SHORT PAPER

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Highly efficient synthesis of the optically active sesquiterpene hydroquinone (+)-zonarol and the sesquiterpene quinone (+)-zonarone†

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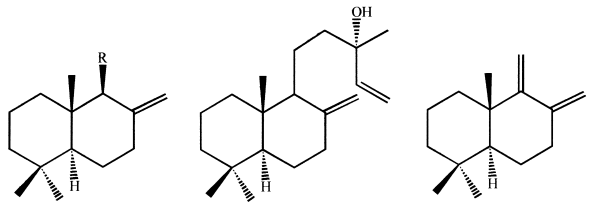
A facile synthesis of the sesquiterpene hydroquinone (+)-zonarol **5** and sesquiterpene quinone (+)-zonarone **6** from manool is reported in 7 and 8 steps, respectively.

Keywords: sesquiterpene, drimane, sesquiterpene hydroquinone, sesquiterpene quinone

A large number of sesquiterpene hydroquinones (and quinones) have been isolated from marine algae and sponges.[1] Sesquiterpene hydroquinones are compounds of mixed biosynthesis, which are constructed from drimane and hydroquinone moieties, and possess a wide range of biological activities.[2] These biologically active sesquiterpene hydroquinones, have been a target for organic synthesis in various laboratories over the past 10 years. Drimanic aldehydes and derivatives have been prepared as intermediates for the synthesis of sesquiterpene hydroquinones.[3a,b] Previously we have reported a new highly efficient synthetic route to the drimane sesquiterpenes (+)-albicanol **1** and (+)-albicanal **2**.[4] In this synthesis the diene **4**, obtained in two steps from manool **3**,[5] was employed as a key intermediate.



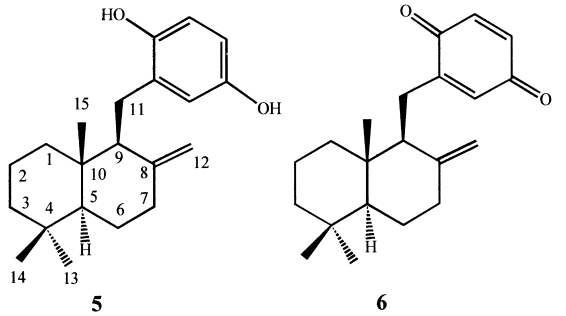
1; R= CH_2OH **3** **4**

2; R= CHO

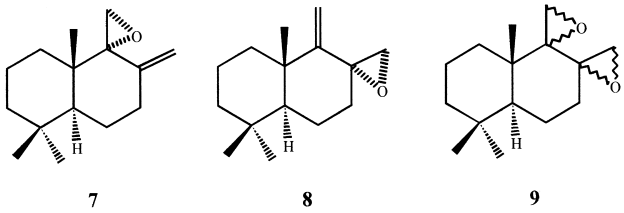
In 1973 Fenical *et al*.[6] isolated (+)-zonarol **5** and (+)-zonarone **6** in very small amounts from the alga *Dictyopteris zonaroides*. In 1993 these compounds were also obtained from same algae by Taniguchi *et al*.[7] and were reported to exhibit a potent feeding-deterrent activity towards the abalone, *Haliotis discus*.

This paper presents a further extension of our work in the synthesis of the sesquiterpene hydroquinone **5** and quinone **6**.

Previously Nakano *et al*.[4] reported that the partial epoxidation of the diene **4** with *m*-chloroperbenzoic acid (MCPBA) afforded monoepoxide **7** (76%), monoepoxide **8** (7%) and stereoisomeric diepoxide **9** (7%). In this synthesis monoepoxide **7** was required as a key starting material. We have modified the reaction conditions and obtained the monoepoxide **7** (84% yield based on reacted starting material) along with 44% of recovered starting material and only small amounts of monoepoxide **8** and stereoisomeric diepoxide **9**. The monoepoxide **7** was isomerised with magnesium bromide in benzene



5 **6**



7 **8** **9**

to (+)-albicanal **2** (67 %) according to the method reported earlier. [4]

The nucleophilic addition of the organolithium compound, derived from hydroquinone, to the aldehyde **2**, was first attempted, using the di-TBS-ether of hydroquinone, but without success. Therefore, we prepared the di-THP-ether of hydroquinone[3b] and tried to couple it with the aldehyde **2** in the presence of *n*-butyllithium, affording a mixture of isomeric benzyl alcohols **10** (90% yield), as shown by the ^{1}H NMR spectrum.

Reduction of the hydroxyl group of the benzyl alcohol **10** with ionic hydrogenation reaction[8] afforded a complex mixture of products. In 1981, Morita *et al*.[9] reported deoxygenation of alcohols with a chlorotrimethylsilane/NaI/zinc system, but this method failed to reduce the alcohol **10**. Reduction with $Li/NH_3/NH_4Cl$[3b, 10] gave a good result, yielding the desired compound **11** in 93 % yield. Deprotection of the THP group with pyridinium *p*-toluenesulfonate[11] gave a (+)-zonarol **5** in 86% yield, whose physical and spectroscopic properties were identical to those reported.[6, 7]

(i) di-THP ether of hydroquinone, *n*-BuLi, THF, 0°C; (ii) $Li/NH_3/NH_4Cl$, THF, –78°C; (iii) TPPA, EtOH; (iv) Jones, acetone

The β stereochemistry of the 11-CH_2 group of this compound was confirmed by a NOESY experiment, which

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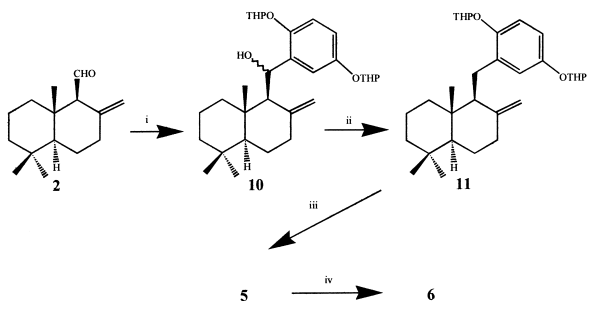
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.



showed NOE cross peaks between 11-CH_2 (δ 2.67), 15-CH_3 (δ 0.78) and 12-H_A (δ 4.66) (see Fig. 1).

Oxidation of compound **5** with Jones reagent[12] afforded (+)-zonarone **6** (97 %), whose physical and spectroscopic data were identical to those reported.[6, 7]

Experimental

Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded with a Bruker Advance-300 and Advance-500 spectometers for solutions in $CDCl_3$. Electron-impact mass spectra (EIMS) and high-resolution mass spectra (HRMS) were obtained on a ZAB HS or Nermag R 10-10 mass spectrometer. The intensity of each peak in the mass spectrum relative to the base peak is reported in parentheses. Rotations were measured at 24°C with a Zeiss '0.01°' polarimeter. THF, ether, and benzene were freshly distilled from sodium benzophenone before use. All other solvents and reagents were obtained from commercial suppliers and were used without further purification. Merck silica gel (70–230 mesh ASTM) was used for column chromatography. TLC was performed on Analtech silica gel 60 G254 and the spots were observed either by exposure to iodine or by UV light. All organic extracts were dried over anhydrous sodium sulphate and evaporated under reduce pressure below 60°C.

Partial epoxidation of the diene **4** *with MCPBA*: To a solution of diene **4** (0.314 g, 1.5 mmol) in CH_2Cl_2 was added small portions MCPBA (0.479 g, 1.5 mmol) at –10°C. After 3 h the reaction mixture was filtered through a small amount of silica gel to remove precipitates. Evaporation of the filtrate gave a crude product, which was chromatographed over silica gel. Elution with hexane yielded unreacted diene **4** (0.137 g, 44% of recovery). Elution with 2% ether in hexane afforded the monoepoxide **7** as an oil (0.161 g, 84% based on reacted starting material); δ_H (300 MHz) 0.81 (3H, s, CH_3-14), 0.87 (3H, s, CH_3-13), 0.97 (3H, s, CH_3-15), 2.84 (2H, AB system *J* 4.6 Hz, CH_2O), 4.73 (1H, m, $=CH_2$) and 4.84 (1H, m, $=CH_2$); δ_C (75.45 MHz) 18.33 (C-2), 19.20 (C-15), 21.80 (C-14), 23.05 (C-6), 30.88 (C-1), 32.92 (C-13), 33.48 (C-4), 33.95 (C-7), 37.86 (C-10), 41.58 (C-3), 48.62 (C-11), 49.68 (C-5), 68.05 (C-9), 110.33 (C-12) and 146.39(C-8). Elution with 5% ether in hexane yielded only small amounts of monoepoxide **8** and stereoisomeric diepoxide **9**. Prolongation of the reaction time for more than 3 h did increase the amounts of stereoisomeric diepoxide **9**.

Isomerisation of the monoepoxide **7** *with magnesium bromide*: The monoepoxide **7** (0.103 g, 0.4 mmol) in dry benzene (5 ml) was refluxed gently with magnesium bromide (0.103 g, 0.5 mmol) for 30 min. The product was extracted with ether and then chromatographed over silica gel. Elution with 1% ether in hexane afforded the aldehyde **2** (69 mg, 67%) as an oil; HRMS *m/z* 220.1835 (M^+, $C_{15}H_{24}O$ requires 220.1827); δ_H (300 MHz) 0.82 (3H, s, CH_3-14), 0.84 (3H, s, CH_3-13), 1.11 (3H, s, CH_3-15), 1.9-2.4 (2H, m, CH_2-7), 2.42 (1H, m, CH-9), 4.45 (1H, bs, $=CH_2$), 4.87 (1H Bs, =CH2) and 9.83 (1H, d, J 3 Hz, CHO); δ_C (75.45 MHz) 15.90 (C-15), 18.70 (C-2), 21.90 (C-14), 23.00 (C-6), 33.43 (C-13), 33.36 (C-4), 33.60 (C-7), 38.90 (C-10), 39.80 (C-1), 41.80 (C-3), 53.90 (C-5), 67.80 (C-9), 109.20 (C-12), 145.00 (C-8) and 205.77(C-11).

Coupling of the aldehyde **2** *with di-THP of hydroquinone*: To a cooled solution of the di-THP ether of hydroquinone (0.247g, 0.88 mmol) in dry THF (3 ml) at 0°C, was added *n*-butyllithium (0.55 ml, 1.6M in hexane). The resulting yellow solution was stirred for 15 min. at 0°C and then slowly warmed to room temperature, stirred for 5 min. and then a solution of aldehyde **2** (0.110 g, 0.5 mmol) in THF (2 ml) was added. The mixture was stirred for an additional 1 h, saturated aqueous NH_4Cl solution was added and extracted with ether. The solvent was evaporated under pressure and the product was chromatographed over silica gel. Elution with 30% chloroform in hexane afforded compound **10** (0.225 g, 90 %); HRMS *m/z* 498.3936 (M^+, $C_{31}H_{46}O_5$ requires 498.3345); δ_H (300 MHz) 0,80 (3H, s, CH_3), 0.82 (3H, s, CH_3), 0.84 (3H, s, CH_3), 3.50 (2H, m, THP-group), 3.90 (2H, m, THP-group), 4.92 (1H, bs, $=CH_2$), 5.08 (1H, bs, $=CH_2$), 5.20 (1H, m, 11-CHOH), 5.27 (1H, m, THP-group), 5.45 (1H, m, THP-group), 6.96 (1H, m, aromatics H), and 6.84 (2H, m, aromatics H).

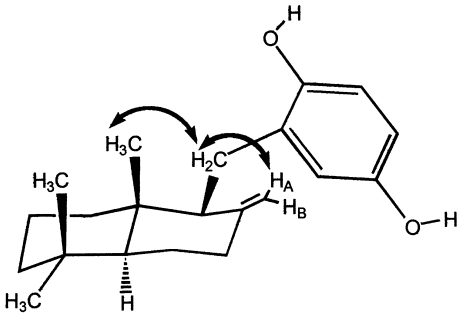


Fig. 1

Deoxygenation of alcohol **10** *with Li/NH_3/NH_4Cl:* A stirred mixture of Li (28 mg, 10 equiv.) in NH_3 (10 ml) and THF (5 ml) at –78°C was added (5 min) to a solution of alcohol **10** (0.2 g, 0.40 mmol) in THF (2 ml) during 5 min. After stirring for an additional 20 min at –78°C, NH_4Cl (0.5 g) was cautiously added to discharge the blue colour, and the NH_3 was allowed to evaporate. After brine was added the product was extracted with ether. The solvent was evaporated under reduced pressure and the product was chromatographed over silica gel. Elution with 10% ether in hexane afforded compound **11** (0.180 g, 93 %); HRMS *m/z* 482.3437 (M^+, $C_{31}H_{46}O_4$ requires 482.3396); δ_H (300 MHz) 0,79 (3H, s, CH_3), 0.81 (3H, s, CH_3), 0.83 (3H, s, CH_3), 2.74 (2H, brd, *J* 6 Hz), 3.54 (2H, m, THP-group), 3.86 (2H, m, THP-group), 4.91 (1H, bs, $=CH_2$), 5.13 (1H, bs, $=CH_2$), 5.26 (2H, m, THP-group), 6.68(1H, m, aromatics H), 6.73 (1H, m, aromatics H), and 7.80 (1H, m, aromatics H).

Deprotection of the compound **11** *with PPTS:* To a solution of compound **11** (0.110 g, 0.2 mmol) in EtOH (2 ml) was added PPTS (0.50 g, 0.19 mmol)at room temperature. This solution was stirred for an additional 2 h at room temperature and then diluted with brine and the product was extracted with ether. The solvent was evaporated under pressure reduced and the product was chromatographed over silica gel. Elution with 40% ether in hexane afforded zonarol **5** as a solid (0.180 g, 93 %); m.p. 152°C (sub.); $[\alpha]_D$ +18° (c 1.4, $CHCl_3$); literature data:[7] m.p. 179–180°C, $[\alpha]_D$ +20.2° (c 0.93, $CHCl_3$); HRMS *m/z* 314.2257 (M^+, $C_{21}H_{30}O_2$ requires 314.2246); EIMS *m/z* 314 (40, M^+), 299 (6), 229 (5), 191 (80), 178 (30), 163 (25), 161 (42), 149 (23), 123 (100), 109 (40), 95 (48), 69 (73), 55 (95), 43 (68); δ_H (300 MHz) 0.78 (3H, s, 15-CH_3), 0.81 (3H, s, 14-CH_3), 0.86 (3H, s, 13-CH_3), 2.67 (2H, brd, *J* 6 Hz, H-11), 4.66 (1H, s, H-12), 4.78 (1H, s, H-12), 6.48 (1H, dd, *J* 8/2.8 Hz, H-4′), 6.58 (1H, d, *J* 2.8 Hz, H-6′) and 6.59 (1H, d, *J* 8 Hz, H-3′); δ_C (75.45 MHz) 14.48 (C-15); δ_C (75.45 MHz) 14.48 (C-15), 19.38 (C-2), 21.71 (C-14), 23.59 (C-11), 24.34 (C-6), 33.60 (C-13), 33.60 (C-4), 38.16 (C-7), 39.12 (C-1), 40.12 (C-10), 42.09 (C-3), 55.60 (C-5), 55.98 (C-9), 107.62 (C-12), 112.89 (C-4′), 115.82 (C-3′), 116.53 (C-6′), 129.79 (C-6′), 147.49 (C-2′), 148.72 (C-8) and 149.02 (C-11).

Oxidation of zonarol **6:** The Jones reagent was added dropwise to a solution of zonarol **5** (50 mg, 0.15 mmol) in acetone (2 ml) at room temperature during 5 min. After decomposing the excess reagent with methanol, the solution was poured onto ice and the product was extracted with ether. The solvent was evaporated under reduced pressure to give zonarone **6** (48 mg, 97 %), as bright yellow crystals. It was recrystallised from methanol to form yellow needles; m.p. 131–132°C; $[\alpha]_D$ +34° (c 1.7, CH_3Cl); literature data[7]: m.p. 129–130°C, $[\alpha]_D$ +34.3° (c 1.00, $CHCl_3$); HRMS *m/z* 312.2120 (M^+, $C_{21}H_{28}O_2$ requires 312.2089); EIMS *m/z* 314 (35, M+2), 312 (52, M^+), 297 (32), 256 (20), 189 (46), 175 (34), 161 (29), 147 (8), 137 (25), 123 (47), 95 (30), 81 (47), 69 (75), 55 (95), 43 (100); δ_H (300 MHz) 0.75 (3H, s, 15-CH_3), 0.79 (3H, s, 14-CH_3), 0.86 (3H, s, 13-CH_3), 1.98 (1H, m, H-9), 2.34 (1H, m, H-7), 2.56 (2H, m, H-11), 4.29 (1H, bs, H-12), 4.75 (1H, bs, H-12), 6.44 (1H, m, H-6′), 6.64 (1H, dd, *J* 9.9/2.4 Hz, H-4′) and 6.72 (1H, d, *J* 9.9 Hz, H-3′); δ_c (75.45 MHz) 14.49 (C-15), 21.69 (C-14), 33.60 (C-13), 54.09 (C-9), 55.56 (C-5), 107.97 (C-12), 132.84 (C-3′), 135.99 (C-5′), 136.85 (C-4′), 149.43 (C-1′), 187.80 (C-2′), and 187.80 (C-6′).

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References

1 D.J. Faulkner, *Nat. Prod. Rep*., 1994, 355.
2 J. Rodriguez, E. Quiñoa, R. Riguera, B.M. Peters, L.M. Abrell and P. Crews, *Tetrahedron*, 1992, **48**, 6667; R. Talpir, A. Rudi, Y. Kashman, Y. Loya and A. Hizi, *Tetrahedron*, 1994, **50**, 4179; S.J. Coval, M.A. Conover, R. Mierzwa, A. King, M.S. Puar, D.W. Phife, J.–K. Pai, R.E. Burrier, M.–S. Ahn, G.C. Boykov, M. Patel, S.A. Pomponi, *Bio. Med. Chem. Lett*. 1995, **5**, 605; S. Chackalamannil, Y. Xia, Y. Wang, M. Tsai, M. Czarniecki, S. Nang, A. Clemmons, H.S. Ahn, G. Boykov, *Biol. Med. Chem. Lett*. 1995, **5**, 2005; S. Urban and R.J. Capon, *Aust. J. Chem*., 1996, **49**, 611; M.A. Belisario, M. Maturo, G. Avagnale, S. De Rosa, F. Scopacasa and M. De Caterina, *Pharmacol. Toxicol*., 1996, **79**, 300.
3 (a) A.F. Barrero, E.J. Alvarez-Manzaneda and R. Chahboun, *Tetrahedron Lett*., 1997, **38**, 8101; A.F. Barrero, E.J. Alvarez-Manzaneda and R. Chahboun, *Tetrahedron*, 1998, **54**, 5635; A.F. Barrero, E.J. Alvarez-Manzaneda, M. Mar Herrador, R. Chahboun and P. Galera, *Bioorg. Med. Lett*., 1999, **9**, 2325; S.C. Welch, A.S.C.P. Rao, *Tetrahedron Lett*., 1977, 505; S.C. Welch, A.S.C.P. Rao, *J. Org. Chem*., 1978, **43**, 1957; K. Mori and M. Komatsu, *Bull. Soc. Chim. Belg*, 1986, **95**, 771; H. Akita, M. Nozawa and H. Shimizu, *Tetrahedron: Asym*. 1998, **1**, 1789; (b) J. Schröder, Ch. Magg and K. Seifert, *Tetrahedron Lett*., 2000, **41**, 5469.
4 T. Nakano, J. Villamizar and M.A. Maillo, *J. Chem. Research (S)*, 1995, 330.
5 T. Nakano, in *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1989, vol 4, p. 403 and refs cited therein; J. Villamizar, *Rev. Latinoamer. Quim*., 1999, **27**, 96.
6 W. Fenical, J.J. Sims, D. Squatrito, R.M. Wing and P. Radlick, *J. Org. Chem*. 1973, **38**, 2383.
7 K. Taniguchi, J. Yamada, K. Kurata and M. Suzuki, *Nippon Suisan Gakkaishi*, 1993, 59, 339.
8 D.N. Kursanov, A.N. Parnes and N.M. Loim, *Synthesis*, 1974, 633.
9 T. Morita, Y. Okamoto and H. Sakurai, *Synthesis*, 1981, 32.
10 G.H. Small, A.E. Minnella and S.S. Hall, *J. Org. Chem*. 1975, **40**, 3151.
11 M. Miyashita, A. Yoshikoshi and P.A. Grieco, *J. Org. Chem*., 1977, **42**, 3772.
12 K. Bowden, I.M. Heibron, E.R.H. Jones and B.C. Weedon, *J. Chem. Soc*., 1946, 39.