SYNTHESIS OF 3,4,4a,12b-TETRAHYDRO-2,5,5-TRIMETHYL-2H-BENZO[b]NAPHTHO[2,3-b]PYRAN-7,12-DIONE

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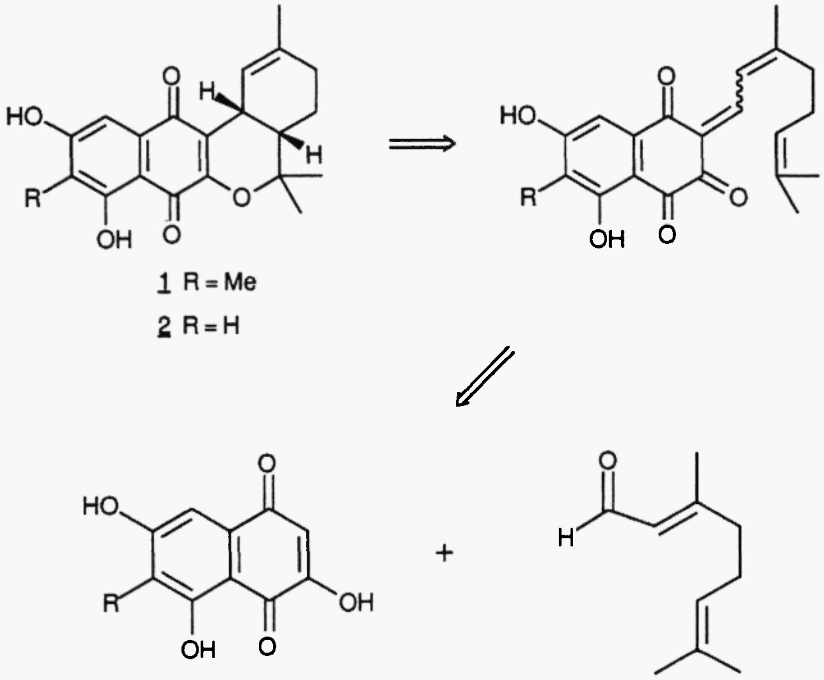
Abstract: The synthesis of benzonaphthopyranoquinone 8 was performed employing a tandem-Knoevenagel hetero-Diels-Alder reaction of 2-hydroxy-1,4-naphthoquinone 3 with citral.

Naturally occurring naphtho[2,3-b]piranoquinones are a growing class of compounds known for their antimicrobial and antitumor activity.(1) As part of a screening for antioxidants, the tetracyclic naphthopiranoquinones naphterpin 1 and 7-demethylnaphterpin 2 have been isolated from *S.* aeriouvifer and *S.* violaceus respectively. (2,3) These metabolites inhibited lipid peroxidation in rat liver microsomes with IC_{50} values comparable to that of vitamin E.



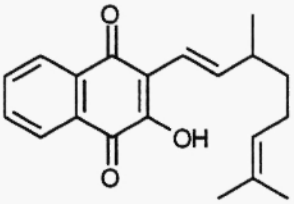
1 R = Me
2 R = H

Scheme 1

The structure elucidation of these new compounds were accomplished upon their spectroscopic properties, and no synthetic attempt is known. Following our studies on the synthesis of heterocyclic quinones with potential biological activity (4) we report here the synthesis of the carbon framework of 7-demethyl naphterpin. (5)

We envisaged that the synthesis of these tetracyclic pyranoquinones could be carried out using a tandem-Knoevenagel hetero-Diels-Alder reaction as depicted in scheme 1. The application of reactions of this type in natural product synthesis have been developed by Tietze (6).To evaluate this route, 2-hydroxy-1,4-naphthoquinone 3, comercially available, was chosen as starting material.

There are some reports on the synthesis of tetracyclic pyranoquinones by reaction of 2-hydroxy-1,4-naphthoquinone 3 with some monoterpenes. Jacobsen et al. (7), for instance, tried to obtain the geranilquinone 4, to evaluate its pesticide property, by reaction of 3 with citronellal. Besides 4, they isolated the tetracyclic pyranoquinones 5 and 6, and suggest that the formation of tetracyclic pyranoquinones depends on the reaction conditions.



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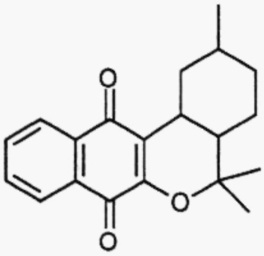

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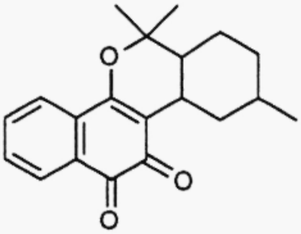

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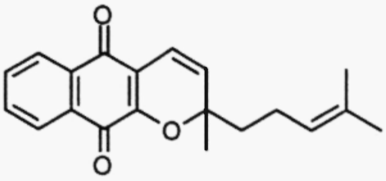
Pinto et al. report the formation of tricyclic pyranoquinone 7 by reaction of 3 with citral in refluxing toluene catalyzed by triethylamine. (8) Therefore, to obtain benzonaphthopyranoquinone derivatives we decided to study the reaction of 2-hydroxy-1,4-naphthoquinone 3 with citral in other solvents.

The reaction of 3 with citral in acetonitrile gave a mixture of quinones 7 (9) and 8 (10) in 21% and 18% yield respectively, after purification by silica gel column chromatography. The benzonaphthopyranoquinone 8 has the same carbon framework of the natural 7-demethyl naphterpin 2.

The ^{1}H-nmr spectrum of 8 shows signals for three methyl groups at δ 1.34, 1.57 and 1.68 ppm; a benzylic-allylic proton at δ 3.47 ppm and a vinylic proton at δ 6.1 ppm , which are similar to those of the natural compound 2. The stereochemistry of 8 was established by spin decoupling experiments. On irradiation of the multiplet at δ 1.6-2.1 ppm, the signals due to H-1 and H-12b were simplified to doblets, J = 5.1 Hz. When the vinylic H-1 proton (δ 6.1 ppm) was irradiated, the signal due to H-12b (δ 3.47 ppm) was simplified to a broad doublet J = 5.7 Hz. When H-12b was irradiated, the signal for H-1 appeared as a broad singlet, confirming the allylic relation of the C-13 methyl group with H-1. The coupling constant between H-12b and H-4a (J = 5.7 Hz) indicates a cis structure for 8. The UV spectral data of quinone 8 are similar to those reported for quinone 8 that has the same chromophore. Such observations are consistent with the structure proposed for 8.

The antioxidant activity of benzonaphthopyranoquinone 8, measured by an electrochemical method (11), is comparable to that of butylated hydroxyanisol (BHA).

Further application of this method to the synthesis of natural 7-demethyl naphterpin 2 is in progress.



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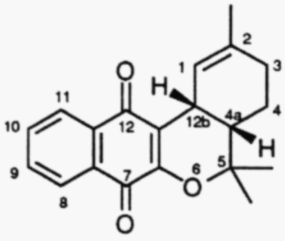

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Acknowledgements

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References and notes

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(9) Spectral data identical to those previously described (8).

(10) Data for compund 8: m.p. 181-183 °C; IR 1675 and1645 (C=O) cm^{-1} ; ^{1}H-nmr (200 MHz, $CDCl_3$): 1.34 (3 H, s, CH_3), 1.57 (3 H, s, CH_3), 1.68 (3 H, s, CH_3), 1.2-2.1 (5 H, m), 3.54 (1 h, br), 6.10 (1 H, br d, J = 5.1 Hz), 7.6-7.7 (2 H, m), 8.0-8.1 (2 H, m); ^{13}C-nmr (50.3 MHz, $CDCl_3$): 20.4, 23.6, 24.9, 25.7, 29.7, 31.2, 39.8, 80.2, 120.4, 123.9, 126.0, 130.9, 132.8, 133.9, 136.0, 152.9, 180.2, 184.7. Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 81.90; H, 6.72.

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