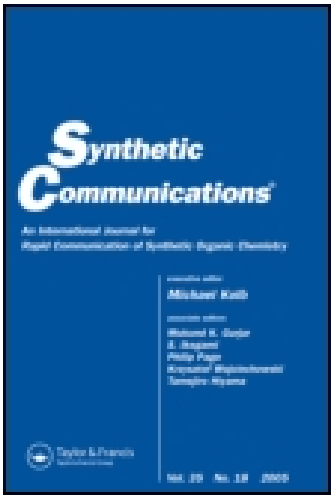

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Abstract: A facile access to optically active (+)-*ent*-chromazonarol *ent*-**1**, isolated from the sponge *Disidea pallescens*, is reported from commercially available (+)-manool **4**.

Keywords: Sesquiterpene, drimane, sesquiterpene hydroquinone, sesquiterpene quinone

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INTRODUCTION

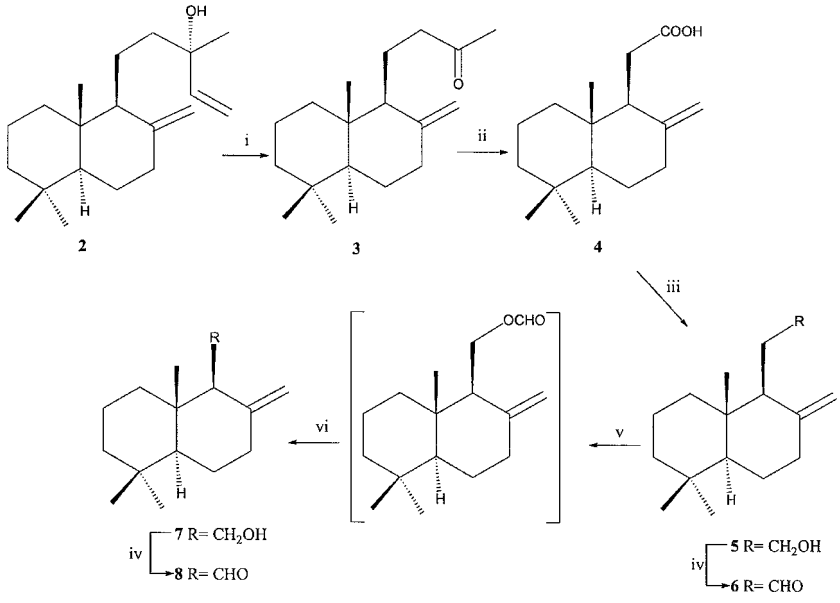
A large number of sesquiterpene hydroquinones (and quinones) have been isolated from marine algae and spongs.[1] Sesquiterpene hydroquinones are compounds of mixed biosynthesis, which are constructed from the combination of a part of sesquiterpenic origin with another part that has a different biogenetic origin, and posses a wide range of biological activities.[2] In 1975 Cimino et al.[3] isolated, from the sponge *Disidea pallescens*, which is a rich source of furan sesquiterpenes, the dextrorotatory (+)-*ent*-chromazonarol ent-**1** with a drimane skeleton. Two years before, in 1973, Fenical and McConnell[4] isolated the levorotatory antipodal isomer (−)-chromazonarol **1** from brown alga *Dictyopteris undulata*, with the rare *ent*-drimane skeleton, along with other fungicidal phenolic isomers.

Drimanic aldehydes and derivatives have been prepared as intermediates for the synthesis of sesquiterpene hydroquinones.[5] Previously we have reported a new synthetic route to sesquiterpene hydroquinones from (+)-manool **2**.[6] In this synthesis the unstable diene, derived in two steps from commercially available (+)-manool **2**, was employed as a key intermediate to obtain drimanic aldehyde albicanal 8.[7] We have recently elaborated a highly efficient synthesis of the optically active labdane-type diterpenes from (+)-manool **2**.[8] The key step in this strategy was the cleavage oxidative of ketone **3** to the acid **4**.[8,9] In the present work we proposed a convenient strategy for the synthesis of optically active sesquiterpene hydroquinones by transformation of homodrimanic acid **4** in the drimanic aldehyde albicanal **8** and confirm the structure proposed for (+)-*ent*-chromazonarol *ent*-**1**.

RESULTS AND DISCUSSION

Oxidative cleavage of ketone **3** with potassium *tert*-butoxide in the presence of oxygen gave an acid **4** with only small amounts of *tert*-butyl ester.[8,9] Reduction of acid **4** with $LiAlH_4$ afforded the alcohol **5**.[8,9] Subsequent oxidation of this alcohol **5** with tetra-*n*-propylammonium perruthenate (TPAP) afforded the aldehyde **6**.[8,10] Baeyer–Villiger oxidation of the alhehyde **6** was effected with rn-chloroperbenzoic acid (Scheme 1).[11] The resulting formiate was immediately hydrolyzed with methanolic potassium hydroxide to the (+)-albicanol **7**. Oxidation of this alcohol **7** with tetra-*n*-propylammonium perruthenate (TPAP)[10] afforded the (−)-albicanal **8** (Scheme 1).

The nucleophilic addition of the organolithium compound, derived from hydroquinone, to the aldehyde **8** was attempted using the di-THP-ether of hydroquinone,[6] in the presence of *sec*-butyllithium, affording a mixture of isomeric benzyl alcohols **9** (93% yield). Separation of these two epimers was not attempted, and their structures were assigned on the basis of their ^1H NMR spectra (Scheme 2).



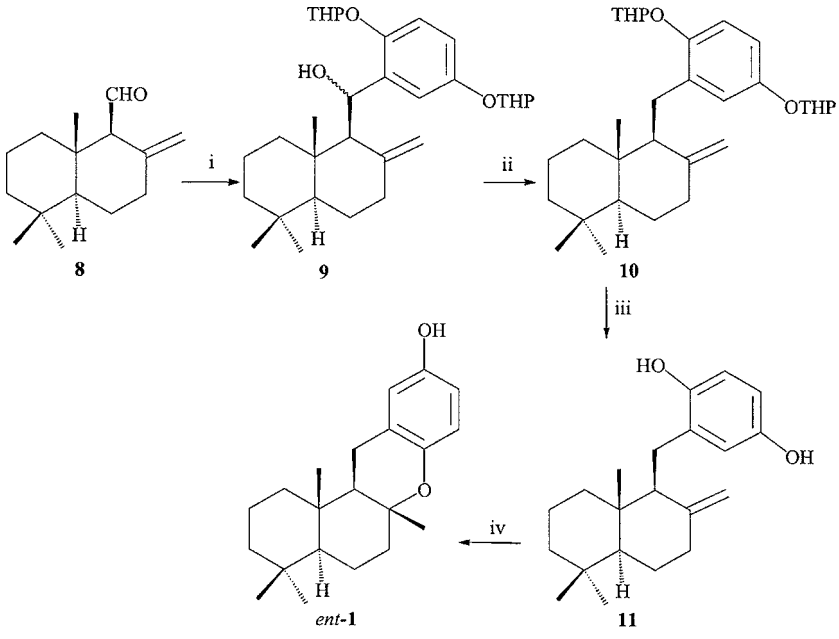
Scheme 1. Reagents and conditions: (i) $KMnO_4$, $MgSO_4$, acetone 20°C, (ii) Potassium *tert*-butoxide, O_2, DME, rt; (iii) $LiAlH_4$, THF, reflux; (iv) TPAP, N-methylmorpholine N-oxide, CH_2Cl_2 (v) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, −78°C, overnight; (vi) 10% methanolic KOH, rt.

Reduction of the hydroxyl group of the benzyl alcohol **9** with $Li/NH_3/NH_4Cl$ yielded the desired compound **10** in 94% yield. Deprotection of the THP group with pyridinium *p*-toluenesulfonate[6] gave an (−)-*ent*-zonarol **11** in 94%, which had spectroscopic data identical to those reported except that the opposite sign for the optical rotation was observed (Scheme 2).[1b]

Treatment of compound **11** with boron trifluoride-etherate afforded almost quantitatively the desired compound *ent*-**1**, whose physical and spectroscopic properties were identical with those reported (Scheme 2).[3] The axial methyl group at C-8 in this compound was confirmed by a nuclear overhauser effect spectroscopy (NOESY) experiment, which demonstrated NOE cross peaks among 15-CH_3 (δ 0.82) and 12-CH_3 (δ 1.15) (Scheme 3). Thus, the absolute configuration of marine *ent*-**1** is 5S, 8R, 9R, 10S.

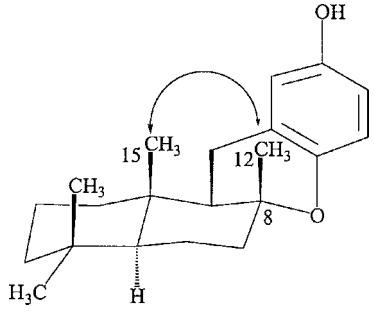
EXPERIMENTAL

Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded with a Bruker Avance-300 and Avance-500 spectrometers. IR spectra were recorded using a Nicolet Magna 560 FT-IR spectrometer. High-resolution mass spectra (HRMS) were



Scheme 2. Reagents and conditions. (i) di-THP ether of hydroquinone, *sec*-BuLi, THF, 0°C; (ii) $Li/NH_3/NH_4Cl$, THF, −78°C; (iii) TPPA, EtOH; (iv) BF_3-Et_2O, CH_2Cl_2, 0°C.

obtained on a ZAB HS or Nennag R 10-10 mass spectrometer, and Kratos MS25RFA. GCIMS spectra were obtained on a Varian Saturn GCIMS 2000. The intensity of each peak in the mass spectrum relative to the base peak is reported in parentheses. Optical rotations were measured at 24°C with Perkin-Elmer 341 polarimeter. Manool resin was purchased from Westchem Industries, Ltd., and purified to obtain (+)-Manool, $[\alpha]_D = +28$



Scheme 3. Stereochemistry at C-8 in *ent*-chromazonarol *ent*-**1** determined by NOESY experiment.

(c 1.5, $CHCl_3$). THF, ether, DME, and benzene were freshly distilled from Na-benzophenone before use. All other solvents and reagents were obtained from commercial suppliers and used without further purification. Merck silica gel (70–230 mesh ASTM) was used for column chromatography. TLC was performed on Analtech silica gel 60 G_{254}, and the spots were observed either by exposure to iodine or by UV light. All organic extracts were dried over Na_2SO_4 and evaporated under reduce pressure below 64 °C.

13,14,15,16-Tetranor-8(17)-labden-12-oic (4)

Potassium *tert*-butoxide (1.48 g, 13.21 mmol) was added to a solution of ketone **3** (2.20 g, 8.39 mmol) in dry DME (10 mL) at room temperature. Oxygen was bubbled through the mixture for 4 h and then diluted with brine, and the product was extracted with ether. The solvent was evaporated under reduced pressure, and the product was chromatographed over silica gel. Elution with 5% ether in hexane yielded only small amounts of *tert*-butyl ester. Elution with 40 % ether in hexane afforded the acid **4** as an oil (1.38 g, 66 %); $[\alpha]_D = -24$ (c 1.9, CH_3Cl); IR (KBr) 2900, 1705, 1650, 890 cm^{-1}; δ_H (300 MHz) 0.66, 0.78, 0.86 (3H each, s, CH_3), 4.51 (lH, s, H-13), 4.75 (lH, s, H-13); δ_C (75.45 MHz) 14.37, 19.21, 21.69, 23.89, 29.67, 30.68, 33.53, 37.46, 38.84, 38.92, 41.95, 52.34, 55.01, 106.47, 148.78, and 180.01; GC/MS m/z 250 (M^+, 52) 235 (100), 233 (19), 191 (30), 153 (34), 137 (79), 95 (55), and 81 (50); HRMS m/z 250.1935 (M^+, $C_{16}H_{26}O_2$ requires 250.2064).

13,14,15,16-Tetranor-8(17)-labden-12-ol (5)

Acid **4** (0.90 g, 3.6 mmol) in THF (4 mL) was added dropwise to a suspension of $LiAlH_4$ (0.30 g, 7.89 mmol) in dry THF (5 mL) at 0°C. This mixture was refluxed for 2 h, and then water was added and extracted with ether. The solvent was evaporated under reduced pressure, and the product was chromatographed over silica gel. Elution with 40% ether in hexane afforded **5** as an oil (0.80 g, 95%); $[\alpha]_D = +28$ (c 2.0, $CHCl_3$), lit.[9] $[\alpha]_D$ +27 (c 2.1, $CHCl_3$); IR (KBr) 3400, 2930, 2850, 1450, 880 cm^{-1}; δ_H (300 MHz) 0.65, 0.77, 0.84 (3H each, s, CH3), 3.48 (lH, m, H-12), 3.68 (lH, m, H-12), 4.50 (lH, bs, H-13), and 4.79 (lH, bs, H-13); δc (75.45 MHz) 14.42, 19.32, 21.64, 24.32, 27.02, 33.53, 33.53, 37.50, 38.19, 39.35, 42.09, 52.80, 55.46, 62.44, 106.33, 148.79; GC/MS m/z 236 (M^+, 67), 221 (57), 203 (43), 177 (94), 137 (100), 95 (98), and 81 (73); HRMS m/z 236.2141 (M^+, $C_{16}H_{28}O$ requires 236.2190).

13,14,15,16-Tetranor-8(17)-labden-12-al (6)

Alcohol **5** (0.1 g, 0.42 mmol) was dissolved in dichloromethane (3 mL) containing both 4 Å molecular sieves (0.200 g) and N-methylmorpholine

N-oxide (117 mg, 0.57 mmol). After stirring the mixture for 10 min, tetra-*n*-propylammonium perruthenate (6.5 mg, 0.0185 mmol) was added, and the reaction was followed by TLC until complete. The reaction mixture was filtered through silica gel and eluted with hexane afforded **6** (83 mg, 8%) as a oil; $[\alpha]_D = +25$ (*c* 1.5, $CHCl_3$), lit.[9] $[\alpha]_D$ +24 (*c* 1.9, $CHCl_3$); IR (KBr) 1724, 1641, 880 cm^{-1}; δ_H (300 MHz) 0.67, 0.78, 0.86 (3H each, s, CH_3), 4.35 (1H, bs, H-13), 4.78 (1H, bs, H-13), and 9.60 (1H, m, H-12); δ_C (75.45 MHz) 14.53, 19.16, 21.66, 23.83, 33.48, 33.48, 37.42, 38.84, 39.29, 39.77, 41.93, 50.89, 55.16, 107.96, 148.47, and 203.50; GC/MS m/z 234 (M^+, 15), 217 (77), 190 (100), 137 (96), 95 (64), and 81 (53); HRMS m/z 234.1985 (M^+, $C_{16}H_{26}O$ requires 234.2010).

Albicanol (7)

$NaHCO_3$ (52.9 mg, 0.63 mmol) was added to a solution of **6** (0.10 g, 0.42 mmol) in CH_2Cl_2 (2 mL). The resulting mixture was stirred at -78°C, and then a solution of MCPBA (0.110 g, 0.64 mmol) in CH_2Cl_2 (3 mL) was slowly added. Stirring was continued at -78°C overnight. Saturated aqueous $NaHCO_3$ solution was added, and mixture was extracted with ether. The solvent was evaporated under pressure to yield the corresponding formiate (0.10 g, 94%), which after treating with 10% methanolic potassium hydroxide (3 mL) at room temperature afforded **7** (84 mg, 95%); mp 72–73°C; $[\alpha]_D = +10$ (*c* 3.9, $CHCl_3$), lit.[7] $[\alpha]_D + 14$ (*c* 3.8, $CHCl_3$); δ_H (300 MHz) 0.69, 0.77, 0.84 (3H, s, CH_3), 2.03 (1H, m, 9-H), 2.40 (2H, m, 7-H), 3.77 (2H, m, CH_2-11), 4.61 (1H, d, $J = 1.5$ Hz, H-12), 4.91 (1H, d, $J = 1.5$ Hz, H-12); δ_C (75.45 MHz) 15.26 (C-15), 19.20 (C-2), 21.71 (C14), 24.20 (C-6), 33.45 (C-4, 33.60 (C-13), 37.86 (C-1), 38.96 (C-7 or C10), 39.00 (C-10 or C-7), 41.97 (C-3), 55.17 (C-5), 58.74 (C-11), 59.17 (C-9), 104.26 (C-12), 147.84 (C-8); HRMS m/z 222.1942 (M^+, $C_{15}H_{26}O$ requires 222.1983).

Albicanal (8)

Alcohol **7** (80 mg, 0.36 mmol) was dissolved in dichloromethane (3 mL) containing both 4 Å molecular sieves (0.200 g) and *N*-methylmorpholine *N*-oxide (63.27 mg, 0.54 mmol). After stirring the mixture for 10 min, tetra-*n*-propylammonium perruthenate (6.3 mg, 0.018 mmol) was added, and the reaction was followed by TLC until complete. The reaction mixture was filtered through silica gel and eluted with hexane to afford **8** (67 mg, 85%) as a oil; $[\alpha]_D = -65$ (*c* 3.5, $CHCl_3$); lit.[7] $[\alpha]_D = -69.8$ (*c* 3.1, $CHCl_3$); IR (KBr) 2720, 1710, 1634, 1465, 880 cm^{-1}; δ_H (300 MHz) 0.83, 0.85, 1.12 (3H each, s, CH_3), 2.11 (2H, m, H-7), 2.42 (1H, m, 9-H), 4.47 (1H, bs, H-12), 4.89 (1H, bs, H-12), 9.84 (1H, d, $J = 3$ Hz, CHO); δc (75.45 MHz)

15.90 (C-15), 21.90 (c-14), 33.43 (c-13), 33.60 (C-7), 38.90 (C-10), 67.80 (C-9), 109.20 (C-12), 205.70 (C-11); HRMS m/z 220.1835 (M^+, $C_{15}H_{24}O$ requires 220.1827).

[2,5-bis-(Tetrahydro-pyran-2-yloxy)-phenyl]-(5,5,8a-trimethy1-2-methylene-decahydro-naphthalen-1-yl)-methanol (9)

sec-Butyllithium (0.54 ml, 1.6 M in hexane) was added to a cooled solution of the di-THP ether of hydroquinone (0.24 g, 0.85 mmol) in dry THF (3 mL) at 0°C. The resulting yellow solution was stirred for 15 min at 0°C, then slowly warmed to room temperature, and stirred for 5 min; then a solution of aldehyde **8** (0.10 g, 0.45 mmol) in THF (2 mL) was added. The mixture was stirred for an additional 1 h, and a 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 **9** (0.210 g, 93%); δ_H (300 MHz) 0.80, 0.82, 0.84 (3H each, s, CH_3), 3.50 (2H, m, THP-group), 3.90 (2H, m, THP-group), 4.92 (1H, bs, H-12), 5.08 (1H, bs, H-12), 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); HRMS m/z 498.3344 (M^+, $C_{31}H_{46}O_5$ requires 498.6938).

(−)-*Ent*-Zonarol di-THP (10)

A stirred mixture of Li (28 mg, 10 equiv.) in NH_3 (10 mL) and THF (5 mL) at −78°C was added to a solution of **9** (0.2 g, 0.40 mmol) in THF (2 mL) over the course of 5 min. After stirring for an additional 20 min at −78°C, NH_4Cl (0.5 g) was cautiously added to discharge the blue color, 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 **10** (0.181 g, 94%); δ_H (300 MHz) 0.79, 0.81, 0.83 (3H each, 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, H-12), 5.13 (1H, bs, H-12), 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); HRMS m/z 482.3394 (M^+, $C_{31}H_{46}O_4$ requires 482.6945).

(−)-*Ent*-Zonarol (11)

A solution of compound **10** (0.10 g, 0.20 mmol) in EtOH (2 mL) was added to 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. The product was extracted with ether. The solvent was evaporated under reduced pressure, and the product was chromatographed over silica gel. Elution with 40% ether in hexane afforded zonarol **11** as a solid (61 mg, 94%); mp 152°C (sub.); $[\alpha]_D = +18$ (*c* 1.4, CH_3Cl); lit.[5] mp 179–180°C, $[\alpha]_D = +20.2$ (*c* 0.93, CH_3Cl); 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, $J = 8$ HZ, 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); 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); HRMS *m/z* 314.2244 (M^+, $C_{21}H_{30}O_2$ requires 314.4622).

Ent-Chromazonarol (*ent*-1)

Boron trifluoride–etherate (22.4 mg, 0.158 mmol) was added, with stirring, to a solution of **11** (25 mg, 0.079 mmol) in CH_2Cl_2 (2 mL) at 0°C. The resulting brown solution was stirred for 5 min at 0°C and then extracted with ether. The solvent was evaporated under reduced pressure, and the product was subjected to column chromatography (hexane/ether 10 : 1) to give compound *ent*-**1** (24.5 mg g, 98%) as colorless oil; $[\alpha]_D = +37$ (*c* 1.4, CH_3Cl)[3]; IR (KBr) 3350 cm^{-1}; δ_H (300 MHz) 0.82 (3H, s, 15-CH_3), 0.86 (3H, s, 14-CH_3), 0.88 (3H, s, 13-CH_3), 1.15 (3H, s, 12-CH_3), 2.01 (1H, m, H-9), 2.54 (2H, br d, H-11), 6.53 (1H, d, $J = 7.2$ Hz, H-3′), 6.54 (1H, d, $J = 3$ Hz, H-6′), 6.60 (1H, d, $J = 7.2$ Hz, 3 Hz, H-4′); δ_C (75.45 MHz) 14.81 (C-15), 18.48 (C-2), 19.72 (C-6), 20.64 (C-12), 21.58 (C-14), 22.46 (C-11), 33.16 (C-4), 33.40 (C-13), 36.75 (C-10), 39.15 (C-1), 41.06 (C-3), 41.78 (C-7), 52.01 (C-9), 56.08 (C-5), 76.90 (C-8), 114.18 (C-4′), 115.76 (C-6′), 117.47 (C-3′), 123.26 (C-1′), 147.07 (C-5′), and 148.53 (C-2′); HRMS *m/z* 314.2248 (M^+ $C_{21}H_{30}O_2$ requires 314.4130).

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