, 1H), 2.04 (''dq'', *J* 13.3, 4.5 and 4.4 Hz, 1H), 2.27 (ddd, *J* 14.5, 8.9 and 4.5 Hz, 1H), 2.28 (ddd, *J* 14.5, 6.3 and 4.4 Hz, 1H), 2.43 (dqd, *J* 11.8, 6.8 and 4.8 Hz, 1H), 3.14 (h, *J* 6.9 Hz, 1H), 6.14 (s, OH); δ_C 15.32 (q, CH_3), 19.54 (q, CH_3), 19.82 (q, CH_3), 22.26 (t, CH_2), 27.89 (d, CH), 30.76 (t, CH_2), 39.76 (d, CH), 138.41 (s, =C<), 141.71 (s, =C-OH), 197.63 (s, >C=O); M^+, 168.1151. Calcd. for $C_{10}H_{16}O_2$: M, 168.1150; (b) 6-hydroxy-diosphenol (**5**) (1.53 g, 9%), m.p. 83.6°C (from hexane/ether, 9 : 1); δ_H 0.75 (d, *J* 6.8 Hz, 3H), 1.02 (d, *J* 6.8 Hz, 3H), 1.90 (dd, *J* 1.5 and 1.0 Hz, 3H), 1.94 (ddd, *J* 13.4, 10.8 and 5.3 Hz, 1H), 1.98 (h, *J* 6.8 Hz, 1H), 2.20–2.30 (m, 2H), 2.45 (dddq, *J* 19.1, 12.1, 4.9 and 1.6 Hz, 1H), 3.22 (s, OH), 5.79 (s, OH); δ_C 16.02 (q, CH_3), 16.88 (q, 2 × CH_3), 27.32 (t, CH_2), 30.60 (d, CH), 32.08 (t, CH_2), 76.40 (s, >C-OH), 131.25 (s, =C<), 141.45 (s, =C-OH), 197.88 (s, >C=O); M^+, 184.1099. calcd for $C_{10}H_{16}O_3$: M, 184.1099.

Synthesis of Diosphenol (3) from Carvomenthone (13). Bromine (15.12 g, 94.6 mmol) was added dropwise during 8 h to carvomenthone (**13**) (6.8 g, 44.16 mmol) in ether (25 cm^3) at −10°C and stirring of the resulting solution was continued for an additional 40 min at −10°C. The reaction mixture was then washed as in **1**, the unstable, waxy residue from the dried

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($MgSO_4$) organic phase in THF (25 cm^3) treated with 3.1 M aqueous sodium hydroxide (194 cm^3, 0.6 mole) during 30 min at 0°C and the reaction mixture stirred for an additional 3 h at 0°C. The reaction mixture was eventually worked up as in **1** to yield a semi-crystalline residue which was recrystallized from hexane to afford pure diosphenol (**3**)[1] (5.3 g, 72%), m.p. 82.5°C (lit.[1] 81.7°C); M^+, 168.1151. Calcd for $C_{10}H_{16}O_2$: M, 168.1150.

6-Hydroxydiosphenol (5). ψ-Diosphenol (**4**) (0.91 g, 5.4 mmol) in dry THF (4 cm^3) was added dropwise during 10 min to a stirred suspension of oil-free sodium hydride (0.14 g, 5.83 mmol) in dry THF (4 cm^3) at 0°C. Stirring was continued for an additional 90 min at 0°C, after which the resulting solution was cooled to −78°C and rapidly added to a preformed solution of 0.073 M dimethyl dioxirane in acetone[8,9] (81.7 cm^3, 5.94 mmol) at −78°C. Stirring of the reaction mixture was maintained at room temp. for 24 h, followed by the addition of a second batch of 0.073 M dimethyl dioxirane in acetone (37.14 cm^3, 2.71 mmol) and continued stirring at room temp. for another 11 h. Evaporation of the volatile material at 25°C under vacuum (25 mm Hg) furnished a residue which was treated with water (10 cm^3) and extracted with ether (3 × 15 cm^3). The residue from the dried ($MgSO_4$) ether extract was separated on a chromatotron as in **1** to yield unreacted ψ-diosphenol (**4**) (0.08 g, 9%) as the first eluate and pure, crystalline 6-hydroxydiosphenol (**5**) (0.65 g, 65%) as the second eluate.

6-Hydroxy-ψ-diosphenol (6). Diosphenol (**3**) (1.0 g, 5.95 mmol) in dry THF (5 cm^3) was added dropwise during 5 min to a stirred suspension of oil-free sodium hydride (0.16 g, 6.66 mmol) in THF (5 cm^3) at 0°C. Stirring was continued for an additional 90 min at 0°C and 15 min at room temp., the resulting grey enolate suspension was cooled to −78°C and rapidly added to 0.043 M dimethyl dioxirane in acetone[8,9] (166.5 cm^3, 7.14 mmol) at −78°C. The reaction mixture was worked up and extracted as in **3** to afford an oily residue which was crystallized from hexane to give white, crystalline 6-hydroxy-ψ-diosphenol (**6**) (0.71 g, 65%), m.p. 75.1°C; δ_H 1.06 (d, *J* 6.9 Hz, 3H), 1.09 (d, *J* 6.9 Hz, 3H), 1.34 (s, 1H), 1.99 (ddd, *J* 13.0, 10.6 and 5.9 Hz, 1H), 2.09 (ddd, *J* 13.0, 7.8 and 3.0 Hz, 1H), 2.30 (ddd, *J* 18.7, 10.6 and 4.8 Hz, 1H), 2.41 (ddd, *J* 18.6, 5.9 and 3.1 Hz, 1H), 3.15 (h, *J* 6.9, 1H), 3.30 (s, OH), 5.88 (s, OH); δ_C 19.53 (q, CH_3), 19.65 (q, CH_3), 20.77 (t, CH_2), 24.32 (q, CH_3), 28.08 (d, CH), 35.41 (t, CH_2), 72.57 (s, >C-OH), 139.82 (s, =C<), 140.53 (s, =C-OH), 197.94 (s, >C=O); M^+, 184.1099. Calcd for $C_{10}H_{16}O_3$: M, 184.1099.

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