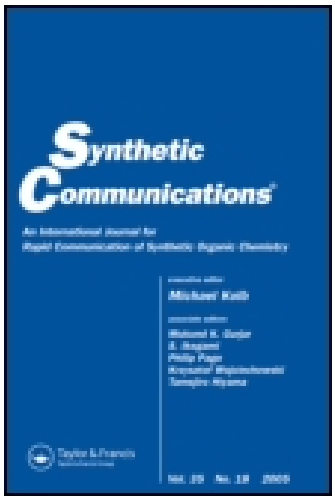

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An Efficient Method for the Synthesis of (+)-Cyclozonarone, Isozonarol $\Delta^{8,9}$ and Isozonarone $\Delta^{8,9}$

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An Efficient Method for the Synthesis of (+)-Cyclozonarone, Isozonarol $\Delta^{8,9}$ and Isozonarone $\Delta^{8,9}$

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ABSTRACT

An efficient method for the synthesis of (+)-cyclozonarone **5**, isozonarol $\Delta^{8,9}$ **6** and isozonarone $\Delta^{8,9}$ **7** via the diene **4**, obtained in two steps from manool **3**, is described.

Key Words: Sesquiterpene hydroquinone; Sesquiterpene quinone; Sesquiterpene benzoquinone; Drimatie.

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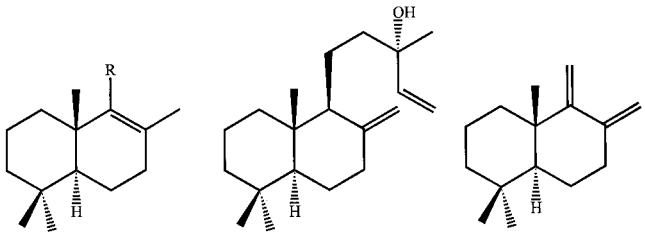
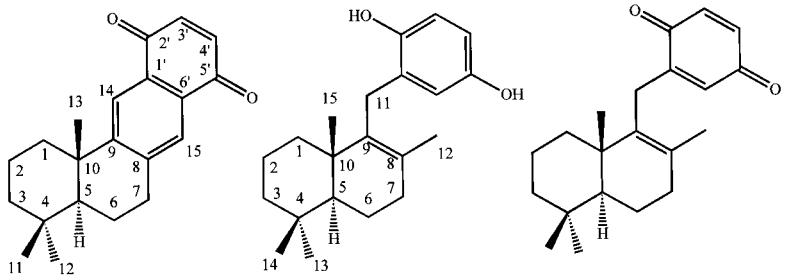
Because of their wide range of biological activities, the sesquiterpene hydroquinones isolated from marine algae and sponges, have been a target for organic synthesis in various laboratories in recent years.[1] A number of their synthesis, in which sclareol, sclareolide, β-ionone and geranyl acetone were utilized as the starting material, have been reported so far.[2] Recently we published a new efficient synthetic route to drimanic sesquiterpenes (+)-bicyclofarnesol **1** and (−)-bicyclofarnesal **2**, via the diene **4**,[3] obtained in two steps from manool **3**.[3,4]



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

In 1996 Kurata *et al.*[5] isolated from algae *Dictyopteris ondulata* (−)-cyclozonarone possessing a potent feeding-deterrent activity toward abalones and assigned the structure **5** to it. Recently, however, Cortés *et al.*[6] reported the synthesis of (+)-cyclozonarone **5** and showed that the structure of the natural product, isolated by Kurata *et al.*, should have the opposite configuration in the A/B ring juncture.

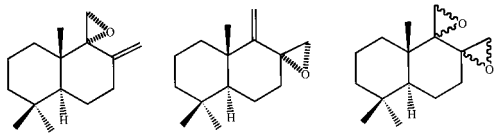
In continuation of our previous work we have synthesized sesquiterpene benzoquinone **5**, isozonarol $\Delta^{8,9}$ **6** and isozonarone $\Delta^{8,9}$ **7**.



5 **6** **7**

Diels-Alder reaction of the diene **4** with *p*-benzoquinone in dry *p*-xylene was carried out by heating the neat mixture in a sealed tube. At 110°C quinone **5** was formed together with two other compounds in minor amounts, as evidenced by the NMR spectra. Above 180°C almost quantitative aromatization occurred and (+)-cyclozonarone was obtained in 90% yield (based on reacted starting material) as a sole product. This compound displayed spectroscopic data identical to those reported for the natural (−)-cyclozonarone, except that the optical rotation was of the opposite sign.[5]

For the synthesis of isozonarol $\Delta^{8,9}$ **6** and isozonarone $\Delta^{8,9}$ **7**, we utilized the monoepoxide **8** as an ideal intermediate which had been prepared in the synthesis of drimane sesquiterpenes **1** and **2**.[3] In preparing the monoepoxide **8** we modified reaction conditions and obtained it (84% yield based on reacted starting material) with only small amounts of isomeric monoepoxide **9** and diepoxide **10**. Subsequent reactions of this epoxide reported previously afforded (−)-bicyclofarnesal **2**.[3]



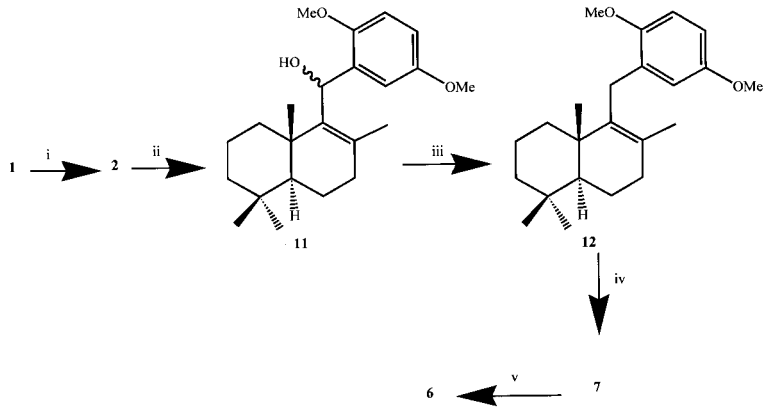
8 **9** **10**

The nucleophilic addition of the organolithium compound, derived from di-methyl-ether of hydroquinone, to the aldehyde **2** in the presence of *n*-butyllithium, afforded a mixture of isomeric benzyl alcohols **11** (85% yield), as evidenced from the ^{1}H-NMR spectrum. Reduction of the hydroxyl group of the benzyl alcohol **11** with ionic hydrogenation reaction[7] afforded the compound **12** (90% yield).

Oxidation of compound **12** with ceric ammoniun nitrate (CAN)[8] afforded the isozonarone $\Delta^{8,9}$ **7** (92% yield based on reacted starting material). The ^{1}H-NMR spectrum showed the absence of metoxy protons, while ^{13}C-NMR spectrum exhibited two quinone carbonyls at 186.56, and 187.01 ppm. Reduction of the quinone **7** with sodium hydrosulfite[8] gave the isozonarol $\Delta^{8,9}$ **6** (80% yield).

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 spectrometers for solutions in $CDCl_3$.



(i) TPPA, *N*-methylmorpholine *N*-oxide, CH_2Cl_2 or PCC, CH_2Cl_2; (ii) di-methyl-ether of hydroquinone, *n*-BuLi, THF, 0°C; (iii) Et_3SiH–CF_3COOH, CH_2Cl_2, −78°C; (iv) CAN, CH_3CN–H_2O, 0°C; (v) $Na_2S_2O_4$, THF–H_2O.

Electron-impact mass spectra (EIMS) and high-resolution mass spectra (HRMS) were obtained on a ZAB HS or Nermag R 10-10 mass spectrometer, and Kratos MS25RFA. 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, 1,2-dimethoxyethane and benzene were freshly distilled from sodium 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 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 reduced pressure below 60°C. Where necessary reactions were carried out under a nitrogen or argon atmosphere.

Diels-Alder reaction of the diene **4** with *p*-benzoquinone. A mixture of the diene **4** (0.3 g, 1.47 mmol) and *p*-benzoquinone (0.43 g, 3.98 mmol) in *p*-xylene (3 mL) was heated in a sealed tube at 180°C for 30 h. The reaction mixture was chromatographed over silica gel and elution with hexane yielded unreacted diene **4** (0.15 g). Elution with 5% diethyl ether in hexane afforded the cyclozonarone **5** (0.204 g, 90% based on reacted starting material) as a yellow oil. $[\alpha]_D = +88$ (*c* 3.5, CH_3Cl); literature data:[5] $[\alpha]_D = -89.1$ (*c* 0.330, CH_3Cl); HRMS *m/z* 308.2141 (M^+, $C_{21}H_{24}O_2$ requires 308.1776); EIMS *m/z* 310 (8, M +2), 309 (20, M +1), 308 (M^+, 20), 294 (25), 293 (70), 237 (28), 225 (70), 223 (50),

212 (25), 211 (100), 197 (45), 69 (80), 55 (73), and 43 (60); δ_H (300 MHz) 0.90, 0.93, 1.15 (3H, s, CH_3), 2.39 (1H, bd), 2.97 (2H, m), 6.83 (1H, d, J= 10.2 Hz), 6.86 (1H, d, $J = 10.2$ Hz), 7.68 (1H, s), and 7.93 (1H, s); δ_C (75.45 MHz) 18.49, 18.95, 21.57, 24.42, 30.62, 33.12, 33.48, 38.44, 38.53, 41.34, 49.61, 122.99, 127.28, 128.97, 129.66, 138.48, 138.79, 142.74, 156.83, 185.17, and 185.17.

Partial epoxidation of the diene **4** with MCPBA. To a solution of diene **4** (0.314 g, 1.53 mmol) in CH_2Cl_2 was added in small portions MCPBA (0.39 g, 2.26 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% diethyl ether in hexane afforded the monoepoxide **8** 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 **9** and stereoisomeric diepoxide **10**. Prolongation of the reaction time for more than 3 h did increase the amounts of monoepoxide **9** and stereoisomeric diepoxide **10**.

Cleavage of the monoepoxide **8** with silica gel-supported zinc borohydride. A solution of silica gel-supported zinc borohydride in 1,2-dimethoxyethane was prepared according to the literature procedure.[9] Zinc borohydride (0.647 g, 6.81 mmol) in 1,2-dimethoxyethane (10 mL) was added under dry nitrogen to silica to silica gel HF_{254} (1 g) and the mixture was stirred at room temperature for 30 min. The monoepoxide **8** (0.5 g, 2.27 mmol) was then added and stirring was continued for 48 h at room temperature. The excess reagent was decomposed by addition of water and the reaction mixture was filtered through silica gel. The crude product (0.498 g) thus obtained was chromatographed over silica gel. Elution with 2% diethyl ether in hexane afforded unreacted monoepoxide **8** (90 mg). Further elution with 4% diethyl ether in hexane yielded (+)-β-bicyclofarnesol **1** (0.390 g, 94%); M.p.: 93–94°C; $[\alpha]_D = +101$ (c, 5.9, $CHCl_3$); EIMS m/z 222 (M+, 11), 207 (8), 204 (16), 191 (86), 189 (72), 121 (57), 95 (88), 69 (64), 41 (100); δ_H (300 MHz) 0.80, 0.85, 0.92 (each 3H, s, CH_3), and 4.05 (2H, AB system, J=12 Hz); m/z 222 (M^+, 11), 207 (8), 204 (16), 191 (86), 189 (72), 121 (57), 95 (88), 69 (64), and 41 (100).

Oxidation of (+)-bicyclofarnesol **1** with tetra-*n*-propylammonium perruthenate. Alcohol **1** (0.18 g, 0.81 mmol) was dissolved in

dichloromethane (5 mL) containing both 4Å molecular sieves (0.405 g) and *N*-methylmorpholine *N*-oxide (0.113 g, 0.96 mmol). After stirring the mixture for 10 min, tetra-*n*-propylammonium perruthenate (14 mg, 0.04 mmol) was added and the reaction followed by TLC until complete. The reaction mixture was filtered through silica gel and elution with hexane afforded (−)-bicyclofarnesal **2** (0.130 g, 82%) as a semisolid; $[\alpha]_D$ −10 (*c*, 3.4, $CHCl_3$); HRMS *m*/*z* 220.1826 (M^+, $C_{15}H_{24}O$ requires 220.2505); δ_H (300 MHz) 0.81, 0.86, 1.15, 1.99 (3H each, s, CH_3), and 10.02 (1H, s, H-11); δ_C (75.45 MHz) 18.2, 18.8, 19.1, 20.1, 21.6, 33.2, 33.3, 36.2, 36.5, 37.5, 41.5, 51.5, 143.6, 153.5, and 192.6. Elution with 4% diethyl ether in hexane afforded unreacted (+)-bicyclofarnesol **1** (20 mg).

Oxidation of (+)-bicyclofarnesol **1** with PCC. Alcohol **1** (0.08 g, 0.36 mmol) was dissolved in dichloromethane (2 mL) and oxidized with pyridinium chlorocromate (0.116 g, 0.53 mmol) at room temperature for 30 min. The reaction mixture was filtered on silica gel and the filtrate was evaporated. The resulting crude product was chromatographed over silica gel. Elution with 1% diethyl ether in hexane afforded (−)-bicyclofarnesal **2** (61 mg, 77%) as a semisolid.

Coupling of the (−)-bicyclofarnesal **2** with di-methyl-ether of hydroquinone. To a cooled solution of the di-methyl-ether of hydroquinone (0.150 g, 1.08 mmol) in dry THF (3 mL) at 0°C, was added *n*-butyllithium (0.8 mL, 1.28 mmol, 1.6 M 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. Then a solution of aldehyde **2** (0.086 g, 0.39 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 reduced pressure and the product was chromatographed over silica gel. Elution with 20% diethyl ether in hexane afforded compound **11** (0.119 g, 85%) as a colorless oil; HRMS *m*/*z* 358.3140 (M^+, $C_{23}H_{34}O_3$ requires 358.2508); δ_H (300 MHz) 0.84, 0.90, 0.92, 1.56 (3H each, s, CH_3), 3.71 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.68 (1H, m, 11-CHOH), and 6.77 (3H, m, aromatics H).

Reduction of compound **11** with Et_3SiH–CF_3COOH. To a solution of compound **11** (0.152 g, 0.42 mmol) in CH_2Cl_2 (2 mL) at −78°C, was added CF_3COOH (2 mL). The solution was allowed to warm to −15°C for more than 1 h and then at room temperature for 24 h. Triethylsilane (1 mL) was then added dropwise. The reaction mixture was stirred for an additional 1 h and then a saturated aqueous $NaHCO_3$ solution was added and extracted with ether. The solvent was evaporated under reduced pressure and the product was chromatographed over silica gel. Elution

with 5% diethyl ether in hexane afforded compound **12** (0.131 g, 90%) as a semisolid; HRMS *m/z* 342.3147 (M^+, $C_{23}H_{34}O_2$ requires 342.2559); δ_H (300 MHz) 0.83 (3H, s, CH_3), 0.92 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.46 (3H, s, CH_3), 2.55 (1H, m), 3.76 (2H, d, *J*=7.5 Hz, H-11), 3.78 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.32 (1H, bs, H-6′), 6.55 (1H, d, *J*=9 Hz, H-4′), and 6.65 (1H, d, *J*=9 Hz, H-3′); δ_C (75.45 MHz) 18.50, 19.04, 20.12, 21.25, 21.70, 26.75, 28.75, 30.90, 33.49, 36.80, 39.01, 41.78, 52.49, 55.51, 55.69, 111.36, 111.38, 114.20, 127.10, 127.50, 139.45, 148.81, and 151.29.

Oxidation of compound **12** with CAN. An aqueous solution (0.5 mL) of CAN (0.114 g, 0.208 mmol) was added to a solution of **12** (0.050 g, 0.146 mmol) in acetonitrile (1 mL) in an ice bath. After stirring for 10 min in ice bath, the mixture was extracted with AcOEt. The combined extracted were washed with brine and dried. The solvent was evaporated under reduced pressure and the product was chromatographed over silica gel. Elution with 5% ether in hexane yielded unreacted compound **12** (11 mg). Elution with 7% ether in hexane afforded quinone **7** as a yellow oil (32.7 mg, 92%); HRMS *m/z* 312.2096 (M^+, $C_{21}H_{28}O_2$ requires 312.2089); EIMS *m/z* 312 (10, M^+), 297 (8), 267 (20), 256 (25), 189 (22), 175 (30), 174 (75), 161 (24), 137 (10), 119 (26), 95 (20), 55 (100), and 43 (80); 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) 18.37, 19.72, 21.30, 21.60, 27.07, 27.51, 28.61, 31.57, 34.20, 39.53, 41.54, 48.08, 50.60, 131.08, 135.25, 135.58, 137.47, 145.90, 152.77, 186.56, and 187.01.

Reduction of quinone **7** with sodium hydrosulfite. An aqueous solution (3 mL) of $Na_2S_2O_4$ (0.115 g, 0.66 mmol) was added to a solution of **7** (30 mg, 0.096 mmol) in THF (1 mL). The mixture was stirred vigorously until the yellow color disappeared. Water was added and the solution was extracted with ether. The solvent was evaporated under reduced pressure and the product was chromatographed over silica gel. Elution with 40% diethyl ether in hexane affording compound **6** (24.2 mg, 80%) as a solid; M.p.: 82–83°C; HRMS *m/z* 314.2250 (M^+, $C_{21}H_{30}O_2$ requires 314.2246); EIMS *m/z* 314 (38, M^+), 297 (6), 229 (8), 191 (75), 178 (20), 163 (16), 161 (30), 149 (20), 137 (10), 123 (72), 109 (25), 95 (30), 69 (65), 55 (100), and 43 (90); δ_H (300 MHz) 0.82, 0.88, 0.97 (3H each, s, CH_3), 1.53 (3H, s, 12-CH_3), 2.11 (2H, m), 3.29 (2H, AB System, *J*=18 Hz), 6.51 (1H, dd, *J*=9 Hz, 3 Hz, H-4′), 6.52 (1H, bs, H-6′), and 6.60 (1H, d, *J*=9 Hz, H-3′); δ_C (75.45 MHz) 18.81, 19.00, 20.16, 20.22, 21.70, 27.83, 29.67, 33.22, 33.51, 36.18, 39.01, 41.57, 51.78, 112.84, 115.77, 116.12, 128.24, 129.95, 137.27, 147.72, and 149.16.

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