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Anionic [4+2] Cycloaddition Strategy to Linear Furocoumarins : Synthesis of 8-Methoxypsoralen and its Isoster

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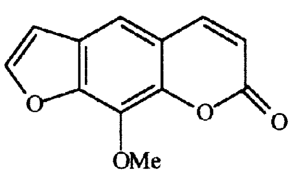
Abstract : The sulfoxide esters **14** and **20d** are successfully annulated with bicyclic enone **8** in the presence of ^{t}BuOLi to provide the pentacyclic ketones **9a** and **21a** respectively in good yields (≥70%) . Flash vacuum pyrolysis of O-methyl derivatives **9b** and **21b** at ~ 500^0 C/.1 mm provide furoindacenones **16b** and **22b** respectively, which in turn are convertible to furocoumarins **1** and **3**. © 1998 Elsevier Science Ltd. All rights reserved.

The linear fused furocoumarins also known as psoralens are photodynamic drugs, which are widely used in photochemotherapy for management of such skin diseases as psoriasis, vitiligo, eczema and mycosis fungoids.[1] Recently, 8-methoxypsoralen **1** has been introduced as a clinically effective drug for the treatment of cutaneous T-cell lymphoma[2] and more notably, 5-methoxypsoralen **2** has been found to have potential utility in the treatment of human immunodeficiency disease (AIDS).[3] In the field of molecular biology, psoralens are used as photochemical reagents for the investigation of nucleic acid structure and function.[4]



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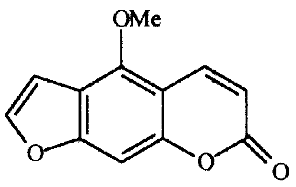

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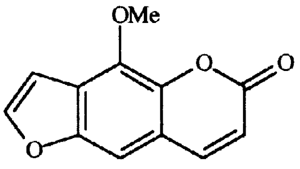

3

The classical synthetic approaches[5] to the linear furocoumarins, for most part, have entailed stepwise elaboration of the two heterocyclic rings beginning from a central aromatic core unit. These are often

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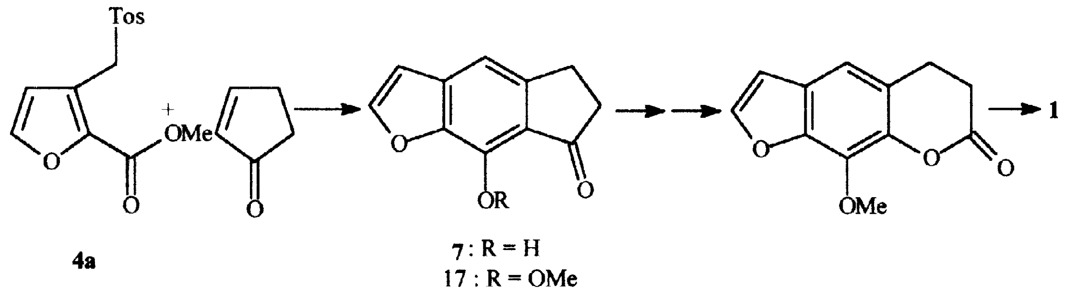
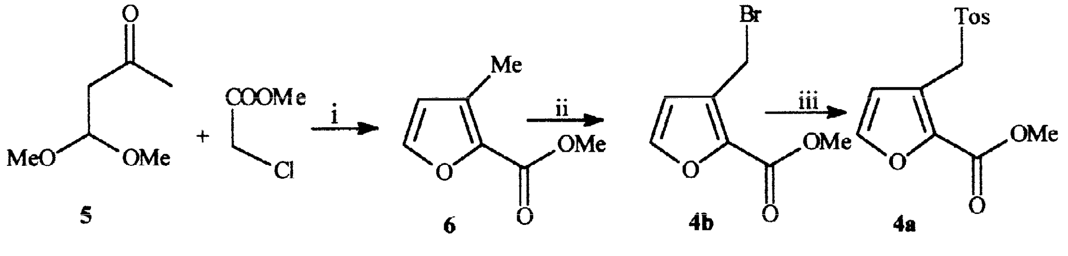
associated with difficulty in controlling regiochemical problems, and low overall yields. There are only two syntheses of linear fused furocoumarins, one by Danheiser[6] et al and the other by Kanematsu[7] et al that have adopted different strategies. Both these studies utilize a 2-substituted furan derivative, and a 6-electron electrocyclic ring closure or an intramolecular Diels-Alder reaction to build up the central aromatic ring. To ensure the regiochemical integrity and convergency, we have adopted anionic [4+2] cycloaddition strategy for the synthesis of linear furocoumarins from 2,3-disubstituted furan derivatives. The preliminary result of this study was recently reported.[8] Now we describe the details of this study ending up in the synthesis of **1** and its successful extension to the synthesis of **3**, a bioisoster of **1** and **2**.

Our initial studies to furocoumarin were directed towards cyclopentenone annulation (Scheme 1) involving anionic cycloaddition strategy.



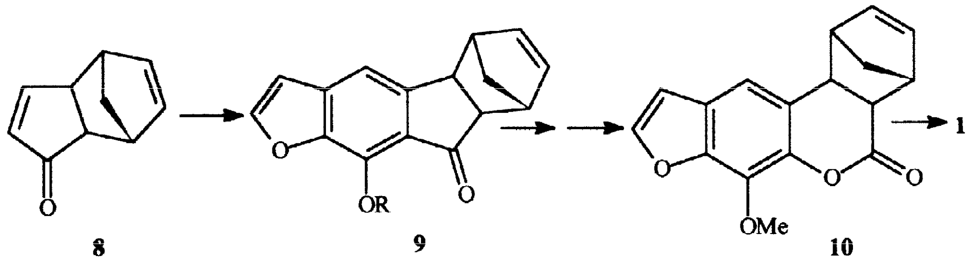
Scheme 1

The anionic [4+2] cycloaddition, alternatively known as Michael-initiated ring closure[9] of a 1,4-dipolar synthon with a Michael acceptor is well documented in the literature for synthesis of fused aromatics like benzothiophene, naphthalene, quinoline and anthracene derivatives. But, it was not investigated for the synthesis of benzofuran derivatives. The intermediate **4a** required in this context was prepared in three steps (Scheme 2).



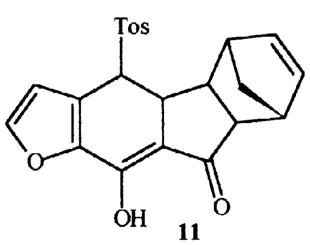
Scheme 2 Reagents and conditions: i, NaOMe, ether and then heat (160°C); ii, NBS, light, (PhCOO)$_2$, reflux; iii, Sodium p-tolylsulfinate, DMF.

Commercially available acetylacetaldehyde dimethyl acetal **5** was allowed to react with methyl chloroacetate in the presence of NaOMe to give a Darzen glycidic ester which on thermolysis at 160^{0}C furnished furan ester **6**[10] (75%). Benzylic bromination of **6** with NBS provided **4b**[11]. The sulfone ester **4a** was then obtained in 87% yield from **4b** by its reaction with sodium *p*-tolylsulfinate in DMF. It was also prepared from **4b** by the method[12] using *p*-toluenesulfinic acid / DBU , albeit in lower yield (~60%). Annulation of **4a** with cyclopentenone was attempted using various bases described in the literature[9] for similar annulations. All the attempts proved to be futile. Even in the presence of ^{t}BuOLi[13], the most popular choice for such reactions, the expected annulation product **7** was not obtained. Instead, the sulfone ester **4a** was reclaimable in 40-50% yield. The failure of the annulation was perhaps due to base promoted polymerisation[14] of cyclopentenone. Anticipating that bicycloenone **8** would be resistant toward base-induced polymerisation due to its rigidity Scheme 3 was planned to be executed. The enone **8**[15] was readily prepared in two steps from commercially available bicyclopentadiene. Treatment of **4a** with enone **8** in the presence of ^{t}BuOLi at - 60^{0}C, followed by warming up the mixture to 0^{0}C, and usual work-up afforded a white amorphous solid which could not be further purified. However, it seemed like a 4:1 mixture of two compounds. The ^{1}H NMR analysis of this mixture indicated the annulation of the enone **8** with retention of tosyl group in the product. The compounds of the mixture were tentatively identified as **11** and **12**.

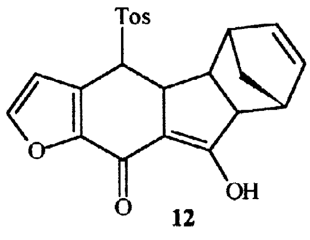


a, R = H
b, R = OMe

Scheme 3

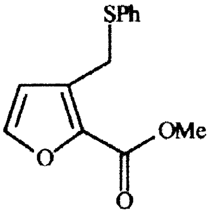


11



12

Since non-aromatization of B ring of **11** and **12** could be due to the cis orientation of the tosyl group with respect to β-hydrogen, we chose to examine reactivity of sulfoxide ester **14** . The ester **14** was obtained in two steps from **4b** by sequential treatment with NaSPh and $NaIO_4$. As expected, the annulation of **14** with enone **8** provided the desired product **9a** in one pot in good yield (73%). According to the original plan, compound **9a** was O-methylated to give **9b** and then subjected to Baeyer-Villiger (B.V.) oxidation under different conditions. The conditions chosen were (a)[16] H_2O_2 (30% w/v), aq NaOH, ether, (b)[17] MMPP, CH_2Cl_2, rt; (c)[17] UHP, Na_2HPO_4, TFAA, CH_2Cl_2; (d) *m*-CPBA, aq. $NaHCO_3$, CH_2Cl_2; (e)[18] H_2O_2 (30% w/v), Conc. H_2SO_4 , $(CH_3CO)_2O$, CH_2Cl_2. In some of the cases, we could isolate the epoxide **15**, stereostructure of which was determined by NOE study, and not the Baeyer- Villiger product **10**, although there are several reports[16] on Baeyer Villiger oxidation of ketones having double bonds. The above failures to effect B. V. oxidation of **9b** prompted us to further modify Scheme 3.



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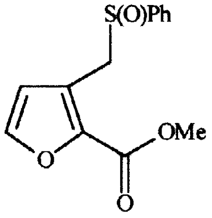
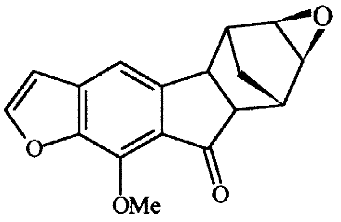


14



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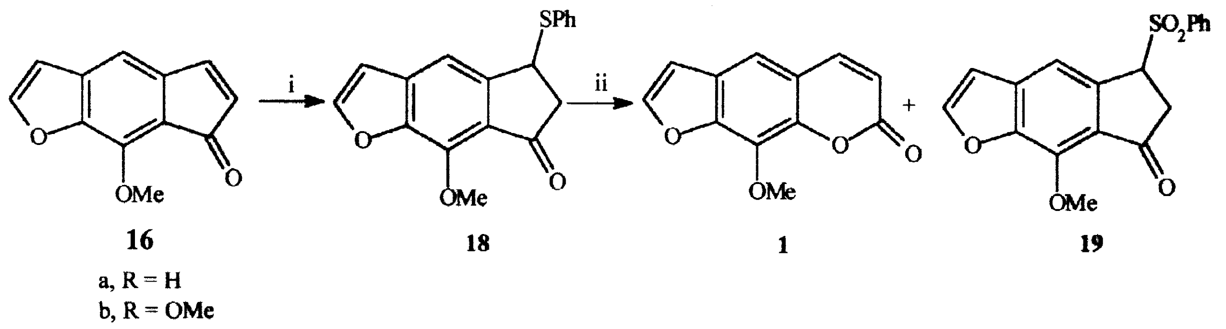
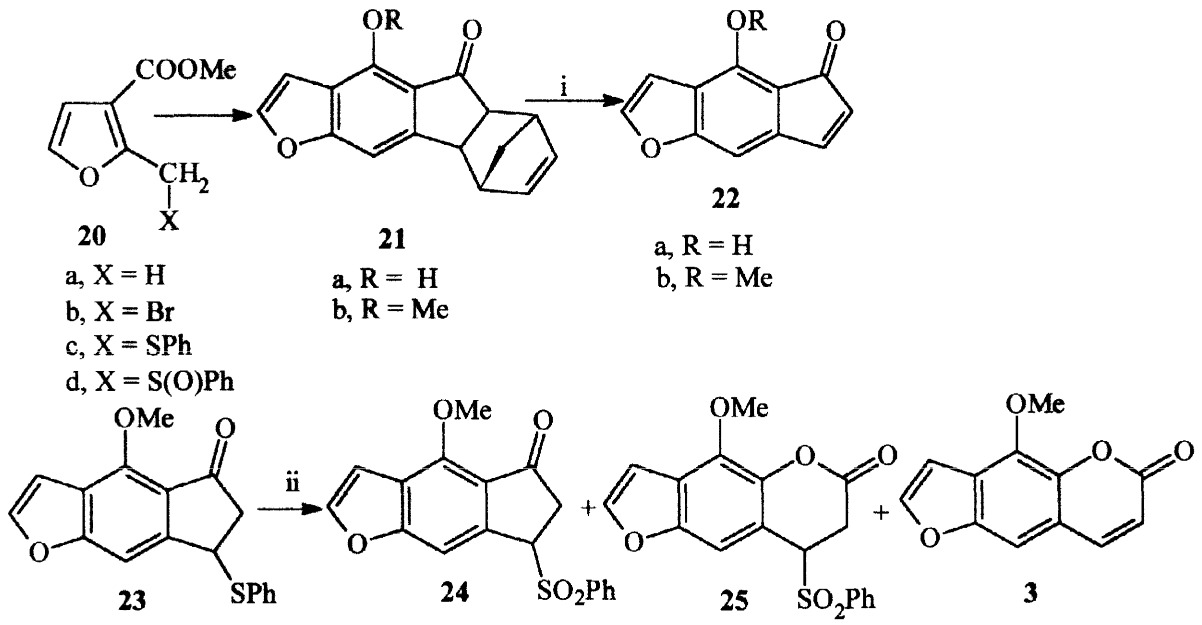
Our attention was then turned to the possibility of Baeyer-Villiger oxidation of furoindenones **16**, with the hope that the double bond in **16** would be less susceptible to epoxidation due to its conjugation to carbonyl group, compared to the double bond in **9b**. Solution phase thermolysis of **9b** in refluxing *o*-dichlorobenzene or diphenyl ether afforded enone **16b** in a trace amount. On the other hand, under flash vacuum thermolytic condition[19] (500^0C , 0.1 mm), **16b** was obtained in almost quantitative yield. The enone **16b** was then subjected to various B. V. oxidation conditions similarly as **9b**. In none of the cases, the desired psoralen **1** was obtained. Similarly B.V. oxidation of **16a** was of no avail. Such failures were, in part ascribed to the instability of **16a** and **16b** towards acidic conditions of B. V. oxidation. It may be noted that simple indenones are very sensitive to acids and form dimers[20]. Consequently, B. V. oxidation of indacenone **17** was considered next to avoid the effect of double bond. But, the selective reduction of carbon-carbon double bond in **16b** to obtain **17** was problematic. Finally, a circuitous path was followed to complete the synthesis of **1** from **16b** (Scheme 4). Treatment of **16b** with thiophenol in the presence of triethylamine provided keto sulfide **18** in 88% yield. Exposure of the sulfide **18** to H_2O_2 / $(CH_3CO)_2O$ / H_2SO_4 furnished the desired methoxalen **1** in 15-20% along with ketosulfone **19** in 40% yield. The possible intermediates could not be isolated. Although the sulfone **19** was inert to B. V. oxidation, it could be converted to the starting enone **16b** by DBU treatment.



Scheme 4 Reagents and conditions i, PhSH, Et_3N; ii, H_2O_2, Ac_2O, H_2SO_4

Having completed the synthesis of methoxalen **1**, we decided to work on the synthesis of isoster **3**.



Scheme 5 Reagents and conditions i, FVP(500°C,0.1mm); ii, H_2O_2, Ac_2O, H_2SO_4

NBS bromination of **20a** provided bromomethyl ester **20b**[22] in good yield. Treatment of **20b** with NaSPh in methanol gave sulfide **20c** which was then oxidised with $NaIO_4$ to afford the key annulating agent **20d**. In analogy with the annulation of **14**, compound **20d** was subjected to annulation with enone **8** in the presence of ^{t}BuOLi to produce **21a** in good yield (70%). Its O-methylated derivative **21b** was prepared in usual manner by the use of Me_2SO_4 and K_2CO_3. Both the pentacyclic ketones **21a** and **21b** underwent smooth flash pyrolysis giving indenones **22a** and **22b** respectively in excellent yields. The enone **22b** tends to undergo decomposition in the presence of laboratory light. For the conversion of **22a** and **22b** to **3**, we restricted B. V. oxidation study to H_2O_2 , Ac_2O, H_2SO_4 system, on the basis of our experience with **16b**. Exposure of **22b** to this condition led to the formation of **3** in ~10% and extensive decomposition of the starting material (Scheme 5). Variation of the reaction conditions, namely temperature, time and the amount of catalyst did not cause any improvement in the yield. More interestingly, the attempts to scale up the reaction resulted in further lowering of the yield. A more efficient conversion of **22** to **3** could be accomplished again through formation of sulfide **23**, which was prepared by thiophenol addition catalysed by triethylamine. Action of H_2O_2, AcOH, H^+ system on **23** furnished **3** in slightly improved yield (~15%) along with two other products **24** and **25** . To establish the intermediacy of **24** , a purified sample of **24** was subjected to the above Baeyer -Villiger condition. Although the desired coumarin **3** was obtained in slightly higher yield, it appeared that both **23** and **24** decompose considerably under the reaction condition and the furan part is responsible for it. Nevertheless, the sulfone **25** could be converted to **3** in almost quantitative yield by DBU treatment.

In conclusion, we have described a new synthetic approach to linear furocoumarins involving furan annulation and flash vacuum pyrolytic retro Diels-Alder reaction as the key steps. Intercalation study of the newly generated psoralen analogues **22** are being carried out in collaboration with Prof. Cafferi of Padova University, Italy.

Experimental

Mps and bps are uncorrected. Unless otherwise stated, ^1H NMR spectra were recorded at 90 MHz (Varian), 100 MHz (JEOL) and 200 MHz (Brucker) for solutions in ^2H chloroform with trimethylsilane as the internal standard. Chemical shifts are presented in δ values and ^1H-^1H coupling constants in Hz . IR spectra were obtained on a Perkin-Elmer model-883 as a KBr pellet (for solids) or neat (for liquids) and the characteristic peaks are presented in cm^{-1}. All solvents used for reactions were purified before use. Ether and tetralydrofuran (THF) were distilled from sodium / benzophenone under an atmosphere of dry argon and dichloromethane from P_2O_5. *tert*- Butyl alcohol was distilled from sodium. Preparation of lithium *tert*-butoxide was carried out by addition of butyllithium (Fluka) to a stirred solution of *tert*-butyl alcohol in THF under an argon atmosphere at 0^0C.

Methyl 3-(p-tolylsulfonylmethyl)furan-2-carboxylate 4a : To a well stirred solution of methyl 3-bromomethyl-2-furoate **4b**[11] (4.0 g, 18 mmol) in dry DMF (65 mL) was added solid sodium 4-methylbenzene sulfinate (8.0 g, 45 mmol) in portions. The mixture was stirred overnight at room temperature and the resultant solidous mass was poured into cold water (600 mL). The white crystalline material precipitated was filtered and recrystallised (CH_2Cl_2-hexane) to give shining crystals of **4a** (4.7 g , 87%) . mp 119 - 120^{0}C; δ_H 7.8 (d, 2 H, *J* 8 , Ar H) , 7.67 (d, 1 H, *J* 1 , Furo-H) , 7.45 (d, 2 H, *J* 8, Ar H) , 6.85 (d, 1 H, *J* 1, Furo-H), 4.75 (s, 2 H, CH_2SO_2Ar) , 3.75 (s, 3 H, $COOCH_3$) , 2.42 (s, 3 H, $ArCH_3$) ; ν_{max} 3131 , 2998, 1721, 1596, 1449, 1309, 1197, 1131, 808; (m/z) 294(M^+), 263, 230, 198, 139(100%), 109, 91, 65; Anal. Calc. for $C_{14}H_{14}O_5S$: C, 57.16; H, 4.76; Found C, 57.10 ; H,4.71.

General procedure for annulation reactions : To a stirred solution of lithium *tert*-butoxide (9 mmol) in THF (15 mL) at -65^{0}C ($CHCl_3$/ liquid N_2 bath) under argon atmosphere was added a solution of furo-1,4-dipolar reagent (3.6 mmol) in THF (15 mL) . The resulting brownish solution was stirred at -65^{0}C for just 5 min after which a Michael acceptor (1.2-1.5 equiv) was added as a solution in THF (5 mL) . The cooling bath was removed after 1-2 h of stirring, and the reaction mixture was brought to room temperature. The formation of annulated product was followed by the appearance of pale greenish fluorescent spots on tlc under UV light. After the reaction reached a steady state (occasionally the reaction mixture was refluxed for complete aromatization) as indicated by tlc, it was acidified with 10% HCl (3 mL) at 0^{0}C. The resulting THF solution was concentrated under reduced pressure and the residue was extracted with ethyl acetate or diethyl ether (2 X 25 mL). The organic phase was worked up as usual. The residue was purified either by column chromatography or by recrystallisation from a mixture of ethyl acetate-hexanes system to furnish the annulated product.

Compounds **11** and **12** : The mixture of compounds **11** and **12** was obtained in 83% yield from the reaction of furosulfone **4a** with bicyclic enone **8** according to the general annulation procedure. The ratio of the major to the minor isomer was 4:1. Major isomer : δ_H 7.73-7.69 (d, 2 H, *J* 8, ArH) , 7.64 (d, 1 H, *J* 1.8, Furo-H), 7.33-7.29 (d, 2 H, *J* 8 , ArH), 7.14 (d, 1 H, *J* 1.8 , Furo-H) , 6.89 (br s, 1 H, ArOH) , 6.22-6.17 (m, 1 H, CH =) , 5.69-5.91 (m, 1 H, CH =) , 4.46-4.40 (d, 1 H, *J* 11.6 , CH SO_2 Ar), 3.48 (br s , 1 H , ring-H), 3.41-3.23 (m, 2 H, ring-H), 3.06 (br s, 1 H, ring-H), 2.60-2.50 (m, 1 H, ring-H) , 2.43 (s, 3 H, $ArCH_3$), 1.73 (AB d, 1 H, *J* 8.5 , $-CH_2-$) , 1.52 (AB d, 1 H, *J* 8.5 , $-CH_2$). It was difficult to completely extract ^{1}H NMR data of the minor isomer . ν_{max} 3450, 2944, 1642, 1602, 1310, 1218, 1134, 811,698 ; (m/z) 408(M^+), 342, 253, 225, 187 (100%), 159, 113, 91, 77 (of the mixture of **11** and **12**).

Methyl 3-(phenylthiomethyl) -2-furoate 13 : To a stirred solution of methyl 3-(bromomethyl)-2-furoate **4b** (5.0 g, 23 mmol) in methanol (12 mL) was added a solution of sodium phenylthiolate (3. 04 g , 23 mmol) in methanol (40 mL) at room temperature under argon atmosphere. The reaction mixture was heated at reflux for 3.5 h and then cooled to room temperature. The contents of the flask were diluted with water (120 mL) and then extracted into diethyl ether (2 X 40 mL). The organic layer was worked up in usual manner to give a pale brownish oil of **13** (88% yield), which was sufficiently pure (95% by NMR) for carrying out the next step. δ_H 7.7-7.15 (m, 5 H, ArH), 7.4 (d, 1 H, *J* 1, Furo-H) , 6.45 (d, 1 H, *J* 1, Furo-H), 4.35 (s, 2 H, CH_2SPh) , 3.84 (s, 3 H, $COOCH_3$); ν_{max} 3062, 2953, 1716, 1589, 1440, 1306, 1195, 746; LCMS, (m/z) 248(M^+), 216, 201, 187, 160, 139, 109(100%), 81, 65.

Methyl 3-(Phenylsulfinylmethyl)-2-furoate 14 : To a solution of methyl 3-(phenylthiomethyl)-2-furoate **13** (5.0 g, 20 mmol) in methanol (65 mL) containing water (2 mL) was added solid sodium periodate (4.6 g, 21.5 mmol) portion wise. The resultant mixture was stirred for 18 h at room temperature and then the solvent was removed under reduced pressure. The resulting crude liquid was purified by column chromatography over silica gel to furnish the sulfoxide **14** (3.5 g, 66%) as a yellowish liquid. δ_H 7.44 (br s, 6 H, ArH , Furo-H), 6.45 (d, 1 H, *J* 1.4 , Furo-H), 4.36 (AB d, 1 H, *J* 12.8 , CH_2SOPh), 4.26 (AB d, 1 H, *J* 12.8 , CH_2SOPh) , 3.74 (s, 3 H, $COOCH_3$); ν_{max} 2954, 1723, 1596, 1444, 1308, 1041, 755 ; LCMS, (m/z) 264(M^+), 233, 186, 139(100%), 125.

10-Hydroxy-5,8-methano-9-oxo-4b, 5,8, 8a, 9-pentahydrofluoreno[2,3-b]furan 9a : Compound **9a** was prepared from furosulfoxide **14** and bicyclic enone **8** by following the general annulation procedure described above. To ascertain complete elimination of phenyl sulfoxide group in the annulation, the reaction mixture was heated at reflux for 3 h under argon atmosphere prior to usual work-up. mp 170 - 171^0 C; yield 73%; δ_H 9.55 (br s, 1 H, ArOH), 7.7 (d, 1 H, *J* 2, Furo-H) , 7.00 (s, 1 H, ArH), 6.71 (d, 1 H, *J* 2, Furo-H) , 5.93-5.88 (m, 1 H, CH =), 5.53-5.48 (m, 1 H, CH =), 3.9-3.84 (m, 1 H, ring-H), 3.30-3.20 (m, 3 H, ring-H), 1.81-1.67 (m, 2 H, ring-CH_2 -); δ_C 210.5, 148.9, 148.8, 142.4, 140.5, 137.4, 133.9, 133.0, 121.6, 108.1, 107.4, 54.1, 52.7, 45.8, 45, 44.7; ν_{max} 3445, 2928, 1660, 1572, 1349, 1262, 700; (m/z) 252(M^+), 224, 186 (100%), 158, 129, 102, 76, 66; Anal. Calc. for $C_{16}H_{12}O_3$: C, 76.20; H, 4.75; Found C,75.88; H, 4.55.

5,8-Methano-10-methoxy-9-oxo-4b,5,8,8a,9-pentahydrofluoreno[2,3-b]furan 9b : A mixture of phenolic compound **9a** (5 g, 19.8 mmol), solid potassium carbonate (12.7 g, 92.4 mmol) and dimethyl sulfate (5.56 mL, 58.21 mmol) in dry acetone (140 mL) was heated at reflux for 7 h with stirring under argon atmosphere. Inorganic solid was filtered off and the residue obtained on concentration was treated with triethylamine (10 mL) for 30 min at room temperature with stirring. The organic layer was separated, washed successively with water (100 mL) , dilute hydrochloric acid (2 N, 100 mL), brine (100 mL), dried

(Na_2SO_4) and concentrated. The residue was recrystallized as a white crystalline solid (96%) from ethyl acetate - hexanes system. mp 161^0 C; δ_H 7.65 (d, 1 H, *J* 2, Furo-H), 7.08 (d, 1 H, *J* 0.8, Ar<u>H</u>), 6.69 (d, 1 H, *J* 2 , Furo-<u>H</u>), 5.93-5.89 (m, 1 H, = C<u>H</u>), 5.48-5.43 (m, 1 H, =C<u>H</u>), 4.30 (s, 3 H, OC<u>H</u>$_3$), 3.80-3.75 (m, 1 H, ring-<u>H</u>), 3.31 (br s , 1 H, ring-<u>H</u>), 3.19-3.13 (m, 2 H, ring-<u>H</u>), 1.73 (AB q, 2 H, *J* 6, - C<u>H</u>$_2$ -) ; δ_C 204.7, 151.5, 148.1, 143.8, 142.6, 136.8, 133.5, 133.4, 125.4, 109.9, 106.9, 60, 54, 52.3, 46.2, 45.6, 43.6; ν_{max} 2972, 1689, 1608, 1468, 1350, 1250, 1095, 772, 698; (m/z) 266(M$^+$), 238, 200, 171, 142, 129, 115, 89, 82, 75, 66, 57; Anal. Calc. for $C_{17}H_{14}O_3$: C, 76.70; H, 5.26; Found C, 77.61; H, 5.20.

General procedure for retro Diels Alder reaction of 9 and 21: A long (40 cm) high quality glass tube open at both ends was fixed horizontally in a pyrolytic chamber connected in series with a rheostat and an ammeter. One end of the glass tube was closed, and a vial containing the substance to be pyrolysed was pushed inside till it was adjacent to the hot coil. A cotton plug was placed to cover the open end and then was connected to a high vacuum pump (0.1 mm). The material in the vial was heated with a spirit lamp till it melted, after the furnace got heated to 400-500^0 C (monitored by a thermocouple). The heating was continued until all the material was collected at the other end of the furnace in the cold zone (most of the material solidified when the glass tube was cooled by a cotton plug dipped in CH_2Cl_2). In all the cases studied, the retro products obtained were pure yellow solids, yields varying in the range 95-100%.

8-methoxy-1-oxa-*s*-indacen-7-one 16a : Compound **16a** was prepared in 98% yield from the annulation product **9a** according to the above pyrolysis procedure. mp 163^0 C; δ_H 7.66 (d, 1 H, *J* 2, Furo-<u>H</u>), 7.43 (d, 1 H, *J* 5.8, C<u>H</u> = CO), 6.80 (s, 1 H, Ar<u>H</u>), 6.71 (d, 1 H, *J* 2, Furo <u>H</u>), 5.9 (d, 1 H, *J* 5.8, =C<u>H</u>CO); δ_C 202.4, 149.5, 147.7, 144.4, 143.1, 138.7, 134.4, 128.5, 109.7, 108.6; ν_{max} 3399, 3112, 1666, 1596, 1465, 1257, 1045, 816, 741; (m/z) 186(M$^+$), 158, 132, 102, 76, 63.

8-Methoxy-1-oxa-*s*-indacen-7-one 16b : Compound **16b** was prepared from **9b** following above general procedure for retro Diels-Alder reaction in quantitative yield as bright yellow solid . mp 83^0 C; δ_H 7.63 (d, 1 H, *J* 2, Furo-<u>H</u>) , 7.39 (d, 1 H, *J* 5.8, C<u>H</u> = CO) , 6.82 (s, 1 H, Ar<u>H</u>), 6.7 (d, 1 H, *J* 2 , Furo-<u>H</u>), 5.84 (d, 1 H, *J* 5.8 , = C<u>H</u>CO), 4.38 (s, 3 H, OC<u>H</u>$_3$); δ_C 195, 147.9, 147.3, 146.7, 141.6, 134, 129, 113.9, 109.9, 108.1, 61.5; ν_{max} 2957, 1682, 1576, 1464, 1335, 1238, 1055, 879, 736; (m/z) 200 (M$^+$, 100%), 171, 142, 129, 115, 101, 88, 75, 63; Anal. Calc for $C_{12}H_8O_3$: C, 72.01; H, 4.00; Found C, 71.8; H, 4.1.

6,7-Epoxy-4b, 5,6, 7,8, 8a, 9-heptahydro-5,8-methano-10-methoxy-9-oxo-fluoreno[2,3-b]furan 15 : To a stirred solution of methoxyfluorenofuran **9b** (0.17 g, 0.67 mmol) in dry dichloromethane (8 mL) at 0^0C was added a solution of *m*-CPBA (0.19 g , 1.38 mmol) and sodium bicarbonate (0.4 g, 4.76 mmol) in water (8 mL) . The biphasic mixture was vigorously stirred for 1 h at 0^0C and was brought to room temperature. After 12 h at room temperature, a little more (~50 mg) of *m*-CPBA was added and stirring was continued for another 12 h. Dichloromethane layer was separated and worked up usually. The crude material was purified by plc to provide the **15** (60 mg, 33.5%) as a white crystalline material. mp 208 ^{0} C; δ_H 7.74 (d, 1 H, *J* 2, Furo-$\underline{H}$), 7.2 (s, 1 H, Ar$\underline{H}$), 6.78 (d, 1 H, *J* 2 , furo-$\underline{H}$), 4.40 (s, 3 H, OC$\underline{H}_3$), 3.8-3.76 (m, 1 H, ring - $\underline{H}$) , 3.17-3.11 (m, 2 H, C$\underline{H}$-O-C$\underline{H}$), 3.06-3.03 (m, 1 H, ring-$\underline{H}$), 2.93-2.9 (m, 1 H, ring-$\underline{H}$), 2.51-2.5 (m, 1 H, ring-$\underline{H}$), 1.68-1.63 (b d, 1 H, *J* 9.7, ring-$\underline{H}$) , 1.21-1.16 (d, 1 H, *J* 9.8, ring-$\underline{H}$) ; δ_C 203.4, 148.6, 148.6, 143.5, 143.1, 137.4, 124.8, 110.4, 107.0, 61.1, 55.2, 49.1, 48.9, 45.3, 40.0, 39.8, 30.2; ν_{max} 2962, 1689,1578,1464, 1352, 1252, 1093, 849; (m/z) 282(M^+), 253, 235, 225, 213, 201, 183, 171, 142, 115; Anal. Calc for $C_{17}H_{14}O_4$: C, 72.36; H, 4.96; Found C, 72.11; H, 4.90.

5,6-Dihydro-8-methoxy-1-oxa -5-phenylthio-s-indacen-7-one 18 : To a stirred solution of enone **16b** (0.5 mmol) in dry dichloromethane (20 mL) at -10^0 C under argon atmosphere, was added thiophenol (0.53 mmol) and a catalytic amount of triethylamine. The resulting solution was stirred for 3-6 h and then was diluted with diethyl ether (30 mL). The organic phase was washed with aqueous potassium carbonate, dried and concentrated to give **18** in 86-90% yields. The compound was recrystallised from chloroform-hexanes mixture. mp 71^0 C; δ_H 7.78 (d, 1 H, *J* 2, Furo-$\underline{H}$), 7.55 - 7.2 (m, 6 H, Ar$\underline{H}$), 6.82 (d, 1 H, *J* 2, Furo-$\underline{H}$), 4.88 (dd, 1 H, *J* 8, 3, C$\underline{H}$SPh), 4.4 (s, 3 H, OC$\underline{H}_3$), 3.22 (dd, 1 H, *J* 18, 8, COC$\underline{H}_2$), 2.82 (dd, 1 H, *J* 18, 3, COC$\underline{H}_2$); ν_{max} 2926, 1701, 1599, 1469, 1344, 1258, 1082, 745.

Baeyer- Villiger oxidation of 18 →1 : To a chilled (-10^0 C) mixture of acetic anhydride (0.9 mL) and conc. H_2SO_4 (0.23 mL) was syringed 30% w/v hydrogen peroxide (0.23 mL, 2.8 mmol) and the contents were stirred for 2 min under argon atmosphere. The peroxide reagent thus obtained was diluted with CH_2Cl_2 (1mL) and then syringed into a solution of the furoidanone **18** (80 mg, 0.26 mmol) in dry CH_2Cl_2 (2.5 mL) at -10^0 C. Stirring was continued for 0.5 h at low temperature and the mixture was stirred for additional 0.5 h and diluted with CH_2Cl_2 (18 mL) . The organic phase was washed with water (3 mL), aqueous sodium bicarbonate (3 mL), and then worked up usually. The residue obtained was subjected to plc to provide methoxalen **1** (8.5 mg, 15%) and sulfone **19** (36 mg, 40.4%).

8- methoxypsoralen 1 : mp 148^0 C (lit^{21} 147 - 148^0 C) ; δ_H 7.77 (d, 1 H, *J* 9.6, CH = CHCO) , 7.7 (d, 1 H, *J* 2.2, Furo-H), 7.36 (s, 1 H, ArH), 6.83 (d, 1 H, *J* 2.2, Furo-H), 6.35 (d, *J* 9.6, CH = CHCO), 4.3 (s, 3 H, OCH$_3$) ; ν_{max} 2933, 1715, 1621, 1580, 1330, 1215, 1087, 867, 753; (m/z) 216 (M$^+$, 100%), 201, 173, 158, 145, 129, 117, 102, 89, 77, 75; Anal. Calc. for $C_{12}H_8O_4$: C, 66.68; H, 3.70; Found C, 66.52; H, 3.72.

5.6- Dihydro-8- methoxy-1-oxa-5-phenylsulfonyl-I-indacen-7-one 19: mp 228^{0}C; δ_H 7.75 (d, 1 H, *J* 2, Furo-H), 7.85-7.5 (m, 6 H, ArH) , 6.95 (d, 1 H, *J* 2, Furo-H), 5.15 - 5.0 (m, 1 H, CHSO$_2$Ph), 4.38 (s, 3 H, OCH$_3$), 3.00 (m, 2 H, COCH$_2$); ν_{max} 2928, 1699, 1589, 1303, 1137, 751; (m/z) 342(M$^+$), 201(100%), 186, 171, 142, 129, 125, 115, 101, 86, 78, 75.

Compounds **3** , **20b, 20c, 20d, 21a, 21b, 22a, 22b, 23** and **24** were prepared according to the procedures described respectively for **1, 4b, 13, 14, 9a, 9b, 16a, 16b, 18** and **19** :

Compound **20b** : thick oil^{22} ; yield 75%; δ_H 7.39 (d, 1 H, *J* 2, Furo-H), 6.68 (d, 1 H, *J* 2 , Furo-H), 4.80 (s, 2 H, CH$_2$Br), 3.88 (s, 3 H, COOCH$_3$).

Compound **20c** : oil ; yield 88% ; δ_H 7.40-7.21 (m, 6 H, ArH , Furo-H), 6.62 (d, 1 H, *J* 2, Furo-H), 4.43 (s, H, CH$_2$SPh), 3.72 (s, 3 H, COOCH$_3$) ; ν_{max} 3423, 2950, 1720, 1598, 1442, 1309, 1196, 1142, 1048, 745; (m/z) 248(M$^+$), 216, 184, 139, 109, 80, 65, 51.

Compound **20d** : mp 85-86^0 C; yield 75%; δ_H 7.46 (s, 5 H, ArH), 7.32 (d, 1 H, *J* 2 , Furo-H), 6.65 (d, 1 H, *J* 2 , Furo-H), 4.51 (AB q, *J* 11,-CH$_2$S(O)Ph), 3.70 (s, 3 H, COOCH$_3$); ν_{max} 3141, 2935, 1714, 1616, 1440, 1387, 1053, 756; (m/z) 264(M$^+$), 233, 186, 139 (100%), 125, 109, 97, 77; δ_C 163, 150.3, 142.9, 142.9, 131.2, 128.8, 123.9, 117.4, 110.9, 55.5, 51.4; Anal. Calc. for $C_{13}H_{12}O_4S$: C, 59.11; H, 4.54; Found C, 58.78; H, 4.43.

Compound **21a** : mp 128^{0}C; yield 70%; δ_H 9.77 (b s, 1 H, ArOH), 7.49 (d, 1 H, *J* 2, Furo-H), 6.94 (d, 1 H, *J* 0.8, ArH), 6.86 (m, 1 H, furo-H), 5.95 - 5.90 (m, 1 H, CH =), 5.56-5.50 (m, 1 H, CH =) , 3.91 - 3.85 (m, 1 H, ring - H), 3.34-3.23 (m, 3 H, ring -H), 1.82-1.68 (m, 2 H, ring CH$_2$ -), 1.80 (AB d, 1 H, *J* 8, - CH$_2$-), 1.70 (AB d, 1 H, *J* 8, -CH$_2$ -); δ_C 209.6, 162, 152, 151.6, 144.4, 133.7, 133.1, 119.9, 115.2, 104.4, 100.5, 53.8, 52.6 (CH$_2$), 45.9, 45.2, 44.9; ν_{max} 3249, 3141, 2931, 1654, 1588, 1311, 1345, 1259;

(m/z) 252(M^+), 186(100%), 158, 130, 102; Anal.Calc. for $C_{16}H_{12}O_3$: C,76.20; H, 4.75; Found C,75.89; H, 4.55.

Compound **21b:** mp 127-128^0 C; yield 87%; δ_H 7.49 (d,1 H, J 2, Furo -H), 7.07 (s,1 H, ArH), 6.94(m, 1 H, furo -H), 5.96-5.91 (m, 1 H, = CH), 5.52 -5.47 (m, 1 H, = CH), 4.19 (s, 3 H, OCH_3), 3.86-3.80 (m, 1 H, ring -H), 3.34 (br s, 1 H, ring-H), 3.20-3.14 (m, 2 H, ring-H), 1.71 (AB q, 2 H, *J* 8.5, - CH_2 -); δ_C 203.5, 161.1, 154.1, 152.0, 144.1, 133.5, 133.3, 124, 117.1, 105.9, 102.1, 60.4, 53, 52.2, 46.2, 45.50, 44.10; ν_{max} 3142, 2962, 1684, 1598, 1470, 1340, 1302, 1254, 1089, 784; Anal Calc. $C_{17}H_{14}O_3$: C, 76.75; H,5.30; Found C, 76.70; H, 5.16; (m/z) 266(M^+), 200(100%), 171, 142, 129, 115, 66.

Compound **22a** : mp 100-102^0 C ; yield 98%; δ_H 8.54 (br s, 1 H, ArOH), 7.52 (d, 1 H, *J* 2 , Furo-H), 7.39 (d, 1 H, *J* 5.8 , CH = CO), 6.86 (d, 1 H, *J* 2, Furo-H), 6.76 (s,1 H, ArH), 5.90 (d, 1 H , *J* 5.8 , = CHCO); δ_C 199.4, 160.3, 151.2, 148.3, 145, 140.7, 128.5, 119.1, 108.2, 105.8, 102.6; ν_{max} 3496, 1675, 1607, 1327, 1265, 1465, 1052, 834, 732; (m/z) 186(M^+,100%), 158, 129, 102, 75, 51.

Compounnd **22b** : mp 82-83^{0}C; yield 95%; δ_H 7.5 (d, 1 H, *J* 2, Furo-H), 7.38 (d, 1 H, *J* 6 , CH =CHCO), 6.90 (m, 1 H, Furo-H), 6.82 (s, 1 H, ArH), 5.84 (d, 1 H, *J* 6, CH= CH CO), 4.28 (s, 3 H, OCH_3); ν_{max} 2938, 1685, 1595, 1468,1329, 1240, 1105, 1059, 891, 846, 722; (m/z) 200(M^+, 100%), 171, 142, 129, 115, 101, 87, 75, 63, 51.

Compound **23** : mp 76-77^{0}C; yield 95% ; δ_H 7.59 (d, 1 H, *J* 2, Furo-H), 7.38-7.27 (m, 6 H, ArH) , 7.04 (d, 1 H, *J* 2, Furo-H), 4.86 (dd, 1 H, *J* 3.2 ,7.6 , CH SPh), 4.25 (s, 3 H, OCH_3), 3.18 (dd, 1 H, *J* 7.6, 19, $COCH_2$), 2.81 (dd, 1 H, *J* 19, 3.2, $COCH_2$); ν_{max} 2923, 1710, 1616, 1590, 1472, 1293, 1089, 845, 745; LCMS, (m/z) 310(M^+), 201(100%), 186, 171, 142, 115, 102, 75, 65, 51; Anal.Calc. for $C_{18}H_{14}O_3S$: C, 69.69; H, 4.51; Found C, 69.29; H, 4.31.

Compound **24** : mp 201-202^0 C; yield 40% ; δ_H 7.68-7.40 (m, 7 H, ArH , Furo-H), 7.03 (m, 1 H, Furo-H), 4.88 (m, 1 H , CH SO_2 Ph), 4.16 (s, 3 H, OCH_3) , 2.96 (unresolved AB q, 2 H, $COCH_2$); ν_{max} 1700, 1587, 1472, 1345, 1298, 1145, 1084; δ_C 196.9, 160.9, 151.4, 145.6, 141.8, 135.6, 133.7, 128.6, 128.3, 120.6, 118.5, 106.1, 105.6, 62.9, 60.9, 39.7; (m/z) 342 (M^+), 259, 201(100%); Anal.Calc.for $C_{18}H_{14}O_5S$: C, 63.17; H, 4.09; Found C, 62.77; H, 3.89; HRMS Calc. for $C_{18}H_{14}O_5S$: 342.05620, found 342.0560.

Compound **25** : mp 153^0C; yield 21%; δ_H 7.7-7.45 (m, 6 H, Furo-H, Ar-H), 7.14 (s, 1 H, ArH), 6.93 (m, 1 H, Furo-H), 4.47 (d, *J* 7.2, CHSO$_2$ Ph), 4.00 (s, 3 H, OCH$_3$), 3.44 (dd, 1 H, J 1.4, 17.6, CH$_2$CO), 3.06 (dd, 1 H, *J* 7.2, 17.8, CH$_2$CO); ν_{max} 1749, 1584, 1478, 1429, 1358, 1305, 1174, 1152, 1080, 990, 731; δ_C 163.2, 151.8, 146.4, 140.6, 135.1, 134.7, 129.5, 129.3, 122.4, 111, 107.7, 104.9, 62.5, 61, 29.5; (m/z) 358 (M^+), 216(100%). HRMS Calc. for $C_{18}H_{14}O_6S$: 358.05111, found 358.0517.

Compound **3** : mp 122-123^0C ; yield 15%; δ_H 7.76 (d, 1 H, *J* 9.6, CH = CHCO), 7.67 (d, 1 H, *J* 2.4, Furo- H), 7.30 (s, 1 H, ArH), 7.01 (m, 1 H, Furo-H), 6.42 (d, 1 H, *J* 9.6, CH = CH CO), 4.21 (s, 3 H, OCH$_3$); δ_C 160.3, 151.9, 147, 144, 141.1, 139.8, 123.2, 116.9, 115.7, 105.0, 103.7, 61.1; ν_{max} 1714, 1619, 1566, 1421, 1351, 1269, 1098, 987, 852; (m/z) 216 (M^+,100%), 201, 173, 145, 131, 89, 63 ; Anal. Calc. for $C_{12}H_8O_4$: C, 66.72; H, 3.73; Found C, 66.78; H, 3.60 ; λ_{max} (nm) 318.

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