# SYNTHESIS AND STEREOCHEMICAL STUDIES OF NEW 2-(2-FURYL)CYCLANONES

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Abstract- A study was conducted on factors influencing product distributions in the two-step formation of novel 2-(2-furyl)cyclanones using $^1H$ nmr coupling constants values and nOe difference experiments. The 3-(2-furyl)norbornan-2-one and 2-(2-furyl)-5,6-dimethoxy-3-methylindan-1-one nuclei were chosen to illustrate pertinent stereochemical criteria which may be exploited in selecting desired derivatives of these species with well defined stereochemistry. These novel adaptable synthons deserved wider recognation as new heterocyclic system promotors.

## INTRODUCTION

2-(2-Furyl)cyclanones (**1**) have been shown to be extremely useful in the synthesis of heteroaromatic nuclei of pharmacological interest.[1] We have been particularly interested in the chemistry of 2-(2-furyl)tetralones, which can be converted into the benzo[*c*]phenanthridine nucleus in a four step synthesis.[1a,b] The naturally occurring alkaloids, nitidine and fagaronine, belong to this heterocyclic family and exhibit many important biological activities.[2]

Our synthetic approach deals with a modification of D'Ascolli's 2-(2-furyl)-1,3-dicarbonyl synthesis[3] and Krapcho's decarboxylation procedure[4] (Scheme 1). In this established reaction,[3] ß-keto-esters act as both solvent and reagent, whilst a large excess of acid is used with respect to the furan promoter. In the step which follows, ß-keto-esters are refluxed in high boiling polar solvents, containing one of several inorganic salts.[4]

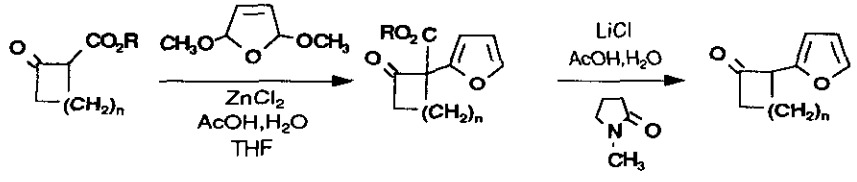
Following our method, using various cyclanonic ß-keto-esters (**2**) (Scheme 1, n= 2 to 4), and avoiding drastic acid media, useful furanic alicyclic synthons (**1**) were isolated in extremely high yields.[5]

In this paper, we wish to report the preparation of 2-(2-furyl)cyclanones (**4**, **5**) (Figure 1). Interestingly, the norbornane moiety has been widely used in therapeutic compounds as well as perfumeries, pesticides

and insecticides. Further synthetic studies in our laboratory centred around this novel synthon led us to the discovery of previously unknown heterocyclic systems and an array of novel compounds.[6]

To elucidate some finer mechanistic details in the reaction sequence leading to 3-(2-furyl)norbornan-2-one (**4**) and 3-methyl-2-(2-furyl)indan-1-one (**5**).[1c] we conducted stereoisomeric studies through nmr experiments, applied to their respective precursors (Figure 1). The rigid molecular framework of the norbornanone system and the five membered unsaturated cyclanone ring system of the indan-1-one derivative (containing an asymmetric centre) provided us with ideal model systems for conformational and stereochemical analyses.

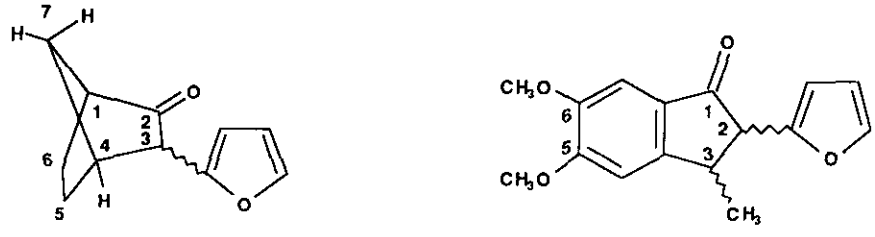
Scheme 1




**2** **3** **1**

n=2,3,4 R= $CH_3$, $C_2H_5$

Figure 1




**4** **5**

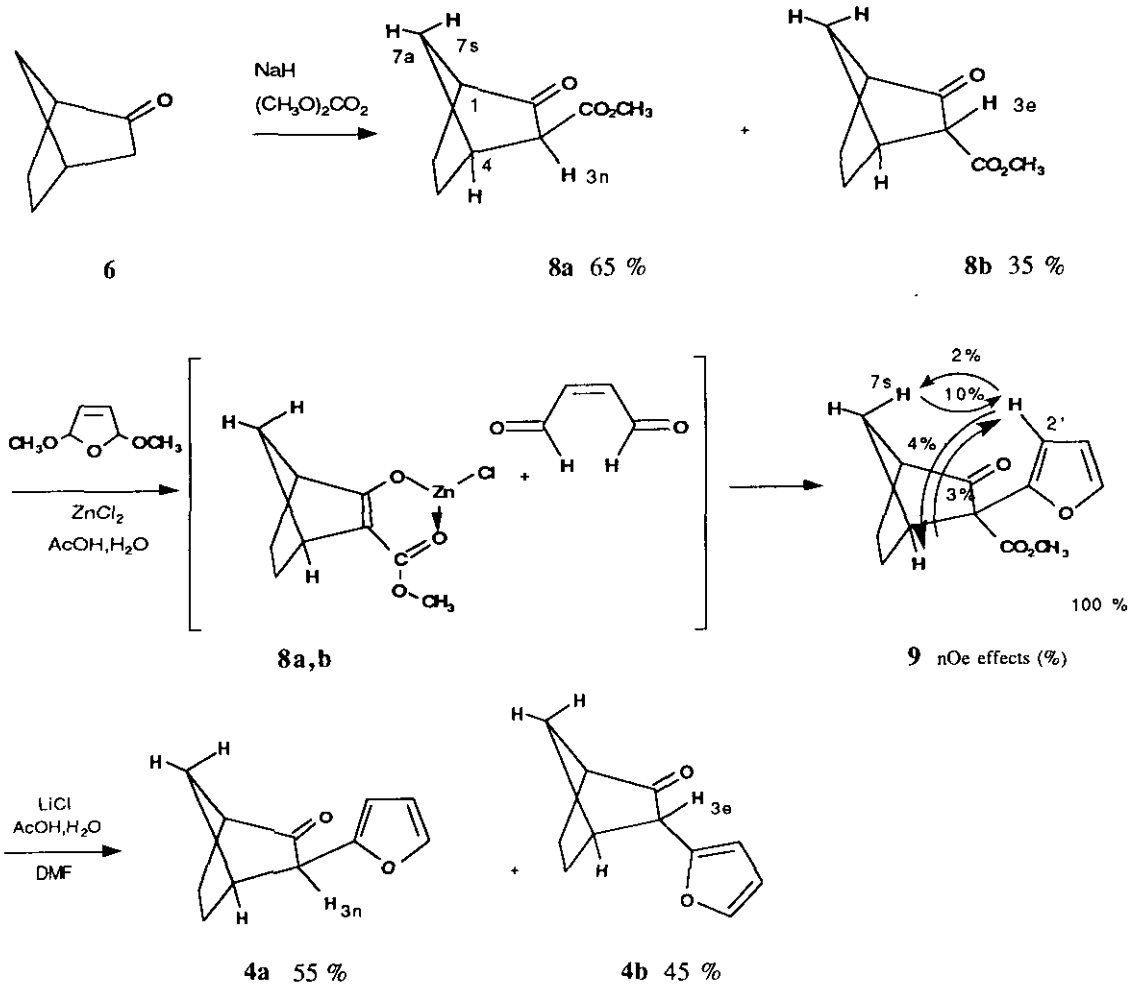
## DISCUSSION

In the first step of this reaction, 2-norbornanone (**6**) (or 5,6-dimethoxy-3-methylindan-1-one (**7**) was carbomethoxylated using dimethyl carbonate in a strong basic medium.[7] In the former case, a 2:1 stereoisomeric mixture of **8a** and **8b** was obtained (Scheme 2), whilst in the latter a 19:1 mixture of both isomers (**10a** and **10b**) was obtained (Figure 2).

The norbornanone system has been widely studied by nmr techniques.[8] Thus, from well established coupling constant considerations, we determined the major product of mixture **8a / 8b** to be that of **8a**, on the basis of it's $^4J$ long range coupling constant ($J$ = 3.5 Hz) between the H-3 and the H-7 *anti* proton

which places the H-3 proton in the *endo* position (Scheme 2).

Scheme 2

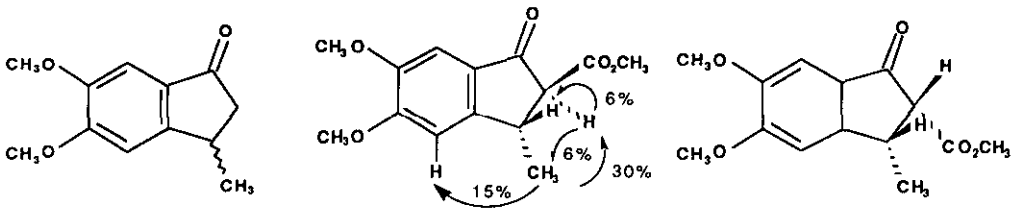



In view of the complicated nature of the $^1H$ nmr spectrum of the stereoisomeric mixture of 5,6-dimethoxy-3-methylindan-1-one, in which many spectral lines are superimposed, the assignment of the *cis* and *trans* isomers could not been determined from coupling constant values. In fact, the coupling constant found between the H-2 and H-3 protons, $J$= 3 Hz, could relate equally to both *cis* or *trans* stereoisomers (dihedral angles of 50° or 110° respectively).

For the main product (**10a**), presaturations of the H-2, H-3 and $CH_3$-ester protons caused enhancements of

the H-3 and the $CH_3$-ester protons, the H-2 proton and the H-2 and H-4 protons respectively (Figure 2).

Figure 2




**7** (±) **10a** nOe effects (%) **10b**

These results are in accord with a *trans* stereoisomeric orientation of the H-2 and the H-3 protons. The *trans* Dreiding's model confirms the value of the dihedral angle to be approximately 115°, when the carbomethoxy moiety is on the opposite side of the methyl group. This is supported by the coupling constant values from the spectrum of the major component of the mixture (2-carbomethoxy-5,6-dimethoxy-3-methylindan-1-one, $J$= 3 Hz for H-2/H-3 *trans*, in accord with the Karplus-Conroy curve[9]).

In this type of reaction, enolate anions are generated from the attack of a strong base, such as sodium hydride, on the corresponding ketones. Thereafter, electrophilic carboxymethoxylation occurs on the less hindered side of the carbanion/enolate anion, where non-bonded repulsions are minimized.[10]

In the electrophilic substitution of norbornanone, both side are relatively hindered. The '*endo* side' may be regarded as being part of a six membered ring and the '*exo* side' a five membered ring. 1,3-Intracyclic interactions help explain why *exo* attack is sligthly favoured. The *exo* over *endo* π-facial selectivity in the norbornyl ring system is not surprising in light of extensive data given in the literature.[11]

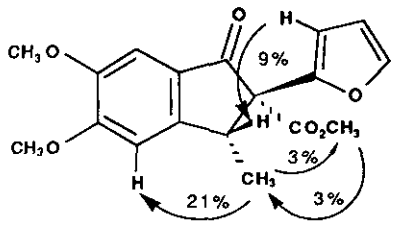
For reasons of clarity, we shall hereafter limit ourselves to the discussion of chemistry of the (*S*)-3-methyl-indan-1-one. In the carbomethoxylation step, the prefered path of approach of the electrophile, giving essentially the *trans* stereoisomer, may be accounted for by the 3-methyl substituent which projects downwards relative to the incoming electrophile (Figure 2). Attack from the lower face would be disfavourable on the grounds of considerable steric hindrance. A similar approach path by the electrophile is shown for the second step of our reaction sequence (Figure 4).

In the second step, 2,5-dihydro-2,5-dimethoxyfuran was added directly to the stereoisomeric mixtures in the presence of zinc chloride, acetic acid and water.

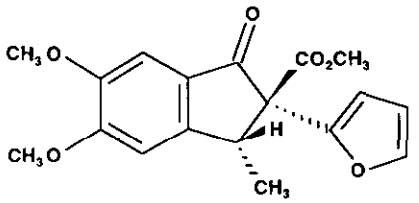
As the carbon atom at position-3 bore no protons, neither $^3J$ nor $^4J$ coupling constants were observed in the norbornane series. NOe difference experiments were thus performed on **9**. From these results, a stereoselectivity was observed (Scheme 2). The 2-(2-furyl) substituent was found to be located exclusively on the *exo* face.

In the 3-methylindan-1-one series, we obtained a mixture of two compounds in a 19:1 ratio (**11a** : **11b**). As before, in the absence of proton coupling, nOe difference experiments were performed (Figure 3). The main product (**11a**) was thus in the configuration where the methyl and furyl groups are antiperiplanar, implying that the carbomethoxy group faces the methyl group.

Figure 3



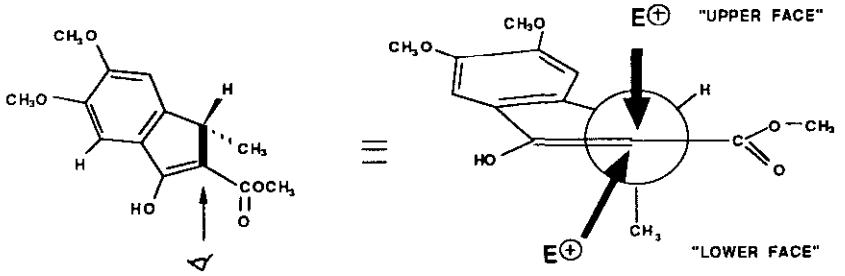

**11a** nOe effects (%)




**11b**

During the reaction, the mild Lewis acid zinc chloride is likely to shift the equilibrium towards the enolic form of the ketone. The reaction was then carried out in the presence of 2,5-dihydro-2,5-dimethoxyfuran, a stable precursor of the labile electrophilic malealdehyde (Scheme 2). The electrophilic attack on the enol favoured the less hindered face. In the indanone series, this corresponds to the attack on the upper face of the enol with the α-methyl group projecting on the underside resulting in the formation of the stereoisomer in which the furan and methyl groups are antiperiplanar (Figure 4). In the norbornane series, the *exo* substitution can be accounted for by the high steric bulk of the furan precursor whose approach *via* the *exo* face is considerably less impeded (Scheme 2).

Figure 4

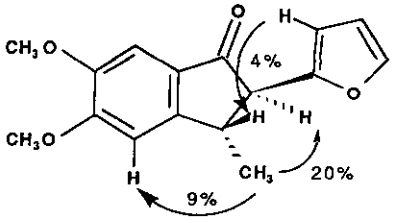



In the final step, which furnishes the 2-(2-furyl)cyclanones, we used a modification of the Krapcho dealkoxycarbonylation method[5] by refluxing the previously isolated 2-carbalkoxy-2-(2-furyl)cyclanones in

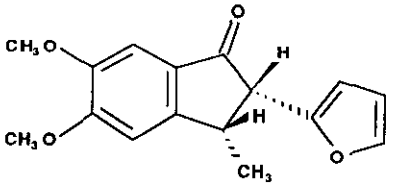
a mixture of lithium chloride (two molar excess), water and acetic acid (a slight excess) in a high boiling polar aprotic solvent (dimethylformamide).

A mixture of 3-methyl-2-(2-furyl)indan-1-ones (**5a**) and (**5b**) was obtained in a 9:1 ratio favouring the *trans* isomer (Figure 5) whereas a 6:5 (*exo/endo*) 3-(2-furyl)norbornan-2-one mixture was isolated (Scheme 2). The proportion of the *endo* stereoisomer was significantly increased with respect to the ratio obtained from similar mixtures of **6**, most probably due to the use of the high boiling solvent, which only slightly favours the *exo* isomer since isomerisation of the *exo / endo* isomer is more likely to occur at elevated temperatures.

Figure 5




**5a** nOe effects (%)




**5b**

The methyl ester group is attacked by the nucleophilic chloride anion. Thereafter, the carboxylate anion decomposes resulting in the evolution of carbon dioxide with the donation of a proton to the natant carbanion. The presence of an equimolar quantity of acid, or better a slight excess, is required to enhance the reaction rate. It is well worth noting that under these conditions, the acid labile furan substituent is preserved.

## CONCLUSIONS

The present method provides a facile and practical synthesis of 3-(2-furyl)norbornanone and 2-(2-furyl)-5,6-dimethoxy-3-methylindan-1-one.

The results presented above, using two examples of asymmetric cycloalkanonic starting materials, demonstrate that it is possible to obtained good stereoselective substitutions, especially for the introduction of the furan nucleus. Further experimental work, using similar cycloalkanone precursors to improve the acyclic diastereofacial selectivity and promote the use of these intermediates, is currently in progress in our laboratory.

Finally, this study represents an another example of the versatility of our synthesis which, after a series of simple transformations, can lead to diverse arrays of functionalized heterocyclic rings.

## EXPERIMENTAL

The $^1H$ spectra were recorded in deuterochloroform solutions (except when stated otherwise) on a JEOL GSX 270 WB spectrometer at 270.5 MHz. Chemical shifts are reported in ppm relative to tetramethylsilane in deuterochloroform, except where otherwise specified. Ir spectra were recorded on Perkin-Elmer 580 or 457 spectrophotometers using potassium bromide discs for solids, or neat liquid films for liquids. Only significant ir bands are quoted. Melting points were determined on a Electrothermal 8100 melting point apparatus and are uncorrected.

In nmr studies, we determined the different values of vicinal and/or long range coupling constants or, when not possible, we conducted nOe difference experiments. The molecular ratios between different stereoisomers, are determined using a pulse delay of 5 seconds.

*3-Methoxycarbonylnorbornan-2-one* (**8**)

The Vebrel *et al.* procedure was employed using toluene as the solvent .[6]

After distillation (124-130°C / 15 mm Hg), the crude product was isolated as a mixture of stereoisomers (80%). Ir: 1765 1730 (C=O) $cm^{-1}$. $^1H$ Nmr ($CDCl_3$): δ 1.90-1.40 (m, $H^{5,6,7a}$), 2.15- 2.08 (m, $H^{7s}$), 2.55-2.65 (m, $H^1$), 2.78 (m, $H^{3x}$), 2.83-2.95 (m , $H^4$), 2.96 (m, $H^{3n}$), 3.60-3.61 (2s, $OCH_3$). Ms (70 eV) m/z (%): 168 ($M^+$, 4), 140 (14), 81 (43), 41 (100).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.26 ; H, 7.19 . Found: C, 65.01 ; H, 7.05.

3-Methoxycarbonyl-3-(2-furyl)norbornan-2-one (**9**)

A solution of 2,5-dimethoxy-2,5-dihydrofuran (66.4 g, 0.51 mol) in 70 ml of tetrahydrofuran was added, simultaneously with a 100 ml of aqueous solution of zinc chloride (50 g, 0.37 mol) in acetic acid (20 ml, 0.34 mol), to a solution of 3-methoxycarbonylnorbornan-2-one (**8**) (84 g, 0.50 mol) in tetrahydrofuran (400 ml). The mixture was then refluxed for 1h and allowed to cool to room temperature. The solvents were removed under reduced pressure and water (300 ml) was added. The aqueous phase was extracted with toluene (3 x 100 ml). The organic phase was washed with water, dried over sodium sulphate and the solvent was evaporated under reduced pressure to give the product as white crystals (mp 70°C) after the addition of ether (101 g, 85%). Ir: 1765 1725 (C=O) $cm^{-1}$. $^1H$ Nmr ($CDCl_3$): δ 1.55-2.00 (m, 6H), 2.74 (*m*, 1H), 3.32 (*m*, 1H), 3.70 (*s*, 3H), 6.33 (*m* , 2H), 7.39 (*m*, 1H). $^{13}C$ Nmr ($CDCl_3$): δ = 23.9 24.2 [C-6, C-5], 34.9 [C-7], 44.0 [C-4] , 49.9 [C-1], 63.2 [C-3], 110.4 108.9 [C-2', C-3'], 143.0 [C-4'], 147.6 [C-1'], 169.3 [$CO_2CH_3$], 207.1 [C=O]. Ms (70 eV) m/z (%): 234 ($M^+$, 54), 174 (34), 41 (100). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.64 ; H, 6.03 . Found: C, 66.58 ; H, 6.19.

3-(2-Furyl)norbornan-2-one (**4**)

A mixture of 3-methoxycarbonyl-3-(2-furyl)norbornan-2-one (**9**)(58.5 g, 0.25 mol), lithium chloride (10.6 g, 0,25 mol), acetic acid (15 ml, 0.26 mol) and water (5 ml, 0.33 mol) was heated under reflux in dimethylformamide (250 ml) for 5 h. After cooling, the solvent was removed under reduced pressure and 500 ml of water was added. The aqueous solution was extracted with toluene (3 x 100 ml), and the organic layer was washed with water, dried and concentrated to give a brown residue which was distilled under reduced pressure (139-145°C/18 mm Hg) (40.3 g, 84%), giving a mixture of stereoisomers.

Ir: 1755 (C=O) $cm^{-1}$. $^1H$ Nmr ($CDCl_3$): δ 1.95-1.40 (m, $H^{5,6,7a}$), 2.10- 2.02 (m, $H^{7s}$), 2.75-2.65 (m, $H^1$), 2.98-2.83 (m , $H^4$), 3.13 (m, $H^{3x}$), 3.45 (m, $H^{3n}$), 6.20-6.15 (m, $H^{3'}$), 6.30 (m, $H^{4'}$), 7.30-7.15 (m, $H^{5'}$). Ms (70 eV) m/z (%): 192 ($M^+$, 4), 176 (17), 107 (100). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.96 ; H, 6.87 . Found: C, 74.48 ; H, 6.43.

2-Methoxycarbonyl-5,6-dimethoxy-3-methylindan-1-one (**10**)

The Vebrel *et al.* procedure described above, was followed. The product was recrystallized from carbon tetrachloride, mp 139°C) (87%). Ir: 1735 1685 (C=O), 1610 1595 (C=C) $cm^{-1}$. $^1H$ Nmr ($CDCl_3$): δ 1.44 (d, *J*= 7 Hz, 1H), 3.27 (d, *J*= 4 Hz, 1H), 3.77 (m, 1H), 3.78 (s, 3H), 3.88 (s, 3H), 3.98 (s, 3H), 6.88 (s, 1H), 7.14 (s, 1H). $^{13}C$ Nmr ($CDCl_3$): δ = 20.3 [C-$\underline{C}H_3$], 37.4 [$\underline{C}$-3], 52.6 [$CO_2\underline{C}H_3$], 56.2 56.3 [$O\underline{C}H_3$], 62.0 [$\underline{C}$-2], 104.5 [$\underline{C}$-4], 105.8 [$\underline{C}$-7], 127.4 [$\underline{C}$-3a], 149.8 [$\underline{C}$-7a], 153.8 156.2 [$\underline{C}$-$OCH_3$], 169.7 [$\underline{C}O_2CH_3$], 197.3 [$\underline{C}$=O]. Ms (70 eV) m/z (%): 264 ($M^+$, 57), 232 (47), 204 (100). Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.61 ; H, 6.10 . Found: C, 63.72 ; H, 6.24.

2-Methoxycarbonyl-2-(2-furyl)-5,6-dimethoxy-3-methylindan-1-one (**11**)

The same procedure described above for **8** was followed. The product was recrystallized from methanol, mp 140°C (82%). Ir: 1745 1705 (C=O), 1610 1595 (C=C) $cm^{-1}$. $^1H$ Nmr ($CDCl_3$): δ 1.48 (d, *J*= 7.3 Hz, 1H), 3.68 (s, 3H), 3.91 (s, 3H), 3.99 (s, 3H), 4.00 (m, 1H), 6.35 (dd, *J*= 3.5 Hz, *J*= 1.5 Hz, 1H), 6.58 (d, *J*= 3.5 Hz, 1H), 6.88 (s, 1H), 7.22 (s, 1H), 7.38 (d, *J*= 1.5 Hz, 1H). $^{13}C$ Nmr ($CDCl_3$): δ = 15.9 [C-$\underline{C}H_3$], 43.0 [$\underline{C}$-3], 52.3 [$CO_2\underline{C}H_3$], 56.1 56.3 [$O\underline{C}H_3$], 65.4 [$\underline{C}$-2], 105.0 105.6 [$\underline{C}$-4, $\underline{C}$-7], 108.4 105.6 [$\underline{C}$-2', $\underline{C}$-3'], 127.3 [$\underline{C}$-3a], 142.4 [$\underline{C}$-4'], 149.9 [$\underline{C}$-7a], 150.2 [$\underline{C}$-1'], 152.0 156.2 [$\underline{C}$-$OCH_3$], 169.5 [$\underline{C}O_2CH_3$], 196.9 [$\underline{C}$=O]. Ms (70 eV) m/z (%): 330 ($M^+$, 83), 271 (56), 59 (100). Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.43 ; H, 5.49 . Found: C, 65.35 ; H, 5.56.

2-(2-furyl)-5,6-dimethoxy-3-methylindan-1-one (**5**)

The same procedure described above for **4** was followed. The product was recrystallized from ether, mp 136°C (70%). Ir: 1690 (C=O), 1605 1590 (C=C) $cm^{-1}$.$^1H$ Nmr ($CDCl_3$): δ 1.50 (d, *J*= 6.4 Hz, 1H),

3.50 (m, 2H), 3.91 (s, 3H), 3.99 (s, 3H), 6.26 (d, $J$= 3.3 Hz, 1H), 6.34 (dd, $J$= 3.3 Hz, $J$= 1.5 Hz, 1H), 6.90 (s, 1H), 7.20 (s, 1H), 7.34 (d, $J$= 1.5 Hz, 1H).$^{13}$C Nmr ($CDCl_3$): δ = 19.70 [C-$\underline{C}H_3$], 39.6 [$\underline{C}$-3], 56.0 56.1 56.2 [$\underline{C}$-2, 2-O$\underline{C}H_3$], 104.4 105.7 [$\underline{C}$-4, $\underline{C}$-7], 110.2 107.3 [$\underline{C}$-2', $\underline{C}$-3'], 127.8 [$\underline{C}$-3a], 142.0 [$\underline{C}$-4'], 149.6 [$\underline{C}$-7a], 153;0 [$\underline{C}$-1'], 151.4 155.9 [$\underline{C}$-O$CH_3$], 200.8 [$\underline{C}$=O]. Ms (70 eV) m/z (%): 272 ($M^+$, 100), 257 (27). Anal. Calcd for $C_{18}H_{18}O_6$: C, 70.58 ; H, 5.88 . Found: C, 70.26 ; H, 6.01.

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