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STEREOSELECTIVE TOTAL SYNTHESES OF (±)-ZONAROL AND (±)-ISOZONAROL

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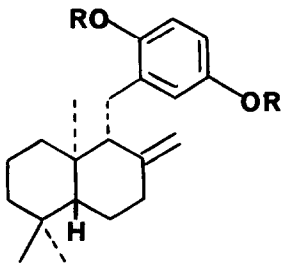
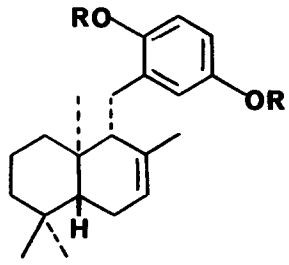
The two naturally occurring hydroquinones zonarol (1b) and isozonarol (2b) were isolated from brown seaweed Dictyopteris undulata found in the Pacific Ocean.[1,2] The structure and absolute stereochemistry of zonarol (1b) and isozonarol (2b) were rigorously defined by degradation and spectroscopy.[1,2,3] These marine natural products were found to be active against the following pathogenic fungi: Phytophthora cinnamoni, Rhizoctonia solani, Sclerotinia sclerotiorum, and sclerotium rolfsii.[1] We wish to report the first stereoselective and total syntheses of both (±)-zonarol (1b) and (±) isozonarol (2b).



1 a R = CH_3
b R = H



2 a R = CH_3
b R = H

The starting material chosen for these syntheses is readily available ketol 3.[4] Wolff-Kishner reduction of ketol 3 using hydrazine-hydrate in diethylene glycol (DEG) in the presence

of potassium hydroxide at 200° gives alcohol 4 in 90% yield.[5,6] Oxidation of alcohol 4 with Jones' reagent affords ketone 5 in 82% yield.[7] Addition of methyllithium in ether at 0° to ketone 5 produces tertiary alcohol 6 in 90% yield. When compound 6 was treated with standard reagents for dehydrating tertiary alcohols ($SOCl_2$, pyr.; $POCl_3$, pyr.; I_2, benzene, Δ; or H_2SO_4, pentane) only substantial quantities of rearranged products were obtained. However, upon heating in anhydrous dimethyl sulfoxide at 155° for 16 hours, compound 6 is smoothly converted to alkene 7 in 77% yield.[8] Epoxidation of alkene 7 using meta-chloroperbenzoic acid in chloroform in the presence of disodium hydrogen phosphate gives a mixture of epoxides 8 in 98% yield. Epoxide ring opening by treatment of compounds 8 with lithium n-propylamide in tetrahydrofuran at reflux for 6 hours produces a mixture of allylic alcohols.[9] Oxidation of this mixture of allylic alcohols with Collins' reagent[10] afords enones 9a and 9b[11] (ratio 32 : 68, respectively) in 69% yield. Enones 9a and 9b are easily separated by column chromatography on E.Merck silica gel-60 using 15% ether: 85% pet-ether (bp 30-60°) as the eluant. Conjugate addition of 2,5-dimethoxyphenylmagnesium bromide Grignard reagent[12] in 1,2-dimethoxyethane (DME) with enone 9b followed by quenching with freshly distilled acetic anhydride gives a crude enolacetate. Treatment of this crude enol-acetate with potassium hydroxide in methanol produces ketone 10 (mp 108-109°) in 70% overall yield from enone 9b.[13]

Wittig reaction of ketone 10 with methylenetriphenylphosphorane in anhydrous dimethylsulfoxide at 80° for 24 hours affords (±)-zonarol dimethyl ether (1a, mp 117-118°) in 93% yield.[14] Treatment of ketone 10 with methyllithium in ether at 0° followed by dehydration of the resulting tertiary alcohol by heating in anhydrous dimethylsulfoxide at 155° for 16 hours gives (±)-zonarol dimethyl ether (1a) and (±)-isozonarol dimethyl ether (2a) (ratio 1 : 4.8, respectively) in 67% yield. Both zonarol dimethyl ether (1a) and isozonarol dimethyl ether (2a) were identical (ir, nmr, glc, and tlc) to the respective dimethyl ethers prepared from natural zonarol (1b) and isozonarol (2b).[15] Synthetic ethers 1a and 2a were smoothly cleaved to (±)-zonarol (1b) and (±)-isozonarol (2b), in 90 and 86% yield, respectively, by treatment with lithium n-butyl mercaptide in hexamethylphosphoramide at 150° for 24 hours.[16]

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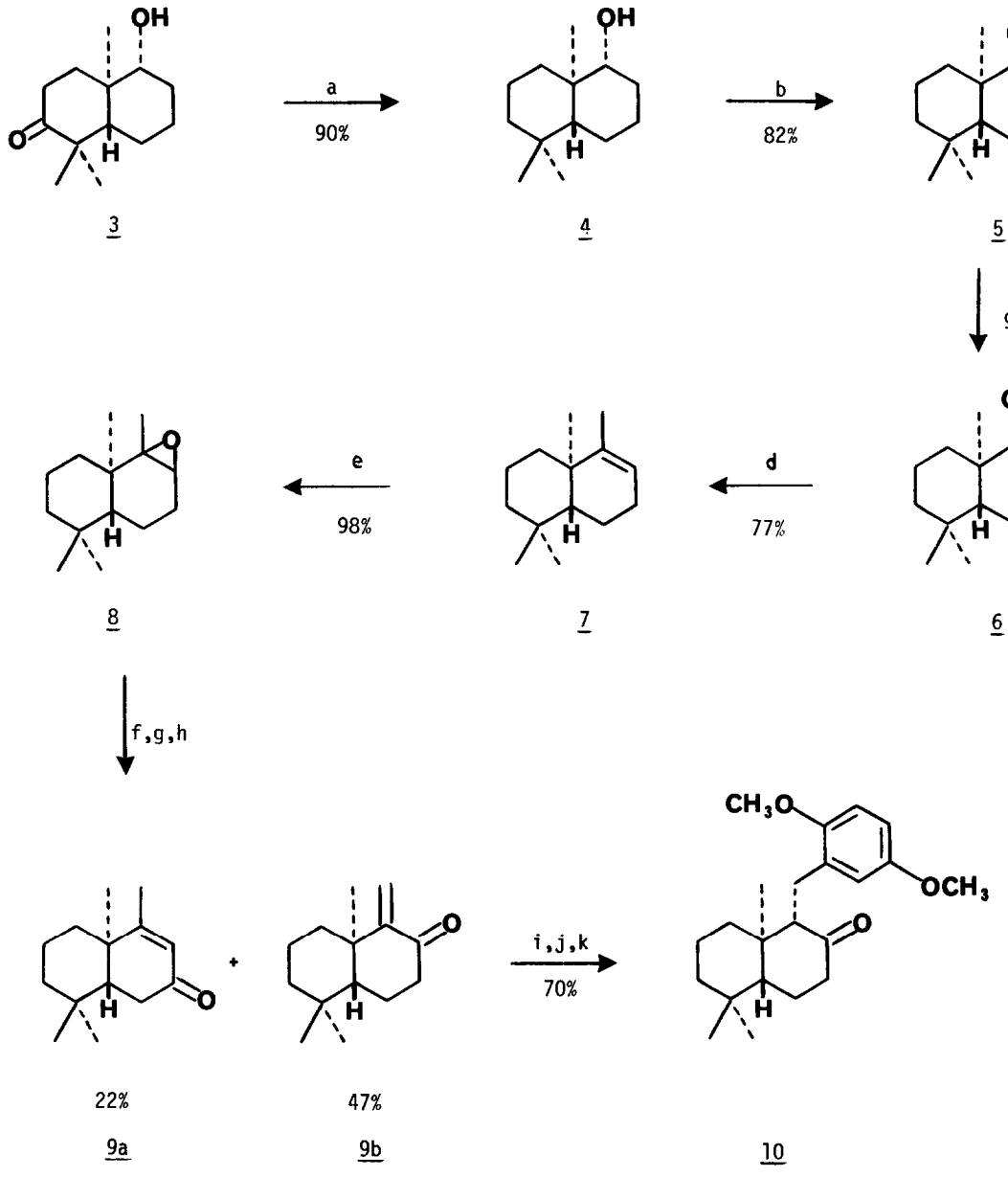

a) N_2H_4, KOH, DEG, Δ; b) CrO_3, H_2SO_4, H_2O, acetone; c) CH_3Li, Et_2O, 0°; d) DMSO, 155°; e) MCPBA, Na_2HPO_4, $CHCl_3$; f) $LiN(nPr)_2$, THF, Δ, 6hr.; g) $CrO_3.Pyr_2$, CH_2Cl_2; h) chromatography, E.Merck, silica gel-60, 15% Et_2O: 85% pet-ether (bp 30-60°) eluant; i) 2,5-dimethoxyphenylmagnesium bromide, DME; j) Ac_2O; k) KOH, CH_3OH.

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15. We are grateful to Professor W. Fenical for providing natural samples of zonarone and isozonarone which were converted to the respective methyl ethers by reduction ($NaBH_4$, CH_3OH) and alkylation (CH_3I, K_2CO_3, acetone).

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