Synthesis of 2-acetyl-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene

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An attempt has been made to synthesise 2-acetyl-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene aiming at its transformation to intermediates for the synthesis of natural products

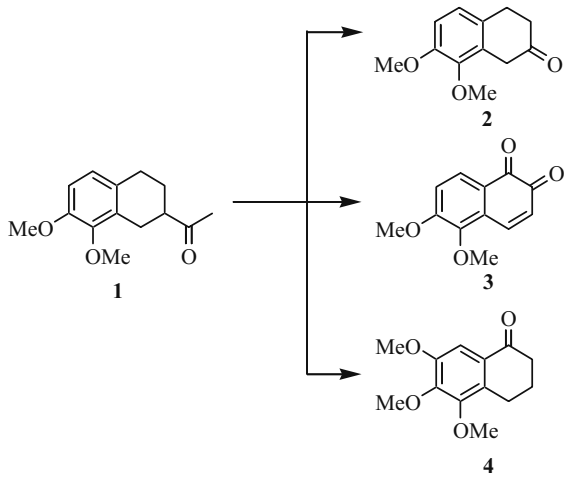
Keywords: Stobbe condensation, 2,3-dimethoxy benzaldehyde, cyclisation, Clemmensen reduction

As a part of our investigation on the transformation[1] of substituted α-tetralones we looked for a versatile intermediate that would permit the synthesis of a variety of compounds suitable for the synthesis of natural products. Our choice fell on 2-acetyl-7,8-dimethoxytetrahydronaphthalene **1** which could be converted into compounds **2, 3** and **4** (Scheme 1) by standard organic reactions.

The compound **2**, has recently been synthesised[2] as an intermediate in the preparation of biologically active of compounds. Compounds **3** and **4** are potential intermediates for the synthesis of morphine[3] and quinone lomandrone[4,5] respectively. The synthetic route for the compound **1** is described below (Scheme 2).

Stobbe condensation[6] of dimethoxy benzaldehyde **5** with diethyl succinate followed by hydrolysis furnished compound **6** which on hydrogenation over Pd/C (10%) yielded the diacid **7**. This was cyclised with conc. sulfuric acid to obtain the tetralonecarboxylic acid **8** in 60% yield. The conversion of **8** into the acid **9** and the alcohol **10** was accomplished by Clemmensen reduction[7] and lithium aluminium hydride reduction respectively.

Selective oxidation with CrO_3·2Py in dichloromethane gave the aldehyde **11** which upon reaction with Grignard reagent (Me MgBr) in dry tetrahydrofuran yielded the alcohol whose transformation into the desired compound **1** was achieved by oxidation with chromium trioxide in pyridine. The spectroscopic data (IR, NMR, mass and ^{13}C NMR) were consistent with structure **1** for the acetyltetrahydronaphthalene. The transformation of compound **1** into the compounds **2, 3** and **4** is under way.

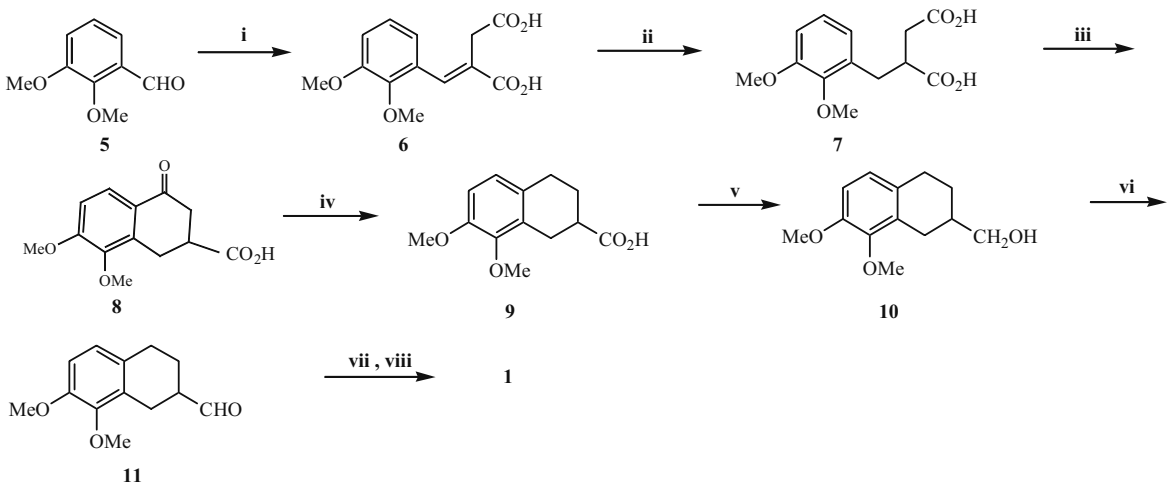


Scheme 1

Experimental

Unless otherwise stated, IR spectra were taken on a Nicolet FT spectrophotometer, Bruker AM 300 MHz spectrometers were employed for the determination of ^1H and ^{13}C NMR spectra, with deuteriochloroform as solvent. Mass spectra were run on a Kratos MS25RFA and for GCMS -ma- Hewlett Packard 5890 Quadrupolar 5972 Series S. The expression "work up" indicates that the reaction mixture was diluted with water, extracted with ether, washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Column chromatography was performed on silica gel (Merck, grade 60, 70–230 mesh). Microanalyses were carried out at the Chemistry Department, IVIC, Caracas, Venezuela.

2,3-Dimethoxybenzylidensuccinic acid (**6**): A solution of 2,3-dimethoxybenzaldehyde **5** (10.12 g, 60.24 mmol) in diethyl succinate (12.11 ml, 73.1 mmol) was added dropwise to a solution of potassium *t*-butoxide prepared from potassium (4.12 g, 0.11 mmol) and *t*-butanol (100 ml). The mixture was gently heated under reflux for 2 h, cooled to room temperature, acidified with hydrochloric acid (20%) and extracted with ether.



Scheme 2 Reagents: (i) Diethyl succinate, *t*-BuOK / *t*-BuOH ; NaOH, MeOH, reflux; (ii) Pd / C, H_2, EtOH; (iii) H_2SO_4, rt, 8hr; (iv) Zn–Hg, HCl; (v) $LiAlH_4$, THF; (vi) CrO_3 –Py, CH_2Cl_2; (vii) MeMgBr, THF; (viii) CrO_3 –Py, CH_2Cl_2.

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The organic extract was washed with a solution of sodium hydroxide (5%), acidified and extracted with ether.

The organic extract was washed, dried and concentrated to obtain a viscous yellow liquid (16.54 g, 93%). It was dissolved in methanol (150 ml), added a solution of methanol (500 ml) containing potassium hydroxide (50 g, 0.89 mol) and stirred at room temperature for 24 h. The resulting solution was concentrated, diluted with water, acidified with concentrated hydrochloric acid and extracted with dichloromethane. The organic extract was washed, dried and concentrated to obtain a solid which on crystallisation in ether afforded the acid **6** (9.71 g, 73%), m.p.147–150°C; ν_{max} 3200–2100 (OH), 1708 (CO) cm^{-1}; ^1H NMR: δ 3.54 (s,2H, CH_2), 3.78 (s,3H), 3.86 (s, 3H) (2,3-OMe), 6.86 (d, 1H, *J* = 7 Hz), 6.94 (d, 1H, *J* = 8 Hz) (4-H, 6-H), 7.07 (t, 1H, *J* = 8 Hz, 5-H), 9.11 (s, 2H, 2 COOH); ^{13}C NMR: δ 177(COOH),172(COOH), 152 (C2), 147 (C3), 140 (C7), 129 (C8), 126 (C1), 124 (C6),121 (C4),113 (C5), 61 (OMe), 56 (OMe), 34 (C9); MS: 248 (M – H_2O), 233 (248 - Me), 217 (248 – MeO). Anal. Cacd. for $C_{13}H_{14}O_6$: C, 58.6; H, 5.3, Found: C, 58.9; H, 5.4%.

2,3-Dimethoxybenzylsuccinic acid (**7**): A mixture of diacid **6** (9.71 g, 40 mmol) and Pd-C (760 mg,10%) in ethanol (200 ml) was stirred under hydrogen for 24 h at room temperature.

The reaction mixture was filtered and evaporated under reduced pressure to give a solid which on crystallisation from ethanol afforded the saturated diacid **7** (9.11 g, 85%) m.p.158–161°C; ν_{max} 3224–2215 (OH), 1712 (CO) cm^{-1}, ^1H NMR: δ 2.31–2.82 (m,4H), 3.28 (q, 1H, *J* = 1.6 Hz, 8-H), 3.78 (s, 3H), 3.81 (s,3H), 6.73 (dd, 1H, *J* = 8 Hz, *J* = 1.6 Hz), 6.87 (dd, 1H, *J* = 8 Hz, *J* = 1.6 Hz) (4H and 6-H), 6.95 (t, 1H, *J* = 8 Hz, 5H), 11.99 (s, 2H, COOH); ^{13}C NMR:176 (COOH), 174 (COOH), 152 (C3), 147 (C2), 131 (C1), 123 (C5), 122 (C6), 111 (C4), 59 (OMe), 54 (OMe), 42 (C8), 34 (C9), 31 (C7); MS: 250 (M– H_2O); Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.2; H, 6.0, Found: C, 58.5; H, 6.2%.

3-Carboxyl-5,6-dimethoxy-α-tetralone (**8**): Acid **7** (9 g, 0.03 mol) was dissolved in concentrated sulfuric acid (69 ml, 1.3 mol) and stirred at room temperature for 8 h.

The reaction mixture was carefully poured into crushed ice and then extracted with dichloromethane. The organic extract was washed, dried and evaporated under reduced pressure. The resulting solid on crystallisation from ether afforded the tetralone **8** (4.51 g, 60%), m.p. 170–173°C; ν_{max} 1710 (COOH), 168O (CO) cm^{-1}; ^1H NMR: δ 2.73–2.85 (m, 2H, 4-H), 3.03–3.17 (m, 2H), 3.35–340 (m, 1H,) (2-H and 3-H), 3.81 (s, 3H), 3.91 (s,3H) (5,6,-OMe), 6.88 (d, 1H, *J* = 8 Hz), 7.83 (d, 1H, *J* = 8 Hz) (7-H,8-H); ^{13}C NMR: δ 194 (CO),178 (COOH),157 (C6),145 (C5), 135 (C10), 125 (C9), 124 (C8), 110 (C7), 60(OMe), 55 (OMe), 40 (C3), 39 (C2), 25(C4); MS: 205 (M^+– COOH), 190 (205 – Me); Anal. Calcd for $C_{13}H_{14}O_5$. C, 62.4; H, 5.6, Found: C, 62.6; H, 5.8%.

2-Carboxy-7,8-dimethoxytetralin (**9**): Tetralone **8** (4.51 g, 0.018 mole) in toluene (180 ml) was heated under reflux for 4 h with amalgated zinc (117 g, 1.8 mol) and hydrochloric acid (122 ml, 20%). The reaction mixture was diluted with water, extracted with dichloromethane, washed, dried and evaporated. The resulting solid substance on crystallisation with ether afforded the carboxy tetralin **9** (3.05 g, 72%); m.p. 160–163°C; ν_{max} 2100–3250 (OH), 1705(CO) cm^{-1}; ^1H NMR: δ 1.75–2.21 (m, 2H)(3-H), 2.69–3.21 (m, 5H) (1-H, 2-H and 4-H); 3.80 (s, 3H), 3.82 (s, 3H), (7,8-OMe), 6.73 (d, 1H, *J* = 8 Hz) (6H), 6.81 (d, 1H, *J* = 8 Hz) (5H), 9.71 (s, 1H, COOH),^{13}C NMR: δ 182 (COOH), 15O (C8), 146 (C7), 129 (C10), 128 (C9), 124 (C5), 110 (C6), 60 (OMe), 56 (OMe), 4O (C2), 28 (C4), 26 (C3), 25 (C1); MS: 236 (M), 190 (M^+–HCOOH); Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.1; H, 6.8, Found: C, 66.3; H, 7.0%.

2-Hydroxymethyl-7,8-dimethoxytetralin (**10**): A solution of the acid **9** (3 g, 13 mmol) in tetrahydrofuran (18 ml) was added dropwise to a suspension of lithium aluminiumhydride (551 mg, 15 mmol) in dry tetrahydrofuran (41 ml). The mixture was heated under reflux for 24 h, cooled and then added dropwise hydrochloric acid (5%), diluted with water and extracted with ether. The extract was washed, dried, and evaporated to obtain an an oil which on purification over a column of silica (eluant hexane:ether 4 : 6) afforded tetralin **10** (2.08 gr, 72%); ν_{max} 3405 (OH),1605 (C=C) cm^{-1}; ^1H NMR: δ 1.18–1.39 (m, 2H, 3-H), 1.84–1.93 (m, 2H, CH_2OH), 2.23–3.03 (m, 4H) (1-H, 4-H), 3.46–3.67 (m, 2H,11-H), 3.78 (s,3H), 3.80 (s, 3H) (OMe), 6.70 (d, 1H, *J* = 8 Hz), 6.78 (d, 1H, *J* = 8 Hz) (5,6-H). ^{13}C NMR: δ 150 (C8), 146 (C7), 130.3, 130 (C10,C9), 123 (C5), 110 (C6), 67 (CH_2OH), 59 (COMe), 56 (OMe), 37 (C2), 28 (C3), 26 (C4), 25 (C1); MS: 222 (M), 204 (M- H_2O), Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.2; H, 8.2, Found: C, 70.5; H, 8.3%.

2-Formyl-7,8-dimethoxytetralin (**11**): Chromium trioxide (6 g, 0.06 mol) was added portionwise to a solution of pyridine (9.7 ml, 0.12 mol) in dichloromethane (150 ml), cooled at 0°C and stirred 15 min under an inert atmosphere. Tetralin **10** (2 g, 0.01 mol) was added to the reaction mixture dissolved in dichloromethane (10 ml) and stirred for 20 min at room temperature. The reaction mixture was filtered and the residue was washed several times with dichloromethane. The combined extract was washed with sodium hydroxide solution (5%), hydrochloric acid (5%), water, dried and evaporated.

The resulting oily material on chromatographic purification (eluant hexane:ether 1:1) afforded the formyl tetralin **11** (1.98 g, 90%); ν_{max} 1720(CO) cm^{-1}; ^1H NMR: δ 1.60 2.10 (m, 2H, 3-H), 2.50–2.68 (m, 1H, 2-H), 2.70–3.10 (m, 4H) (1-H, 4-H), 3.79 (s, 6H) (7-OMe, 8-OMe), 6.69–6.78 (2H, ABq, *J* = 8 Hz) (5-H, 6-H), 9.73(s, 1H, CHO). ^{13}C NMR: δ 203 (CHO), 150 (C8), 146 (C7), 129 (C10), 128 (C9), 123 (C5), 110 (C6), 59 (OMe), 55 (OMe), 46 (C2), 27 (C4), 22 (C1, C3). MS: 220 (M^+), 191 (M^+ –CHO). Anal. Cacd. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3, Found: C,71.2; H, 7.5%.

2-Acetyl-7,8-dimethoxytetralin (**1**): Methylmagnesium bromide (3M, 5.7 ml, 17.mmol) in tetrahydrofuran was added dropwise under nitrogen to a solution of the formyltetralin **11** (1.91 g, 8.6 mmol) dissolved in tetrahydrofuran (80 ml). After stirring the resulting solution at room temperature for 4 h, it was cooled in an ice bath and added dropwise to water and extracted with ether. The organic extract was dried and evaporated to obtain the alcohol as an oil (1.93 g) which, without purification, was used for oxidation.

Chromium trioxide (4.90 g, 49.2 mmol) was added in several portions to a solution of pyridine (8 ml, 98 mmol) and dichloromethane. The crude alcohol (1.93 g) dissolved in dichloromethane (15 ml) was added to the resulting mixture after being stirred for 15 min and then stirred for 20 min at room temperature. The reaction mixture was filtered and washed with dichloromethane. The combined organic extract was washed successively with sodium hydroxide (5%), hydrochloric acid (5%) and water. The extract was dried, evaporated and chromatographed (eluent hexane:ether 8 : 2) to afford 2-acetyl-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene **1** (1.41 g, 74%); ν_{max} 1708 (CO)cm^{-1}; ^1H NMR: δ 1.60–2.10 (m, 2H, 3-H), 2.22 (s, 3H, COMe), 2.60–3.12 (m, 5H, 1-H, 2-H, 4-H), 3.78 (s, 3H), 3.80 (s, 3H) (7-OMe, 8-OMe), 6.69-6.78 (AB_q, 2H, 5-H, 6-H, *J* = 8 Hz); ^{13}C NMR: δ 25 (C3, C4, C1), 28 (MeCO), 47 (C2), 56 (OMe), 59 (OMe), 110 (C6), 123 (C5), 128 (C9), 129 (C10), 146 (C7), 150 (C8), 211 (CO); MS: 234 (M), 191 (M- MeCO). Anal. Cacd for $C_{14}H_{18}O_3$: C, 71.8; H, 7.7, Found: C, 72.0; H, 7.9%.

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