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A SIMPLE SYNTHESIS OF γ-CYCLOHOMOCITRAL

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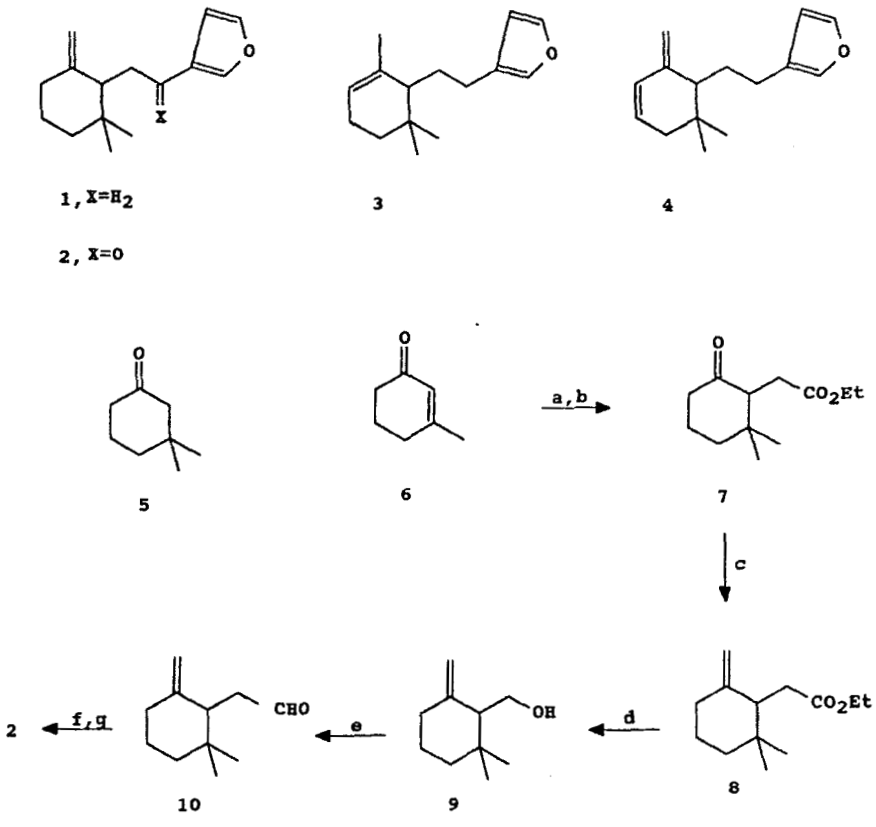
Abstract.- A simple and efficient synthesis for γ-cyclohomocitral (10), a key and versatile intermediate for the synthesis of some furanosesquiterpenes, is described. The formal total synthesis of (±) Pallenscensone (2) was accomplished.

A number of sesquiterpenes containing a cyclohexane and furan units e.g. (+)-dihydropallescensin-2 (1), (+)-Pallescensone (2), Pallescensin-1 (3) and Pallescensin-2 (4) have been isolated from marine sponges[1-3]. A singular case is the (+)-Pallescensone (2), a new furanosesquiterpene isolated in 1987 from *Dictyodendrilla cavernosa.* The structure of (2) was elucidated based on spectroscopic evidence[2]. Interestingly, two years previous to the isolation of the natural product, pallescensone in its racemic form had been prepared[4] as a key intermediate in the synthesis of (±) ancistrofuran and its steroisomers.

Several strategies have been followed in order to synthetize the above mentioned furanosesquiterpenoids (1-4), including cyclizations reactions[5], classic Claisen[4] and Azaclaisen rearrangements[6]. In these approaches an appropriate



a) MeMgI; b) $BrCH_2CO_2Et$; c) Wittig; d) LAH, THF; e) PDC/CH_2Cl_2;

f) 3-Bromofuran, t-BuLi, -78°C ; g) PDC/CH_2Cl_2

sustituted cyclohexane moiety has been used as a key intermediate for their synthesis[4-7], consequently these types of cyclohexane derivatives have emerged as a highly attractive targets for synthesis. In the present work we describe a facile and efficient synthesis of γ-cyclohomocitral (10), a key and versatile intermediate for the synthesis of several natural products, including

furanosesquiterpenes[4,6,8]. Thus, the synthesis of (10) was carried out following Scheme 1.

The regioselective alkylation of the non-symmetrical ketones like (5) at their hindered position has been achieved generating "the desired anion" via the well known copper (I) catalized 1,4-conjugate addition reaction between the α,β unsaturated ketone (6) and a Gringnard reagent, producing after the addition the enolate anion which can normally be trapped with a variety of electrophiles[9]. Indeed, when ketone (6) was treated with 1.1 equivalent of methylmagnesium iodide in the presence of cuprous iodide or BF_3 in ether at -5°C, the 1.4 addition reaction took place and the corresponding enolate was generated and alkylated with 2-bromoethylacetate to give the ketone (7) in 77% yield. A classical Wittig reaction between ketone (7) and methyl-triphenylphosphonium iodide with butyllithium in THF, gave the corresponding alkene-ester (8) in 85% yield. Attempts to convert straightforwardly the ester (8) into aldehyde (10) using 1.1 equivalent of DIBAL-H as reducing agent under various conditions proved futile, giving a mixture of the alcohol (9) and unreacted starting material. However alcohol (9) was readily prepared by reduction of ester (8) with LAH in 96% yield. The (s)-enantiomer of this alcohol (9) had previously been prepared[6] for the synthesis of (+)-dihydropallescensin-2 (1). The convertion of (9) into γ-cyclohomocitral (10) was carried out in 90% yield by the treatment of (9) with PDC. The formal total synthesis of (±)-(2) was thus accomplished in a one-pot procedure in 85% yield from (10) following our slightly modified version of the method described by R. Baker[4].

In summary, this approach provides a convenient four-step synthesis of γ-cyclohomocitral, an important intermediate for the synthesis of several furanosesquiterpenes from comercially available 3-methyl,2-cyclohexene-1-one as starting material in 56.5% overall yield.

EXPERIMENTAL

The ir spectra were recorded on a Nicolet FT-5SX spectrophotometer, the ^1H NMR spectra were obtained on a Varian-Gemini 200 and a Varian VXR 300S instruments with TMS as internal standard. Mass spectra were recorded with a Hewlett-Packard 5985-B spectrometer with gc/ms system, compounds were introduced through the direct reaction probe.

Ethyl,2,2-dimethyl,6-oxocyclohexylacetate (7).

In a 100 ml three-necked round bottom flask equipped with a magnetic stirrer and argon atmosphere 0.2204 g (9.07 mmol) of magnesium and 1.288 g (9.07 mmol) of methyl iodide in 20 ml of anhydrous ether were placed and stirred at r.t. until the magnesium was dissolved. The reaction mixture was cooled to -5°C and finelly powdered coprous iodide (200 mg) was added. After stirring for 30 min, a solution of 1.0 g (9.07 mmol) of freshly destilled 3-methyl,2-cyclohexene-1-one in 10 ml of anhydrous ether was added and the mixture was further stirred for 1.5 h at the same temperature. After this time, 20 ml of anhydrous HMPA and a solution of 1.51 g (9.07 mmol) of α-bromoethylacetate in 5 ml of HMPA were added dropwise and the reaction mixture stirred for 15 h at r.t. After the addition of a saturated solution of NH_4Cl and ether, the organic layer was separated and the aqueous layer was extracted (2 x 15 ml) with ether. The combined organic layers were washed with brine and water, dried on anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified on a silica gel column using a mixture of hexane ethylacetate (93:7) as eluent to give 1.49 g (77%) of (7) as a colorless oil. IR (film): 2962, 2936, 1735, 1712, 1461, 1323, 1175 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.72 (s, 3H), 1.06 (s, 3H), 1.25 (t, 3H, J=7.5Hz), 1.50-2.00 (m, 4H), 2.20 (dd, 1H, J=3.0Hz, J=17Hz) 2.37 (m, 2H), 2.69 (dd, 1H,

J=17Hz, J=10Hz), 2.85 (dd, 1H, J=10Hz, J=3.0Hz), 4.10 (q, 2H, J=7.5Hz); MS: m/z 212 (M^+, 3), 41 (100). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.73; H, 9.35.

Ethyl,2,2-dimethyl,6-methylenecyclohexylacetate (8).

In a round bottom flask fitted with a reflux condenser, magnetic stirrer and argon atmosphere, a suspension of triphenylphosphonium iodide (3.43 g, 8.49 mmol) in 20 ml of anhydrous THF was treated with a solution of 5 ml of n-butyllithium (2N in THF) and the reaction mixture was stirred for 4 h at room temperature. After this time, a solution of 1.80 g (8.49 mmol) of the ketoester (7) in 10 ml of anhydrous THF was added dropwise and the reaction mixture was heated under reflux for 8 h. After cooling, ether (20 ml) was added and the precipitate was removed by filtration. The filtrate was washed with water, dried over magnesium sulfate and the solvent removed under reduced pressure. The residue was chromatographed on a silica gel column using pentane as eluent to yield 1.52 g (85%) of the alkene (8) as a colorless oil. IR (film): 3075, 2930, 1737, 1156, 892, 757 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.79 (s, 3H), 0.95 (s, 3H), 1.23 (t, 3H, J=8Hz), 1.40 (m, 2H), 1.55 (m, 2H), 2.05 (m, 1H), 2.20 (m, 1H), 2.42 (m, 3H), 4.1 (t, 2H, J=8Hz), 4.55 (s, 1H), 4.75 (s, 1H), 4.75 (s, 1H); MS: m/z 210 (M^+, 5)), 41 (100). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.17; H, 10.49.

2,2-Dimethyl,6-methylenecyclohexylethanol (9).

A solution of the vinylcyclohexane (8), (4.0 g, 19 mmol) in anhydrous THF (25 ml) was added dropwise to a suspension of lithium aluminium hydride (0.75 g, 20 mmol) in THF (10 ml) and stirred vigorously at room temperature for 5 h. The reduction complex was decomposed by the dropwise addition of 5

ml of water and filtered. The filtrate was washed with water, dried on anhydrous sodium sulfate and the ether evaporated to give the crude reaction product which was purified by column chromatography on silica gel using a mixture of hexane ethylacetate (90:10) as eluent to give 3.07 g (96%) of the alcohol (9) as a colorless oil. IR (film): 3337, 3067, 2929, 1644, 1453, 1052, 889 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.82 (s, 3H), 0.91 (s, 3H), 1.63 (m, 6H), 1.92 (dd, 1H, J=5Hz, J=15Hz), 2.1 m, 2H), 3.62 (m, 2H), 4.62 (m, 1H), 4.80 (m, 1H); MS: m/z 168 (M^+, 0.3), 153 (M^+-15, 5), 41 (100). Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.63; H, 12.24.

γ-Cyclohomocytral (10).

To a well-stirred solution of 3.0 g (17.8 mmol) of alcohol (9) in 30 ml of dry dichloromethane was added 6.71 g (17.8 mmol) of pyrdinium dichromate in small portions and the reaction mixture stirred at room temperature for 24 h. After this time, ether was added and the solid removed by filtration. The filtrate was passed through silica gel, the solvent was removed under reduced pressure and the residue purified by column chromatography using a mixture of hexane ethyl acetate (93:7) as eluent to afford 2.67 g (90%) of the γ-cyclohomocitral (10). IR (film): 3072, 2927, 2717, 1726, 1457, 894 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.79 (s, 3H), 0.98 (s, 3H), 1.40 (m, 2H), 1.57 (m, 2H), 2.20 (m, 2H), 2.50 (m, 3H), 4.52 (s, br, 1H), 4.82 (s, br, 1H), 9.65 (t, 1H); MS: m/z, 166 (M^+, 4), 41 (100). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.38; H, 10.77.

(+)-Pallescensone (2).

In a two-necked round bottom flask equipped with a magnetic stirrer and argon atmosphere a solution of 1.38 g (9.03 mmol) of 3-bromofuran in

anhydrous THF (10 ml) was placed and cooled to -78°C. A solution of tert-butyllithium (15 ml, 1.33 M in THF) was added and stirred for 40 min. A solution of 1.5 (9.04 mmol) of γ-cyclohomocitral in a mixture of 6 ml of anhydrous THF and 15 ml of anhydrous HMPA was added dropwise and the mixture stirred at -78°C for further 1.5 h. After the addition of a saturated solution of NH_4Cl and ether, the organic layer was separated, washed with brine, water, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The crude reaction product was diluted with anhydrous methylene chloride and 3.2 g (8.54 mmol) of pyridinum dichromate was added and the mixture stirred at room temperature for 24 h. After this time, ether was added and the solid was removed by filtration. The filtrate was passed through silica gel. The solvent was removed under reduced pressure. Flash chromatography of the residue afforded 0.8 g (85%) (±) Pallescensone (2). The spectral properties were found to be identical with those reported for this compound[2].

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