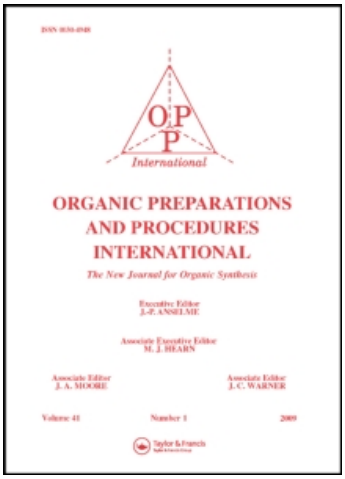

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PREPARATION OF 1,2,3,4-TETRAHYDRO-6-METHOXY-5-METHYLNAPHTHALENE-2-ONE

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PREPARATION OF 1,2,3,4-TETRAHYDRO-6-METHOXY-5-METHYLNAPHTHALENE-2-ONE

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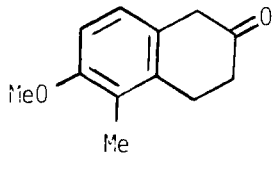
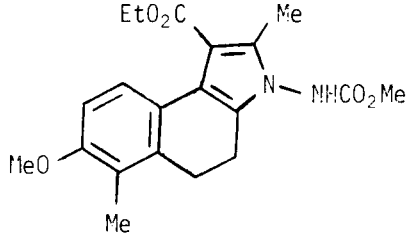
In our recent total synthesis[1] of the cytotoxic phytolexin juncusol, 1,2,3,4-tetrahydro-6-methoxy-5-methylnaphthalene-2-one (1) served as starting material. The overall yield of the preparation of tetralone 1 from naphthalene-2,6-diol[2] is reported to be 12%. Because of our interest in the development of a practical total synthesis of juncusol, we succeeded in improving the efficiency of the Davis and Forrest procedure and obtained tetralone 1 in 72% yield from naphthalene-2,6-diol.[2]



1

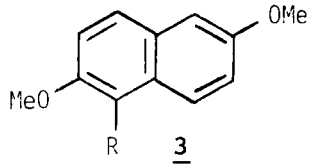


2

Refluxing an aqueous sodium hydroxide solution of naphthalene-2,6-diol and dimethyl sulfate is reported to give 2,6-dimethoxynaphthalene (3a) in 53% yield; this transformation has now been performed in 98% yield using methyl iodide-potassium carbonate in DMF at room temperature. Formylation with DMF-phosphorus oxychloride gave 2,6-dimethoxy-1-naphthaldehyde (3b) which was converted to 2,6-dimethoxy-1-methylnaphthalene (3c) in 85% yield by Wolff-Kishner reduction.[3]

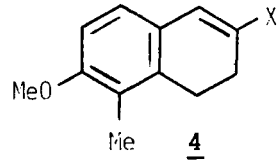
In contrast to previous work,[2] we elected to isolate enol ether 4a,

obtained from sodium in refluxing isoamyl alcohol reduction of 3c, by a solvent extraction procedure. Using this technique, crystalline 4a is



3

a, R = H; b, R = CHO; c, R = Me



4

a, X = OMe; b, X = pyrrolidinyl

obtained in 87% yield on a 21 g reaction scale. Subsequent 1N hydrochloric acid hydrolysis of 4a gives tetralone 1 (99% yield) as a lightly colored oil.[4] The purity of this material was convincingly demonstrated by conversion of 4a via enamine 4b to analytically pure, crystalline pyrrole 2 in 82% yield.[1]

Acknowledgment.- This work was supported by the National Institutes of Health (Grants GM 26568 and CA 25787).

EXPERIMENTAL SECTION

Preparation of 2,6-dimethoxynaphthalene (3a).- A solution of naphthalene-2,6-diol dihydrate (5.0 g, 0.025 mol, Aldrich Chemical Co.) and methyl iodide (6.5 mL, 0.10 mol) in DMF (65 mL) together with finely ground anhydrous potassium carbonate (14 g, 0.10 mol) was stirred at room temperature for 24 h. The reaction mixture was poured into water (300 mL), after which precipitated 3a was collected. The crude product was dissolved in methylene chloride and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent gave 4.6 g (98%) of lightly colored, crystalline 3a of sufficient purity for the next operation. ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.93 (s, 6H), 7.03-7.30 (m, 4H), 7.67 (d, 2H, J = 8 Hz).[2]

Preparation of 2,6-dimethoxy-1-methylnaphthalene (3c).- To a solution of 2,6-dimethoxynaphthalene (3a) (24.7 g, 0.131 mol) and dry DMF (13.0 mL, 0.140 mol) in dry toluene (24 mL) was added phosphorus oxychloride (13.0

mL, 0.140 mol). After heating for 3 h at 100° under a drying tube, the solution was cooled to room temperature and then poured into an ice-water bath cooled, saturated ammonium acetate solution (120 mL). After stirring for a few min, the resulting mixture was extracted with benzene (3 x 200 mL). The combined organic extract was washed with 6N HCl (3 x 100 mL), brine (3 x 100 mL) and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent gave 25.4 g (90%) of lightly colored, crystalline 2,6-dimethoxy-1-naphthaldehyde (3b),[2,3] ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.56 (s, 3H), 3.66 (s, 3H), 6.70-7.08 (m, 3H), 7.57 (d, 1H, J = 9 Hz), 8.86 (d, 1H, J = 9 Hz), 10.3 (s, 1H).

To crude (3b) (25.4 g, 0.118 mol) suspended in diethylene glycol (180 mL) was added 85% hydrazine hydrate (19 g, 0.32 mol). After heating the mixture at 100° for 10 min and cooling to room temperature, potassium hydroxide pellets (85% KOH, 56 gm, 0.18 mol) were added. The resulting mixture was heated to reflux until nitrogen evolution ceased (~30 min) and cooled to room temperature, after which water (500 mL) was added. The resulting precipitate was collected and washed with water (300 mL). The crude product was dissolved in methylene chloride (500 mL) and dried with anhydrous magnesium sulfate. Filtration and evaporation of solvent gave 22.2 g (94%) of lightly colored, crystalline (3c) of sufficient purity for the next operation, ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.53 (s, 3H), 3.90 (s, 6H), 7.07-8.10 (m, 5H).[2]

Preparation of 1,2,3,4-tetrahydro-6-methoxy-5-methylnaphthalene-2-one (1).- To a solution of 3c (21 g, 0.10 mol) in refluxing isoamyl alcohol (310 mL) under a nitrogen atmosphere was added sodium in chips (35 g, 1.5 mol) over 4 h. Refluxing was continued until all sodium was consumed (~30 min), after which the solution was cooled to room temperature and water (400 mL) was added. The isoamyl alcohol was removed by distillation with water;

distillation was terminated when the boiling point reached 100°. The aqueous layer was extracted with methylene chloride (3 x 200 mL) and the combined organic extract was washed with brine (3 x 200 mL) and dried with anhydrous magnesium sulfate. Filtration and evaporation of solvent gave 17.8 g (87%) of yellow crystalline enol ether 4a, ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.11 (s, 3H), 2.40 (t, 2H, J = 7.2 Hz), 2.78 (t, 2H, J = 7.2 Hz), 3.64 (s, 3H), 3.78 (s, 3H), 5.48 (s, 1H), 6.57 (d, 1H, J = 9.0 Hz), 6.79 (d, 1H, J = 9.0 Hz).[2]

A solution of 4a (10 g, 0.049 mol) in THF (180 mL) and 1N HCl (80 mL) was heated at reflux temperature for 3 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and extracted with ether (3 x 200 mL). The combined organic extract was washed with 1N sodium bicarbonate (3 x 150 mL), brine (3 x 150 mL) and dried with anhydrous magnesium sulfate. Filtration and evaporation of solvent gave 9.2 g (99%) of a lightly colored oil, 1, ^{1}H NMR (60 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.48 (t, 2H, J = 7.2 Hz), 3.05 (t, 2H, J = 7.2 Hz), 3.50 (s, 2H), 3.80 (s, 3H), 6.72 (d, 1H, J = 9.0 Hz), 6.96 (d, 1H, J = 9.0 Hz).[2]

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