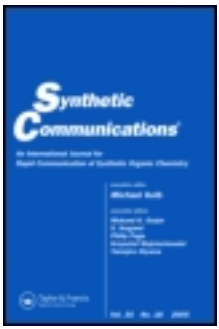

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An alternative Route to (±)-Warburganal Synthon

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An alternative Route to (±)-Warburganal Synthon+

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Abstract - The transformation of the ketone (1) to the unsaturated diester (11) a potential intermediate for the warburganal (12) is described. The Wittig reaction of theketone (1) with methylenetriphenylphosphorane afforded the olefin (2) which reacts with Woodward's reagent (MeCOOAg, I_2 and MeCOOH and H_2O) to give the diol (13). This on heating with dimethylsulfoxide afforded the tetralin (14)

Reported herein is an alternative synthesis of the diester (11)[1,2] which proved a valuable intermediate for the synthesis of (±)-warburganal (12) whose several syntheses[1,3,4] have been accomplished owing to its interesting biological properties[5,6] including antifeedant and molluscicidal activities. The present work depicted in Scheme I, was undertaken in connection with our program aimed at the development of new routes for the synthesis of bioactive terpenes.[7,8]

The ketone (1)[9] was selected as starting material for our synthetic investigation. Its transformation to the olefin (2) with diiodomethane, samarium iodide, tetrahydrofuran, hexamethylphosphoramide and N,N-dimethylaminoethanol[10] was not successful. This transformation also could not be achieved by treatment of the ketone (1) with diiodomethane, zinc and titanium tetrachloride.[11] Finally the desired olefin (2) was obtained by the use of Wittig reaction by refluxing the ketone (1) for 24 hr with triphenylmethylphosphonium bromide and sodamide in toluene.[12] Its spectroscopic

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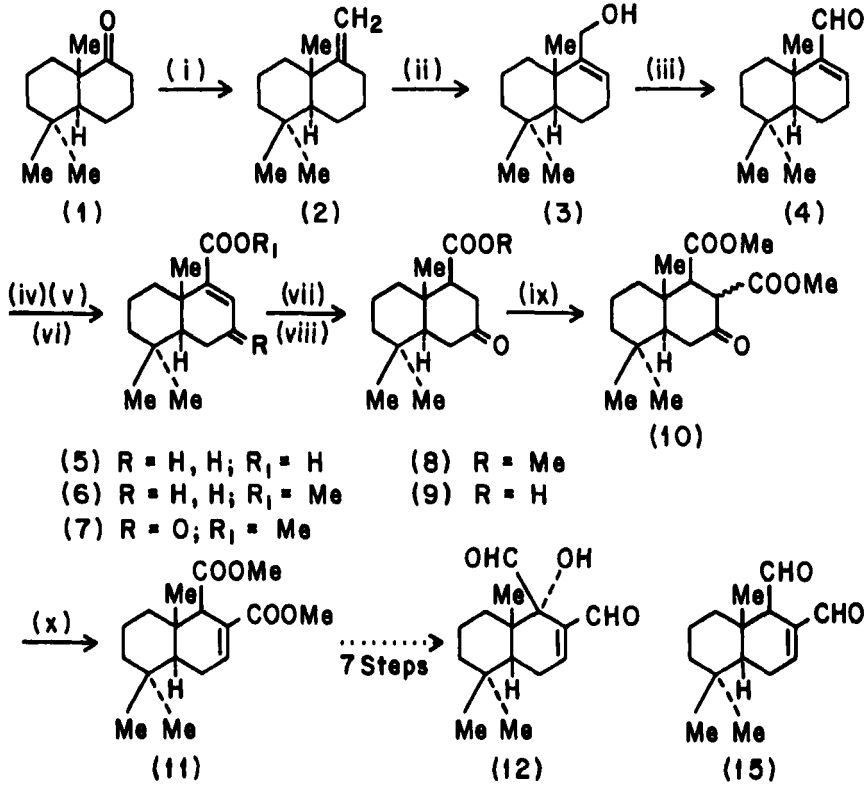
+ Dedicated to Professor Alex Nickon on the occasion of his retirement as Editor of Tetrahedron Report.



Reagents: (i) Ph_3P^+MeBr, $NaNH_2$, Toluene, (ii) SeO_2, MeCOOH, 2hr, 70°C, Na_2CO_3, MeOH, (iii) TPAP, NMO, (iv) Ag_2O, (v) DMAP, MeOH, DCC (vi) CrO_3, CH_2CL_2, 3,5 dimethyl pyrazole, (vii) H_2, Pd-C(5%), EtOH, (viii) K_2CO_3, MeI, Me_2CO, (ix) NaH, $CO(COOMe)_2$, Dioxane, (x) $NaBH_4$, MeOH TsCl, Py, LiBr, Li_2CO_3, DMF.

Scheme I

data confirmed the structure. The olefin (2) was subjected to photooxygenation[13] to give the unsaturated alcohol (3), however most of the olefin (2) was recovered. Different reaction conditions, i.e.,use of different sensitizers, change in irradiation time , use of lamps of different intensity, etc.,were investigated unsuccessfully. Thus an alternative method was tried which consisted in treatment of the olefin (2) with selenium dioxide and acetic acid[14] for 2 hr at 70°C. On careful purification the resulting material afforded the alcohol (3) in 79% yield. The alcohol (3) on oxidation[15] with 4-methylmorpholine-N-oxide and tetrapropylammonium perruthenate produced the aldehyde (4) in 80% yield. It was also observed that treatment of the olefin (2) with selenium dioxide and acetic acid for 4 hr led to the formation of the aldehyde (4) in very good yield. When the time period was extended to 6 hr, then the yield of the aldehyde (4) was low and a complex mixture was obtained. Decomposition set in soon after the purification of the aldehyde (4) over silica gel and several spots of lower R_f were obtained (tlc). Thus in subsequent experiments the aldehyde (4) was directly used for the oxidation experiment. Oxidation[16] of the aldehyde (4) with silver (I) oxide afforded the acid (5) which presented a complicated ^1H NMR spectrum. It seemed that during oxidation partial migration of the double bond occurred. Thus without purification acid (5) was esterified[17] with methanol in presence of dicyclohexylcarbodimide and N-dimethylaminopyridine to obtain the unsaturated ester (6) whose spectroscopic properties were identical with those reported previously.[18,19] The transformation of the alcohol (3) to the unsaturated ester (6) by treatment with manganese oxide and subsequently sodium cyanide, acetic acid, manganese dioxide and methanol[20] was not successful. The unsaturated ester (6) proved to be a valuable intermediate for the diterpenoid quinone royleanone[19] and thus our approach for the synthesis of the unsaturated ester (6) suggests an additional route for the synthesis of royleanone. Allylic oxidation of the ketoester (6) with chromic acid and 3,5-dimethylpyrazole in dichloromethane afforded the α,β-unsaturated ketoester (7) which was converted to the saturated ketoester (8) by catalytic hydrogenation with Pd-C (5%) in methanol. The β-configuration of the carboxylate group of the ketoester (8) was confirmed by esterification of the already reported[21] acid (9) with methyl iodide and acetone and comparison of its its spectral data with those of the ketoester (8).[22]

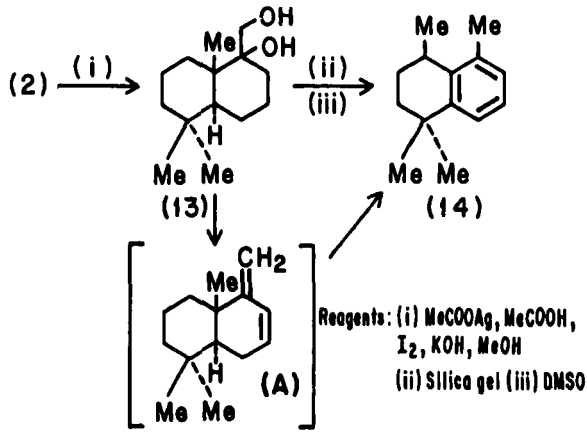
With the completion of the synthesis of the ketoester (8), we now addressed the final problem, ie, its transformation to the diester (11). The ketoester (8) on methoxycarbonylation with dimethyl carbonate afforded compound (10), whose ^1H

NMR spectrum was complicated, probably due to contamination with a small amount of enol tautomer. The compound (10) was reduced with sodium borohydride to the corresponding alcohol whose tosyl derivative on heating with lithium carbonate in dimethyl formamide yielded the desired unsaturated diester (11) in excellent yield. Its spectroscopic data were identical with those reported.[1] As the unsaturated diester (11) has already been converted[1] to (±)-warburganal (12), our alternative approach for the synthesis of the unsaturated diester (11) constitutes a potential intermediate for warburganal.

In relation to the above mentioned studies, an attempt was also made to prepare the alcohol (3) by an alternative route for its conversion to the aldehyde (4). Treatment of the olefin (2) with Woodward's reagent (MeCOOAg, I_2 and MeCOOH and H_2O) followed by alkaline hydrolysis of the resulting product gave the diol (13). The crude diol showed a strong hydroxyl group at 3550 cm^{-1} in the IR spectrum and exhibited a molecular ion m/z 190 (M^+-$2H_2O$) in the mass spectrum. In the ^1H NMR spectrum no signals of olefinic protons were observed, thus clearly indicating the formation of the diol (13). The crude material underwent aromatization affording the tetralin (14) in high yield on heating with dimethylsulfide. The desired alcohol (3) could not be isolated even in low yield. This situation was not anticipated and we believe that both of the hydroxyl group of the diol (13) underwent dehydration yielding the intermediate (A) which underwent aromatization to the tetralin (14) . (Scheme II).

It is also worthwhile to mention that an attempt to purify the diol (13) over silica gel afforded the tetralin (14) in major amount whose identity was confirmed by comparison (tlc and spectral data) with an authentic sample previously described. A negligible amount of the alcohol (3) was obtained whose identity could only be established by the infrared and mass spectrum.

The present synthesis of the diester (11) involves more steps than the published procedures[1,2] but it has been accomplished utilizing less expensive reagents and simple experimental procedures. The new compounds have been obtained in excellent yield and the overall yield (24%) is quite satisfactory. As the diester (11) has been converted to polygodial (15)[1], our alternative approach for the synthesis of the diester (11) would also constitute for polygodial (15). It can be observed the development of an alternative route for the synthesis of the unsaturated ester (6) which has proved a potential intermediate for the synthesis of the diterpenoid quinone royleanone.[19] The novel and interesting rearrangement of the



Scheme II

diol (13) to the tetralin (14) during heating with dimethylsulfoxide and also during its purification on silica gel is an interesting aspect of the present synthesis. During the synthesis of the ester (11), it has been noted that there are certain organic reactions which are very useful for the synthetic transformations of monocyclic compounds but their use is very limited when applied to bicyclic compounds.

Experimental

Unless otherwise stated, IR spectra were taken on Nicolet FT and NMR spectra recorded on Brucker AM-300 and Varian A-90 spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were carried on Dupont 21-492B. The expression work-up indicates that the solution was diluted with water, extracted with ether, washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography was carried out on silica gel, Merck, grade 60, 70-230 mesh and tlc plates were coated with silica gel and the spots were located by exposing to UV light. Microanalyses were carried out in the Chemistry Department, IVIC, Caracas.

4,4,8a-Trimethyl-8-methylene-trans-decalin (2) - A solution of $Ph_3P^+MeBr^-$ (1.84 g) and sodamide (Aldrich) (306 mg) in dry toluene (60 mL) was heated for 5 hr under nitrogen, cooled to room temperature, treated with a solution of the ketone

(1) (500 mg) in dry toluene (20 mL), and heated gently for
10 hr. The reaction mixture was washed with water, dried and toluene was evaporated. The resulting product on purification over silca gel (10 g) (eluant hexane) afforded the olefin (2) (420 mg, 85%); Rf: 0.45; NMR: δ 0.98 (s, 3H), 1.02 (s, 3H), 1.12 (s, 3H) (4,4,8a-Me), 4.77 (m, 2H, 8-CH_2): MS: m/z 192 (M^+) and 177 (M^+ -Me); Anal. Calcd. for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.46; H, 12.61.

4,4,8a-Trimethyl-Δ^8-hydroxymethylene-trans-octahydronaphthalene (3) - To a solution of the olefin (2) (405 mg) in glacial acetic acid (20 ml) was added freshly sublimed selenium dioxide (1.22 g). The mixture was stirred for 2 hr at 70°C. The acid was removed under pressure and the residue in methanol (20 mL) was treated with potassium carbonate (1.8 g). The reaction mixture was extracted with chloroform, washed and dried. The resulting product on purification on silica gel (6 g)(eluant hexane:ether 7:3) afforded the alcohol (3) (346 mg; 79%); Rf: 0.32; IR: 3450 cm^{-1} (OH), NMR: δ 1.01 (s, 3H), 1.04 (s, 3H), 1.13 (s, 3H) (4,4,8a-Me), 3.92 (m, 2H, CH_2OH), 6.02 (t, 1H, 7-H); MS: 208 (M^+) and 193 (M^+-Me). Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.74;
H, 11.64.

4,4,8a-Trimethyl-Δ^8-formyl-trans-octahydronaphthalene (4) - To a solution of the alcohol (1.02 g) in dry dichloromethane (120 mL) was added 4-methylmorpholine-N-oxide (350 mg), stirred for 10 min and tetrapropylammonium perruthenate was added (55 mg), stirred at room temperature and diluted with dichloromethane (50 ml). The organic extract was washed with a solution of sodium sulfite, saturated ammonium chloride solution, and saturated solution of cupric sulfate. The organic extract was dried and evaporated to obtain the oily material which was passed rapidly on chromatographic column of silica gel (15 g) (eluant hexane:ether 70:30) afforded the aldehyde (4) (810 mg, 80%); Rf: 0.38; IR: 1659 cm^{-1} (CO), NMR: δ 0.98 (s, 3H), 1.01 (s, 3H), 1.12 (s, 3H) (4,4,8a-Me), 4.86 (t, 1H, 7-H), 9.68 (s, 1H, CHO); MS: m/z 206 (M^+), 191 (M^+-Me) and 177 (M^+-CHO). The aldehyde (4) had a tendency to decomposition during its purification by column chromatography as was evidenced by tlc and thus a satisfactory elemental analysis could not be obtained.

4,4,8a-Trimethyl-Δ^8-carbomethoxy-trans-octahydronaphthalene (6) - To a stirred solution of silver nitrate (1.36 g) and the aldehyde (4) (805 mg) in a mixture of ethanol (20 mL) and water (15 mL) was added a solution of sodium hydroxide (165 mg NaOH in 24 mL of water). The reaction mixture was stirred for 2 hr, filtered through celite and evaporated the filtrate to a small volume. The residue was diluted with water, washed with ether and then acidified with hydrochloric acid (20 mL, 6N). The resulting mixture was extracted with ether, washed with brine and dried. Removal of the solvent yielded the acid (5) (710 mg), m.p. 210-222°C, IR: 1708 cm^{-1} (CO), 3520 cm^{-1} (OH), m/z 222 (M^+) and 207 (M^+-Me). The product was contaminated with three products of very similar Rf value in tlc and thus its NMR spectrum was very complicated.

To the crude acid (5) (705 mg) in dicloromethane (10 mL) was added 4-dimethylaminopyridine (25 mg) and dry methanol (2 mL). The reaction mixture was cooled to °C and then treated with dicyclohexylcarbodimide (802 mg) and stirred for 20 min at °0 and then 4 hr at room temperature. The reaction mixture was filtered and the filtrate was evaporated to obtain an oily residue. This was dissolved in hexane, washed with dil. hydrochloric acid, dil. sodium bicarbonate solution and then with brine, dried and evaporated. The residue obtained on chromatographic purification on silica gel (10 g) (eluant hexane;ether 3:7) yielded the ester (6) (774 mg,84%), Rf: 0.29; IR: 1720 cm^{-1} NMR δ 1.02 (s, 3H), 1.06 (s, 3H), 1.12 (s, 3H) (4,4,8a-Me), 3.76 (s, 3H, OMe), 6.12 (t, 1H, 7-H), MS: m/z 236 (M^+) and 191 (M^+- 3 Me). Anal. calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.26; H, 10.26.

4,4,8a-Trimethyl-Δ^8-carbomethoxy-6-keto-trans-octahydronaphthalene (7) - To a suspension of chromium trioxide (1.84 g) in dry dichloromethane (50 mL) at -25°C was added rapidly 3,5-dimethylpyrazole (1.78 g). The reaction mixture was stirred for 35 min and then a solution of the unsaturated ester (6) (605 mg) in dichloromethane (2 mL) was added. The resulting dark solution was stirred at -25°C for 5 hr, and then a solution of the sodium hydroxide (5M, 55mL) was added. The usual workup followed by chromatographic purification of the resulting product on silica gel (8 g) (eluant hexane:ether 3:7) afforded the ketone (7), (576 mg, 90%), Rf: 0.26; IR (cm^{-1}): 1725 (ester CO), 1645 (CO), ^1H NMR: δ 0.98 (s, 3H), 1.01 (s, 3H), 1.08 (s, 3H) (4,4,8a-Me), 3.68 (s, 3H, OMe), 5.21 (s, 1H, 7-H), MS: m/z

250 (M^+). Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.02; H, 8.89.

4,4,8a-Trimethyl-8-carbomethoxy-6-keto-trans-decalin (8) - A mixture of the ketoester (7) (575 mg) in ethanol (30 mL) and Pd-C (5%, 150 mg) was stirred under hydrogen at atmospheric pressure for 8 hr. Workup and chromatographic purification over silica gel (8 g) (eluant hexane:ether 7:3) afforded the saturated ketoester (8)' (550 mg, 95%), Rf: 0.24; IR: 1735 (ester CO), 1719 (CO), ^1H NMR: δ 1.01 (s, 3H), 1.04 (s, 3H), 1.12 (s, 3H) (4,4,8a-Me), 3.65, (s, 3H, OMe), MS: m/z 237 (M^+-Me), 205 (M^+-Me-MeOH), 177 (M^+-Me-MeCOOH). Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.43; H, 9.61.

Esterification of 4,4,8a-Trimethyl-8-carboxy-6-keto-trans-decalin (9) - To a solution of the acid (9) (220 mg) in acetone (20 mL) was added dry potassium carbonate (250 mg) and methyliodide (3 mL) and heated under reflux for 10 hr. The workup followed by chromatographic purification over silica gel (5 g) (eluant hexane:ether 7:3) yielded the ketoester (8) (174 mg, 75%) Rf: 0.34 and its spectroscopic data (NMR and IR) were identical with those reported for the above mentioned ketoester (8).

4,4,8a-Trimethyl-7,8-dicarbomethoxy-trans-octahydronaphthalene (11) - A mixture of the ketoester (8) (450 mg), sodium hydride (300 mg, 50% dispersion oil), dimethyl carbonate (1.28 g) and 1,2-dimethoxyethane (20 ml) was stirred and heated at 80-85°C for 2 hr under nitrogen. Work-up afforded the compound (10) (585 mg), MS: m/z 175 (M^+-Me 2 MeCOOH). Attempts to purify the product (10) by chromatographic purification proved fruitless and thus was used directly for the next step.

To a solution of the compound (10) (580 mg) in ethanol (15 ml), cooled to 0°C, was added sodium borohydride (100 mg) and stirred for 30 min. Workup afforded an alcohol, IR (cm^{-1}) 3450 (OH), 1725 (CO). To the crude alcohol (525 mg) in pyridine (6 mL) was added p-toluenesulfonyl chloride (400 mg), stirred for 24 hr at room temperature and then poured on ice. Workup afforded the tosylate (592 mg) which was used directly for the next step.

A mixture of the tosylate (592 mg) and anhydrous lithium bromide (602 mg), lithium carbonate (602 mg) in dimethylformamide (15 ml) was heated in an

oil bath 130-140°C for 3 hr. Workup followed by chromatographic purification over silica gel (10 g) (eluant hexane:ether 8:2) afforded the desired product (10) (446 mg, 85%), m.p. 82-83°C (lit.[1] 82.5-83°C), Rf: 0.24; IR: 1730 (CO), 1725 (CO); ^{1}H NMR: δ 0.88 (s, 3H), 0.92 (s, 3H), 0.98 (s, 3H) (4,4,8a-Me), 1.24 (dd, m, J=4, 10 Hz, 4a-H), 3.22 (ddd, J=2, 2.5, 4 Hz, 1-H, 8-H), 3.72 (s, 3H, OMe), 3.75 (s, 3H, OMe), 7.04 (ddd, J=2, 3, 6 Hz, 6-H), MS: m/z 294 (M^+). Anal. calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90%. Found: C, 69.44; H, 8.94.

1,5,5,8-Tetramethyl tetralin (14) - To the olefin (2) (405 mg) in acetic acid (12 mL) was added silver acetate (1.12 g) and iodine (802 mg), stirred 1 hr at room temperature and treated with acetic acid (2 mL), water (1 mL), and heated at 90-95°C for 5 hr. The solution was cooled, treated with sodium chloride, filtered and the residue was washed several times with chloroform. The combined filtrate was concentrated and the resulting material was treated with methanol (5 mL) and potassium hydroxide (2 g) and heated for 12 hr at 40°C. Work-up afforded the diol (13) (430 mg), IR 3490 (OH), MS: m/z 226 (M^+), 208 (M^+-H_2O), 190 (M^+-$2H_2O$).

The crude diol (13) (425 mg) on chromatographic purification on silica gel (10 g) (eluant hexane:ether 8:2) yielded the tetralin (14) (352 mg, 90%), Rf: 0.62; ^{1}H NMR: δ 0.88 (s, 3H), 0.92 (s, 3H), 1.12-1.15 (m, 1H, 8-Me), 2.01 (s, 3H, 1-Me), 6.98-7.11 (m, 3H, aromatic protons), MS: m/z 188 (M^+), 173 (H -Me), 158 (M^+-2Me). Anal. Calcd. for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 89.35; H, 10.73.

The diol (13) (205 mg) in dimethylsulfoxide (5 mL) was heated on oil bath at 150-160°C under nitrogen. Work-up followed by chromatographic purification over silica gel (eluant hexane:ether 8:2) afforded the tetralin (14) (175 mg) whose spectroscopic properties were identical with those previously mentioned.

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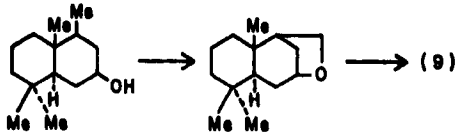
followed by further oxidation with chromic acid in acetic acid at room temperature.



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