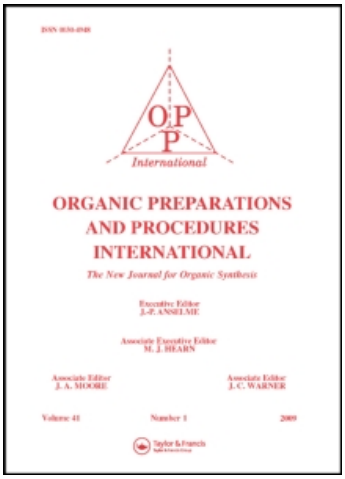

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AN OPTIMIZED PREPARATION OF 2,3-DIHYDRO-1-METHYL-4-OXONAPHTHALENE-1-CARBOXYLIC ACID

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AN OPTIMIZED PREPARATION OF 2,3-DIHYDRO-1-METHYL-4-OXONAPHTHALENE-1-CARBOXYLIC ACID

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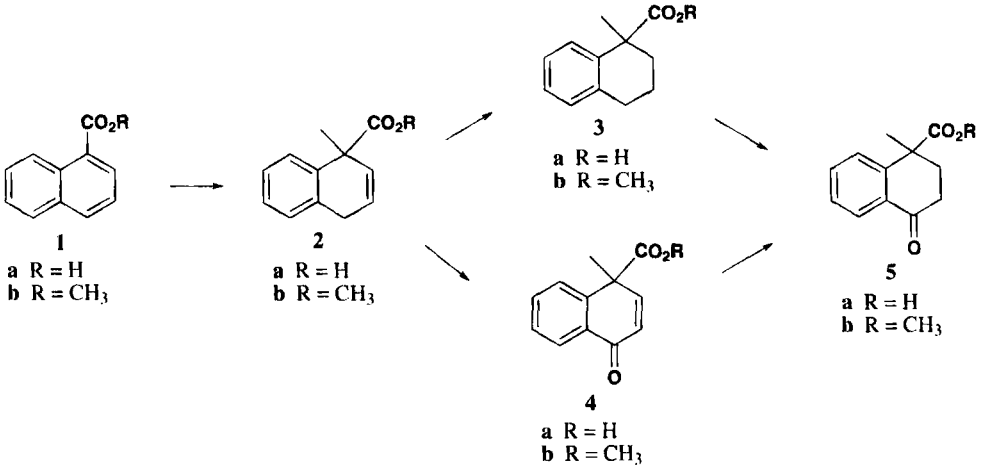
The reductive alkylation of benzylic ketones has become a very useful synthetic reaction[1] and preliminary experiments have shown that with the desired latent functionality, α-tetralones may easily be transformed into angularly alkylated decalins. We now report the preparation of a C-4 disubstituted α-tetralone **5**, which promises to be an advantageous intermediate for the stereoselective synthesis of highly oxygenated decalins contained in natural products with biological importance.[2-4] This simple sequence of transformations allows the preparation of **5** from the readily available 1-napthoic acid (**1a**).



According to the previously reported results on Birch alkylations of naphthoic acids and esters,[4,5] it was decided to carry out two parallel synthetic sequences starting from **1a** and **1b** respectively. Treatment of **1a** in tetrahydrofuran-ammonia with sodium followed by the addition of methyl iodide,[4] gave the monoalkylated product **2a** in 95% yield. This reaction does not require the addition of an external proton-source because the acid moiety itself provides it. However, we observed that the reductive methylation of the methyl ester **1b** produced a mixture of **2b** and its 4-methyl derivative in different ratios, which are difficult to separate.

An alternative reaction using the inverse addition method,[6] provided the monoalkylated methyl ester **2b** as the sole product albeit in only 77% yield. It is possible to rationalize this result as a dilution effect where the amide concentration is negligible and only the monoanion species reacts.

Of the two possible routes for the preparation of **5**, the reduction of the double bond of **2** followed by benzylic oxidation on **3** gave better results than the other involving the benzyl-allylic oxidation of **2** followed by reduction of **4**. The best results for the reduction step (96%) were obtained using 10% Pd/C-32 psi H_2 in ethanol. All the attempts to employ the catalytic chromium methods (PDC-tBuOOH, PCC-Celite)[7,8] for the transformation of **3** (**a** or **b**) into **5** failed. Compound **5** was finally obtained by the benzylic oxidation of **3** with CrO_3 in acetic acid at low temperature (0-10° to room temperature).[9] The yield from **3a** (75% of keto acid **5a** as an oily solid) was better than that obtained from the corresponding ester **3b** (54% yield of keto ester **5b** as an oil) after careful chromatographic purification.

In summary, we have described a three-step-reaction sequence for the rapid and high yield preparation of 2,3-dihydro-1-methyl-4-oxo-1-naphthalenecarboxylic acid **5a**, an oxygenated C-4 disubstituted tetralone, from acid **1a**. The procedure can be run on a 5-10 gram scale without complications.The synthetic route described here is superior to that starting with ester **1b**.

EXPERIMENTAL SECTION

All reactions were carried out under a dry oxygen-free nitrogen atmosphere. All solvents were distilled routinely and dried prior to use. Thin layer chromatography (tlc) analyses were performed on aluminum foil plates coated with 0.1 mm Merck silica gel 60 GF_{254}. Melting points were determined on Ernst Leitz hot-stage microscope and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200-E NMR spectrometer, in $CDCl_3$ solutions with TMS as an internal standard; the chemical shifts are expressed in δ values downfield from TMS. IR spectra were determined on a Bruker FT-IR IFS 25 spectrophotometer. Mass spectrometric analysis was obtained at LANAIS-Universidad de Buenos Aires (UBA), on homogeneous samples verified by tlc. using three solvent systems. Elemental analyses were obtained at Atlantic Microlab Inc. (Georgia, USA) .

For naming and describing the spectral data of the compounds, we used the numbering of base compounds derived from naphthalene-1-carboxylic acid.

Synthesis of 4-Hydro-1-methylnaphthalene-1-carboxylic Acid (2a).- Ammonia (175 mL), was condensed into a dried, three-necked round-bottomed flask equipped with a cold finger condenser, mechanical stirrer and maintained at -78°, under a slight positive pressure of dry nitrogen. Then a solution of the acid **1a** (3 g, 17.4 mmol) in tetrahydrofuran (35 mL) was introduced by means of a double-needle liquid transfer; sodium (1.2 g, 52.2 mmol) was then added in small portions and the resulting blue suspension was stirred for 30 additional minutes. Methyl iodide (4.9 mL, 81.9 mmol) was added, and the mixture was stirred for an additional 30 minutes. The cooling bath was removed, and the ammonia was allowed to evaporate. The residue was diluted with water (20 mL) and ethyl ether (20 mL), the pH of the solution was adjusted to 2-3 by the careful addition of 6N hydrochloric acid with cooling. The aqueous layer was then separated and extracted with ether (3x15 mL). The combined organic extracts were washed with water until neutral, dried over anhydrous sodium sulfate. The organic extract was filtered and evaporated to yield **2a** (95%) as a white crystalline solid, mp.115.5-116°, *lit.*[4] mp.115-115.5°.

IR (KBr): ν 3430, 3000, 2960, 1730, 1660, 1380, 1260, 1240, 1110, 1050, 990, 880, 770 cm^{-1}; ^1H NMR: δ 7.35 (m, 1H, ArH), 7.18-7.26 (m, 3H, ArH), 6.01 (m, 1H, olefinic), 5.79 (broad d, J=10.0 Hz, 1H, olefinic), 3.47 (m, 2H, CH_2, benzylic), 1.63 (s, 3H, CH_3); ^{13}C NMR: δ 181.3 (COOH), 136.4 (q), 133.2 (q), 129.2 (CH), 128.4 (CH), 126.9 (CH), 126.7 (CH), 126.3 (CH), 125.5 (CH), 46.9 (C1), 29.6 (C4), 26.6 (CH_3).

The physical constants and spectral NMR data were identical to those previously described.[4]

Synthesis of 2,3,4-Trihydro-1-methylnaphthalene-1-carboxylic Acid (3a).- A solution of **2a** (4 g, 21.6 mmol) in 95% ethyl alcohol (100 mL) and 10% Pd/C catalyst (2 g) at 25° was placed in a Parr Series low-pressure hydrogenation apparatus at 3.33 atmospheres and was hydrogenated for 14 hours. Completion of the reaction was determined by ^1H NMR. The suspension was filtered into a sintered glass funnel with a silica gel pad and the catalyst was washed with solvent (3 x 5 ml). The catalyst must not be allowed be become dry at any time during the above filtration procedure. After removal of the catalyst by filtration, the solution was dried and evaporated *in vacuo* to yield **3a** as white crystalline solid (quantitative yield), mp. 110.3-111° (from isopropyl ether). IR (KBr): ν 3400, 2990, 2900, 1740, 1380, 1265, 1230, 1100, 1056, 900, 840, 750 cm^{-1}; ^1H NMR: δ 7.28 (m, 1H, ArH), 7.12 (m, 3H, ArH), 2.80 (t, 2H, benzylic, J=5.6 Hz), 2.55 (m, 1H), 1.80 (m, 3H), 1.56 (s, 3H, methyl); ^{13}C NMR: δ 183.4 (COOH), 138.2 (q), 136.5 (q), 129.2 (CH), 128.0 (CH), 126.6 (CH), 125.8 (CH), 46.0 (C1), 35.1 (CH_2), 29.7 (CH_2), 27.2 (CH_3), 19.6 (CH_2).

Anal. Calcd for $C_{12}H_{14}O_2$: C,75.75; H, 7.42. Found: C,75.69; H, 7.40

Synthesis of 2,3-Dihydro-1-methyl-4-oxonaphthalene-1-carboxylic Acid (5a).- A flask fitted with a magnetic stirrer, was charged with **3a** (1 g, 5.32 mmol), and glacial acetic acid (10.8 mL). The mixture was cooled to 10° and a solution of chromium (VI) trioxide (1.6 g, 0.016 mol) in AcOH:H_2O mixture (6 mL, 4:1) was gradually added. Stirring was continued while the mixture was allowed to reach room temperature overnight. The mixture was then poured into 20 mL of water and the organic compound was taken up in ethyl ether (3 x 10 mL), washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was allowed to dry in a dessicator under vacuum, in the presence of sodium hydroxide pellets, for the complete elimination of acetic acid. The ketoacid **5a** was purified by vacuum distillation (with a short-path distillation apparatus) to give an oily solid (75%), bp. 98°/2 mm.

IR (film): ν 3480, 2960, 1730, 1690, 1460, 1340, 1300, 1260, 1200, 1100, 840, 770 cm^{-1}; ^1H NMR: δ 8.06 (d 1H, J=4.2 Hz, ArH), 7.47 (m, 3H, ArH), 2.74 (m, 3H, aliphatic), 2.1 (m, 1H, aliphatic), 1.70 (s, 3H, methyl); ^{13}C NMR: δ 197.9 (C-4), 179.9 (COOH), 144.8 (q ArH), 133.9 (CH), 131.3 (q ArH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 45.5 (C1), 34.9 (CH_2), 33.4 (CH_2), 25.5 (CH_3). EIHRMS Calcd for $C_{12}H_{12}O_3$ (M^++1): 205.07864, Found for (M^++1): 205.0865.

Anal. Calcd for $C_{12}H_{12}O_3$: C,70.56; H, 5.93. Found: C,70.55; H, 5.82

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