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A NEW SYNTHESIS OF DESMETHOXYENCECALIN

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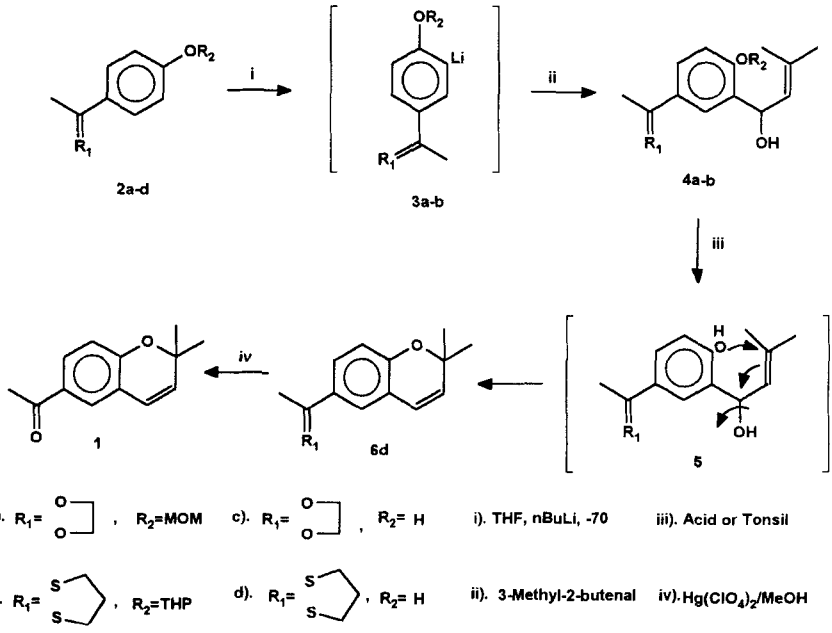
Abstract.- A new synthesis of the title compound using aryllithium salts as key intermediates is described. The synthetic approach is mainly based on a cyclization reaction that mimics the process by which is believed benzopyran rings are formed in nature.

Desmethoxyencecalin (**1**), a natural product containing a 2H-chromene ring system was first isolated from *Helianthella uniflora*[1] and later from *Gattum flourensia*[2], and its structure determined by spectroscopic methods. More recently, this compound was also isolated along other chromenes from *Blepharispermum subsessile* during a screening program of Indu plant extracts for the isolation and identification of natural ocurrent insects control agents[3]. From all of chromenes isolated, only (**1**) showed biological activity[3]. Indeed, desmethoxyencecalin exhibited oviposition deterrant activity against the potato tuber moth *Phthorimaea operculella.*

Several procedures including the preparation[1,4] of (**1**), have been described for the synthesis of 2,2-dimethyl-2H-chromenes, among them, the

reaction of coumarins with Grignard[5], oxidation of chromans[6], thermal ring closure rearrangement of propargyl phenyl ethers[7] and cyclization of 2-isoprenyl phenols catalized by palladium (II) salts[8]. The aromatic lithiation reaction has been widely applied to the synthesis of condensed aromatic heterocyclic compounds, however few 2,2-dimethyl-2H-chromenes have been synthetized through this method[9]. Here we describe a new synthesis of the title compound by utilizing aryllithium as key intermediates. The synthetic route to (**1**) (Scheme) is mainly based on a cyclization reaction of an allylic-benzylic carbinol (**5**), process which mimics the way by which is believed benzopyran rings are formed in nature[10]. So the synthesis of (**1**) was carried out as follows.



In a different set of experiments, the 4-hydroxyacetophenone was treated either with ethylene glycol and p-toluensulfonic acid or 1,3-propanedithiol in the

presence of BF_3 at room temperature to give the corresponding ketal (**2c**) and the 1,3-dithiane (**2d**) in 75% and 96% yield respectively. The hydroxyl group were in turn protected by reacting the ketal (**2c**) with chloromethyl methyl ether and the tioketal (**2d**) with dihydropyran to afford the compounds (**2a**) and (**2b**) in 69% and 91% yield respectively. The aromatic lithiation reaction was carried out under argon atmosphere by treatment of (**2a**) and (**2b**) with n-butyllithium at room temperature in either anhydrous ether or THF. The 1,2-addition reaction was performed by adding freshly destilled 3-methyl-2-butenal to the corresponding lithium salts **3a** and **3b** affording the allylic-benzylic alcohols (**4a**) and (**4b**) in 54% and 81% yield.

In order to transform the protected hydroxyl and ketone groups in their parent functionalities and to carry out the subsequent cyclization in one pot reaction to afford (**1**), the alcohol (**4a**) was treated under the usual acid conditions[11] affording in all the cases the desired product (**1**) in very low yield. Attempts to improve the yield of the reaction under various conditions[12] proved futile.

In a previous report[13] we described a selective method to cleave tetrahydropyranyl ethers with tonsil, a comercially available Mexican bentonitic earth, which seems to have similar behaviour as Lewis acid[14]. Thus, in order to improve the yield of the synthesis of (**1**), we decided to protect the carbonyl compound with an acid resistant group i.e. a thioketal, and the hydroxyl group as its tetrahydropyranyl ether and to carry out the deprotection with tonsil. Indeed, when (**4b**) was treated with tonsil in wet acetone under reflux for 4 h, the chromene (**6d**) was obtained in 83% yield.

Finally, the synthesis of (**1**) was accomplished in 53% overall yield starting from 4-hydroxyacetophenone by regenerating the carbonyl compound in the usual manner[15] in 90% yield.

In summary an alternative synthesis to the desmethoxyencecalin was performed via a cyclization reaction, which mimics the process by which is believed benzopyrane rings are formed in nature and using aryllithium compounds as intermediates.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. The ^{1}H-NMR were recorded on a Varian-Gemini 200 (200MHz) instrument either in $CDCl_3$ or C_6D_6 with TMS as internal standard. The IR spectra were run on a Nicolet FT-55X spectrophotometer. Mass spectra were obtained with a Hewlett Packard 5985B spectrometer with gc/ms system, compound were introduced through the direct insertion probe.

4-(2-Methyl-(1,3)-dioxan-2-yl)phenol (2c). This compound was prepared following the general procedure described by Eliel et al.[16], 75% yield, mp 74-76°. IR ($CHCl_3$): 3595, 3361, 1611, 1512, 1433, 1375, 1038, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.65 (3H, s), 3.82 (2H, m, A,A'), 4.01 (2H, m, B,B'), 6.75 (2H, m, A,A'), 7.32 (2H, m, B,B'); MS: m/z 180 (M^+, 0.1), 165 (100).

4-(2-Methyl-(1,3)-dithian-2-yl)phenol (2d). To a well stirred solution of 3.0 g (22 mmol) of 4-hydroxyacetophenone in 15 ml of dry CH_2Cl_2 was added dropwise 1.6 ml of $BF_3.Et_2O$ and 2.65 ml (2.86 g, 26 mmol) of 1,3-propanedithiol at 0°C. After the addition, the reaction mixture was stirred at room temperature for 2 h. After this time, water (100 ml) was added and the organic layer was separated, washed with water, dried over anhydrous Na_2SO_4

and the solvent removed under reduced pressure affording 4.81 g (96%) of (**2d**). mp 65-66°. IR ($CHCl_3$) 3359, 3355, 3032, 2979, 2910, 2833, 1608, 1506, 1426, 1045, 1369 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.83 (3H, s), 1.95 (2H, m), 2.75 (4H, m), 5.71 (1H, s, exchangeable with D_2O), 6.82 (2H, m, A,A'), 7.75 (2H, B,B'); MS: m/z 226 (M^+,28), 152 (100).

2-Methyl-2-(4-methoxymethylenoxyphenyl)-(1,3)dioxolane. (2a). In a round bottom flask fitted with a magnetic stirrer and nitrogen atmosphere, sodium hydride and anhydrous THF were placed and the system swept with nitrogen. The suspension was cooled to 0° and a solution of 10 g (56 mmol) of ketal (**2c**) in 10 ml of anhydrous THF was added dropwise via hypodermic syringe. After stirring for 30 min at room temperature the reaction mixture was again cooled to 0° and a solution of 5.4 g (5.1 ml, 67 mmol) of chloromethyl methyl ether and 5 ml of THF was added via a syringe and the mixture stirred for 1 h at room temperature. After this time, the solvent was removed under reduced pressure and CH_2Cl_2 was added, cooled with an ice bath and a 10% solution of NaOH was added dropwise. The organic layer was separated and the aqueous layer was extracted (2 x 20 ml) with CH_2Cl_2. The combined organic layers were washed with water, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was chromatographed by column chromatography on silica gel using a 95:5 mixture of hexane:ethyl acetate as eluent to give 8.6 g (69%) of (**2a**) as a white solid. mp 30°, IR (film): 3040, 2955, 2892, 1610, 1508, 1433, 1096, 837 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.63 (3H, s), 3.45 (3H, s), 3.81 (2H, m, A,A'), 4.05 (2H, m, B,B'), 5.15 (2H, s), 6.95 (2H, m, B,B'), 7.41 (2H, m, B,B'); MS: m/z 224 (M^+,0.4), 45 (100). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.42; H, 7.01.

3-Methyl-1-[2-methoxymethylenoxy)-5-(2-methyl-(1,3)dioxan-2-yl)phenyl]-2-butenol (4a). In a three-necked round bottom flask equipped with magnetic stirrer and argon atmosphere a solution of 3.3 g (15 mmol) of (**2a**) in 30 ml of anhydrous ether was placed and 1.6 M solution of n-butyllithium in hexane (1.15 g, 11.3 ml, 18 mmol) was added and the mixture stirred for 2 h at room temperature. After this time, the yellow pale suspension formed was cooled to -10°C and a solution of 1.26 g (1.5 ml, 18 mmol) of freshly destilled 3-methyl-2-butenal in anhydrous ether was added dropwise via a hypodermic syringe and stirred at room temperature overnight. The reaction mixture was diluted with AcOEt and the organic layer washed with water, dried over anhydrous Na_2SO_4 and the solvent eliminated under reduced pressure. The residue was chromatographed on silica gel and using a 95:5 mixture of hexane-ethyl acetate as eluent to afford 2.45 g (54%) of (**4a**) as an oil. IR (film): 3598, 3006, 2934, 2828, 1609, 1494, 1376, 1191, 1155, 1075, 1038, 1000 cm^{-1}; ^1H NMR (C_6D_6): δ 1.65 (3H, s), 1.72 (3H, d, J=1Hz), 1.75 (3H, d, J=1Hz), 3.15 (3H, s), 3.45 (2H, m, A,A'), 3.62 (2H, m, B,B') 4.85 (2H, m), 5.52 (1H, dq, J=8Hz, J=1Hz), 5.81 (1H,d, J=8Hz) 7.05 (1H, d, J=8Hz), 7.45 (1H, dd, J=8Hz, J=3Hz), 7.92 (1H, d, J=3Hz); MS: m/z 308 (M^+,7), 231 (100). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.37; H, 7.90.

Desmethoxyencecalin (1) from (4a). To a well-stirred solution of 3 g (97 mmol) of alcohol **4a** in 30 ml of acetone was added 0.5 ml of hydrochloric acid and sitrred for 3 h at room temperature. After this time, the acetone was removed under reduced pressure without heating and the residue diluted with CH_2Cl_2 and water. The organic layer was washed with a 10% solution of $NaHCO_3$, water, dried over anhydrous Na_2SO_4 and the solvent evaporated. The

residue was chromatographed using a 9:1 mixture of hexane-ethyl acetate to afford 460 mg (17%) of chromene (**1**).

2-Methyl-2-(4-tetrahydropyran-4-yloxy)-(1,3)-dithiane. (2b). To a solution of 6.2 ml (5.7g, 68 mmol) of 2H-dihydropyrane in 15 ml of ethyl acetate and 0.5 ml of concentrated hydrochloric acid, was added during 10 min. a solution of 4.5 g (20 mmol) of thioketal (**2d**) in 20 ml of ethyl acetate and the reaction mixture was vigorously stirred at room temeprature for 24 h. After this time, 15 ml of a 10% solution of NaOH was added and the organic layer was separated, washed with water, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The solid residue was crystallized from methanol to give 5.62 g (91%) of (**4b**) as white crystals. mp 80-81° IR ($CHCl_3$): 2948, 2855, 1605, 1503, 1442, 1425, 1335, 1072, 1035 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.65-1.90 (8H, m), 1.78 (3H, s) 2.73 (4H, m), 3.61 (1H, m), 3.83 (1H, m) 5.37 (1H, m), 7.05 (2H, m, A,A'), 7.78 (2H, m, B,B'); MS: m/z 310 (M^+,6.2), 152 (100%). Anal. Calcd for $C_{16}H_{22}O_2S_2$: C, 61.90, H, 7.14. Found: C, 62.07; H, 7.09.

3-Methyl-1-[2-(tetrahydropyran-4-yloxy)-5-(2-methyl-(1,3)-dithian-2-yl) phenyl]-2-butenol (4b). This compound was prepared following the same procedure described for the preparation to alcohol (**4a**), Oil: IR (film): 3580, 3300, 2920, 2870, 1670, 1200, 1030, 970, 910 cm^{-1}; ^1H NMR (C_6D_6): δ 1.52 (8H, m), 1.65 (1H, d, J=1Hz), 1.75 (1H, d, J=1Hz), 1.83 (3H, s), 2.45 (4H, m), 2.71 (1H, br, exchangeable with D_2O), 3.35 (1H, m), 3.65 (1H, m), 5.25 (1H, m), 5.65 (1H, dq, J=9Hz, J=1Hz), 5.91 (1H, d, J=9Hz), 7.15 (1H, d ,J=8Hz), 7.85 (1H, dd, J=8Hz, J=2Hz), 8.30 (1H, d, J=2Hz); MS: m/z 310

(M^+-THP). Anal. Calcd fro $C_{21}H_{30}O_3S_2$: C, 63.92, H, 7.66. Found: C, 70.17; H, 7.55

2,2-Dimethyl-6-[2-methyl-(1,3)dithian-2-yl]2H-chromene. (6d). A well stirred solution of 0.3 g (0.76 mmol) of alcohol (**4b**) in 30 ml of acetone, 3 g of tonsil and 0.5 ml of destilled water was heated under reflux for 4 h. The reaction was monitored by tlc. After this time the tonsil was filtered and washed with acetone. The filtrate was dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was chromatographed using a 95:5 mixture of hexane-ethyl acetate as eluent to afford 184 mg (83%) of chromene (**6d**). IR (Film): 2970, 2883, 1658, 1432, 1278, 1127, 1062, 1020 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.41 (6H, s), 1.55 (2H, m), 1.78 (3H, s), 2.71 (4H, m), 5.57 (1H, d, J=10Hz), 6.33 (1H, d, J=10Hz), 6.75 (1H, d, J=8Hz), 7.55 (1H, dd, J=8Hz, J=2Hz), 7.75 (1H, d, J=2Hz); MS: m/z 292 (M^+, 5). Anal. Calcd for $C_{16}H_{20}OS_2$: C, 65.74, H, 6.89. Found: C, 6.93; H, 6.73.

Desmethoxyencecalin (1) from (6d). The dethioacetalization reaction was carried out following the method reported by Fujita et al.[15] in 90% yield. The spectral properties were found to be identical with those reported for this compound[1].

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