Synthesis of (+)-Cyclozonarone and the Absolute Configuration of Naturally Occurring (−)-Cyclozonarone

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Synthesis of (+)-cyclozonarone (**1**) has been achieved using (−)-polygodial (**3**) as chiral starting material. The absolute configuration of naturally occurring (−)-cyclozonarone was established as 5*R*,10*R* by comparison of spectral data and optical rotation with those of (+)-cyclozonarone.

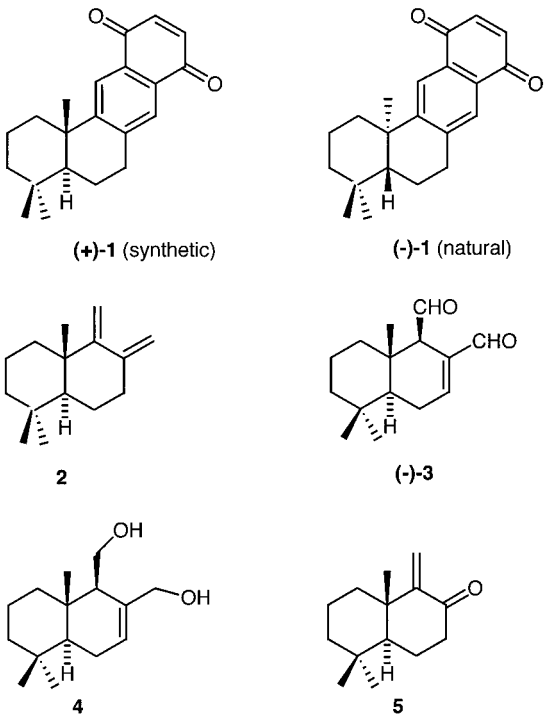
Marine flora and fauna have proven to be a source of compounds showing a great variety of chemical structures and a wide range of biological activities.[1] Substances of mixed biogenesis that are based on farnesyl hydroquinone are found in brown algae of the genus *Dictyopteris*.[2]

Cyclozonarone (**1**) is a sesquiterpene benzoquinone derivative, which was isolated from the brown algae *Dictyopteris undulata* (family Dictyotaceae) and reported as a potent feeding-deterrent toward young abalones.[3] The structure of the natural product was established by spectroscopic evidence. However, the absolute configuration remained unknown, since it was only suggested, based on biogenetic reasons.[3] To establish the absolute configuration of (−)-cyclozonarone and as part of a program aimed at syntheses of drimane−quinone derivatives,[4] in this work we describe the first enantiospecific synthesis of compound **1**.

Our synthetic strategy for the preparation of **1** was based on the Diels−Alder reaction of diene **2** with *p*-benzoquinone (Scheme 1). Since the previously reported synthesis of **2** via manool[5] was not possible, because manool is commercially unavailable, alternative methods were used to prepare **2** starting from natural (−)-polygodial (**3**). Compound **3** was converted to the known bicyclic intermediates **4** and **5** according to our previously published procedure.[6]

Reaction of enone **5** with Tebbe reagent[7] gave **2** in poor yield (16%; 23.4% based on recovered starting material). Alternatively, diene **2** was prepared from unsaturated diol **4** (Scheme 1). Catalytic hydrogenation of **4** afforded diol **6** (82% yield). Saturated diol **6** had been previously prepared from (−)-sclareol.[8] Compound **6** was dimesylated to give **7** (93%). Double elimination of mesylic acid with potassium *tert*-butoxide in DMF afforded diene **2** in good yield (45%). Diene **2** was submitted to Diels−Alder reaction with *p*-benzoquinone in refluxing benzene. The initial adduct expected (**8**) could not be detected due to enolization−oxidation[9] to quinone **9** (49% yield), which occurred during the workup and purification process. Together with **9**, minor amounts of **1** and **10** were detected in the mixture by ^{1}HNMR. The mixture of **1**, **9**, and **10** was subjected to DDQ oxidation in benzene under reflux conditions to afford (+)-cyclozonarone (**1**) (94% yield).

Compound **1** displays spectroscopic data identical to those of the natural (−)-cyclozonarone except that the opposite sign for optical rotation was observed ($[\alpha]^{16}_D$ +93.2 (*c* 1.4, $CHCl_3$); lit.[3] $[\alpha]^{19}_D$ −89.1 (*c* 0.330, $CHCl_3$)). Thus, the absolute configuration of natural cyclozonarone is 5*R*,10*R*.



Experimental Section

General Experimental Procedures. Melting points were measured on a Stuart-Scientific SMP3 apparatus and are uncorrected. Optical rotations were obtained for $CHCl_3$ solutions on a AA-5 automatic polarimeter, and their concentrations are expressed in g/100 mL. NMR spectra were recorded on a Bruker AM-200 and a Bruker Avance DRX-300 spectrometer. Chemical shifts are expressed in ppm downfield relative to TMS (δ scale) in $CDCl_3$. Carbon multiplicity was established by a DEPT pulse sequence. Elemental analyses were obtained on a Fisons-Carlo-Erba FA-1108 Automost microanalyzer. For analytical TLC, Merck silica gel 60 in a 0.25 mm layer was used. Chromatographic separations were carried out by a conventional column on Merck silica gel 60 (230−400 mesh) using hexane−EtOAc gradients of increasing polarity. All organic extracts were dried over magnesium sulfate and evaporated under reduced pressure, below 65 °C. Compounds **4** and **5** were obtained according to ref 6.

Diene 2. Method A. Methylenation of enone **5** (240 mg, 1.17 mmol) with Tebbe reagent (0.5 M, 0.5 mL, 2.5 mmol) following the described experimental procedure[7] afforded **2** (38 mg, 16%) as an oil. $[\alpha]^{16}_D$ −189.35 (*c* 5.07, $CHCl_3$) (not described before). The ^{1}H NMR spectrum data were in good agreement with the previously reported data.[5] ^{13}C NMR ($CDCl_3$, 50 MHz) (not described before): δ 161.8 (C-9), 150.1

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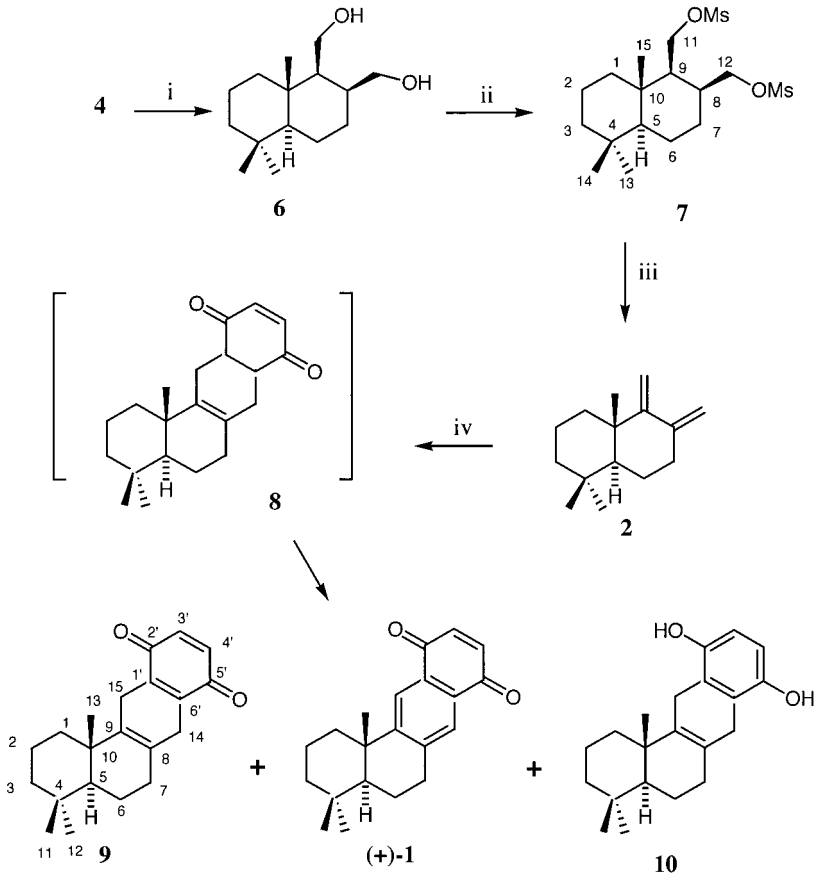
Scheme 1[a]



[a] Reagent (i) H_2, PtO_2; (ii) CH_3SO_2Cl, Py; (iii) *t*-BuOK, DMF; (iv) *p*-benzoquinone.

(C-8), 108.9 (C-12), 103.1 (C-11), 52.5 (C-5), 42.3 (C-3), 40.2 (C-10), 37.6 (C-1), 35.9 (C-7), 33.8 (C-4), 33.5 (C-13), 22.7 (C-6), 22.1 (C-14), 20.7 (C-15), 19.2 (C-2).

Method B. Catalytic hydrogenation of diol **4** (1.0 g, 4.2 mmol) with PtO_2 (100 mg) gave the known saturated diol **6** [8] (830 mg, 82%). Diol **6** (400 mg, 1.66 mmol) was esterified by CH_3SO_2Cl (0.8 mL, 9.96 mmol) and dry pyridine at −15 °C. After the usual workup and column chromatography, dimesylate **7** was obtained (610 mg, 93%) as white crystals (hexane): mp 115−116 °C; $[\alpha]^{18}_D$ +42 (*c* 2.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.47−4.41(1H, dd, J = 10.0, 5.0, H-11), 4.34−4.20 (3H, m, J = 10.0, 2H-12 and 1H-11), 3.04 (3H, s, H_3CSO_2), 3.03 (3H, s, H_3CSO_2), 2.38−2.35 (1H, m, H-8), 2.05−2.0 (1H, m, Ha-7), 1.8−1.9 (1H, ddd, J = 5.0 Hz, H-9), 0.91−0.97 (1H, dd, J = 12.0, 2.0 Hz, H-5), 0.89 (3H, s, H-13), 0.80 (6H, s, H-15 and H-14); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 68.9 (C-12), 67.2 (C-11), 55.9 (C-5), 51.5 (C-9), 41.5 (C-3), 39.0 (C-1), 37.1 (C-10), 34.5 (C-8), 33.3 (C-13), 33.1 (C-4), 28.3 (C-7), 21.4 (C-14), 18.3 (C-2), 17.3 (C-6), 16.5 (C-15); *anal*. C 51.59%, H 8.39%, S 15.95%, calcd for $C_{17}H_{32}O_6S_2$ (396.56), C 51.49%, H8.14%, S 16.14%. Compound **7** (470 mg, 1.206 mmol) in dry DMF (5.0 mL) was treated, at −15 °C under N_2 atmosphere, with *t*-BuOK (1.326 g, 11.23 mmol). The mixture was stirred at −15 °C for 8 h and then allowed to warm to room temperature. Usual workup and column chromatography gave diene **2** (108 mg, 45%), with physical properties and spectroscopic data identical to those obtained by method A.

Diels−Alder Reaction of 2 with *p*-Benzoquinone. *p*-Benzoquinone (60 mg, 0.33 mmol) was added to a solution of diene **2** (40 mg, 0.20 mmol) in dry benzene (6 mL). The reaction mixture was warmed to reflux temperature, under N_2 atmosphere, for 28 h. After evaporation of the solvent and column chromatography, quinone **9** (30 mg, 49%) was obtained as a yellow oil: $[\alpha]^{16}_D$ +70 (*c* 3.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.7 (2H, s, H-3′ and H-4′), 3.03−2.91 (4H, m, H-14 and H-15), 1.00 (3H, s, CH_3), 0.89 (3H, s, CH_3), 0.85 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 187.2 (C-2′)#, 187.0 (C-5′)#, 140.3 (C-6′), 139.2 (C-1′), 136.4 (C-4′), 136.1 (C-3′), 134.2 (C-9), 122.7 (C-8), 51.1 (C-5), 41.6 (C-3), 37.4 (C-10), 36.8 (C-1), 33.3 (C-4), 33.2 (C-12), 31.5 (C-15), 29.9 (C-7), 22.9 (C-14), 21.6 (C-11), 19.4 (C-13), 18.9 (C-2), 18.6 (C-6) (# interchangeable signals).

Oxidation of 9. DDQ (70 mg, 0.31 mmol) was added to a solution of **9** (30 mg, 0.097 mmol) in benzene (6 mL). The mixture was warmed to reflux temperature for 4 h. After evaporation of the solvent and column chromatography, (+)-cyclozonarone (28 mg, 94%) was obtained as an oil: $[\alpha]^{16}_D$ +93.18 (*c* 1.395, $CHCl_3$). ^{1}H NMR and ^{13}C NMR spectra are in good agreement with those of natural (−)-cyclozonarone, except for opposite sign of optical rotation.

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