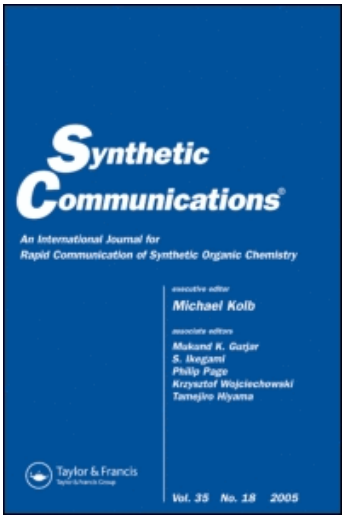

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AN IMPROVED TOTAL SYNTHESIS OF (±)- PODOCARPIC ACID BY A CYCLIALKYLATION ROUTE

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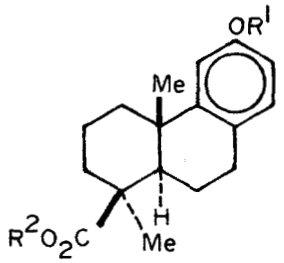
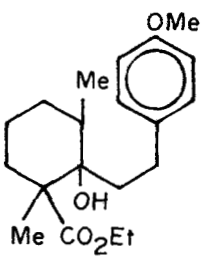
A number of total syntheses of (±)- podocarpic acid (1) have been described[1]. King, King and Topliss[2] first identified one of the products from nonstereoselective cyclization of (4) with polyphosphoric acid as (±)- ethyl-O-methylpodocarpate (2) and correlated that with the corresponding acid (3), prepared in an extremly poor yield (ca 0.4%)[3] by Bhattacharyya[3], and Haworth and Moore[4] by cyclization of (5) with a mixture of sulfuric acid and acetic acid. More recently Mancini, Fringuelli and Taticchi[5] prepared (3) (in 4.8% yield) by repeating Haworth's cyclization of (4). In continuation of our studies on cyclialky-



1, $R^1 = R^2 = H$
2, $R^1 = Me$; $R^2 = Et$
3, $R^1 = Me$; $R^2 = H$
8, $R^1 = R^2 = Me$



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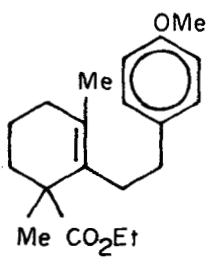

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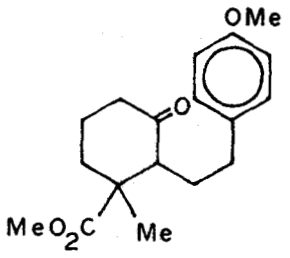

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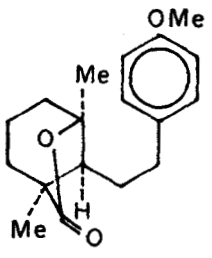
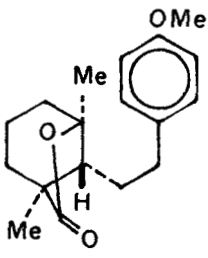


7a



7b

lation reactions[6] we report here an improved stereoselective total synthesis of (1) by a cyclialkylation route.

The key starting material for our synthesis is the easily accessible keto-ester (5)[7]. This on reaction with an excess of methylmagnesium iodide followed by refluxing p-toluenesulfonic acid in benzene, partial alkaline hydrolysis of the resulting mixture, and subsequent treatment with hydrochloric acid afforded a mixture of diastereomeric lactones

(7a) and (7b) in a ratio of ca 9:1, as revealed from the ^{1}H NMR spectrum. The stereochemistry of the major epimer (7a) has been assigned from an analogy[6,8] of the preparation of similar lactones with identical stereochemistry. The cyclization[4] of this mixture of lactones (7a) and (7b) with a refluxing 1:9 mixture of sulfuric acid- acetic acid afforded the acid (3) in 41% yield as the only isolable crystalline product. Acid (3) was esterified with diazomethane and the resulting methyl ester (8) was identical with an authentic sample[9] with respect to mixed m.p., IR and ^{1}H NMR. As the conversion of (3) to (±)- podocarpic acid (1) has already been reported[4], the present synthesis therefore, constitutes a total synthesis of (±)- podocarpic acid.

EXPERIMENTAL

Preparation of the Lactone Diastereomers (7a and 7b) Mixture.

To a well stirred ice-cold solution of the keto-ester (6)[7] (7.6g, 26 mmol) in 100 ml dry diethyl ether an ethereal solution of methylmagnesium iodide [prepared from 1.2g (0.05g atom) of magnesium and 6g of methyl iodide in 20 ml of dry diethyl ether] added dropwise over a period of 1 h under nitrogen. Stirring

in the cold was continued for 40 min followed by 30 min at room temperature and 1 h at reflux. After decomposition of the complex with an ice cold saturated ammonium chloride solution the ether layer was separated and the aqueous layer was extracted with diethyl ether. The combined ether layer were successively washed with water, 5% sodium thiosulfate solution, water and dried over anhydrous sodium sulfate. The crude product after removal of solvent was refluxed for 8 h with 500mg of p-toluenesulfonic acid monohydrate in 200ml of dry benzene under nitrogen atmosphere using a water separator. The cold reaction mixture was washed with 5% sodium bi-carbonate solution followed by water. After removal of the solvent the residue was distilled to afford 6.3g of a light yellow thick liquid, b.p. 175-190° C (0.2mm Hg); I.R. (neat) 1765 (very strong) and 1725 (medium) cm^{-1}. This mixture was refluxed under nitrogen for 2 h with a mixture of 2.5g of potassium hydroxide in 10ml of water and 40ml of ethanol. Most of the ethanol was removed in vacuo, and the residue, after being diluted with water, was extracted with diethyl ether. The aqueous alkaline layer was acidified with an excess of concentrated hydrochloric acid and heated on a steam bath for 15 min. The cooled reaction mixture was extracted with diethyl ether. The ethereal layer was

washed with cold 2% sodium hydroxide solution and water. The residual brown liquid, after removal of ether, was distilled to afford 2.4g (34% overall yield) of the mixture of diastereomeric lactones (7a) and (7b), b.p. 175-180° C (0.2 m.m. Hg) in a ratio of ca 9:1 as revealed from the relative integrations of the quaternary →C-Me and -O→C-Me singlets at δ 1.17 and 1.41, and δ 1.06 and 1.30 respectively assigned to (7a) and (7b); I.R. (neat) 1765 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39.

Found : C, 75.13; H, 8.53.

Cyclization of the 9:1 mixture of Lactones (7a) and (7b): (±)-O-Methyl Podocarpic Acid (3).

The aforementioned 9:1 mixture of lactones (7a) and (7b) (500mg; 1.7 mmol) was gently refluxed for 8 h with a mixture of 5ml of acetic acid and 0.5ml of 98% sulfuric acid under nitrogen. The dark brown reaction mixture was poured into ice-water and extracted with ethyl acetate (30ml x 3). The combined ethyl acetate extracts were thoroughly extracted with 2% potassium hydroxide solution and water, and dried over anhydrous sodium sulfate. The removal of the solvent left a small amount of a brown residue (IR 1765 cm^{-1}) which was not investigated further. The aqueous alkaline

layer was acidified with 6N hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extracts were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude gummy solid on recrystallization once from ethyl acetate afforded the acid (3) (204mg; 41%) m.p. 196-198° C (dec) (lit[4], 194-195° C; lit[3], 196-197° C).

(±)-Methyl O-methyl podocarpate (8).

The above acid (100mg) was esterified with an excess of ethereal diazomethane. After evaporation of the solvent the residue was dissolved in 1:1 diethyl ether-pet ether (b.p. 60-80° C) mixture and filtered through a short column of neutral alumina (4g) to afforded 98mg (97%) of (±)-methyl-O-methyl podocarpate (8), m.p. 135° C (lit[3], 136-137.5° C); ^{1}H NMR: $\delta(CCl_4)$ 0.98 (s, 3H), 1.23 (s, 3H), 1.32-2.83 (m, 11H), 3.58 (s, 3H), 3.67 (s, 3H) and 6.32-6.80 (m, 3H).

This is identical (IR, ^{1}H NMR and mixed m.p.) with a sample, m.p. 135° C, prepared by O-methylation of an authentic sample[9] of (±)- methyl podocarpate (40mg) with methyl iodide (6 ml) in acetone (20 ml) in the presence of anhydrous potassium carbonate (1.5g) by a standard method[10].

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