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Tandem annulation strategy for the convergent synthesis of benzonaphthopyranones: total synthesis of chartarin and *O*-methylhayumicinone

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Abstract

A Hauser-initiated tandem annulation has been developed for the rapid regiospecific synthesis of benzonaphthopyranones via formation of two rings in one-pot operation. This strategy has been generalized with benzonaphthopyranones **26**, **29**, **32**, and **35**. It has also been employed in a short synthesis of chartarin (**3**) and *O*-methylhayumicinone (**67**).

Keywords: Hauser annulation; Benzonaphthopyranone; Chartreusin; Chrymutasin; Hayumicin

1. Introduction

Aromatic polyketides featuring oxygenated benzonaphthopyranone motifs are of considerable interest due to their biological activity and structural intricacies. They exhibit a wide range of biological activities (Fig. 1).[1] Chartreusins (e.g., **1**), chrymutasins (e.g., **2**), hayumicins (e.g., **5**), gilvocarcins (e.g., **6**), and arnottin I (e.g., **7**) are few selective aromatic polyketide antibiotics that share a benzonaphthopyranone moiety. Chartreusin (**1**), the most studied member and first isolated in 1953 from the culture broth and mycelial cake of *Streptomyces chartreuses* was fully characterized in 1964. It shows significant chemotherapeutic activity against cancer cell lines (ascitic P388, L1210 leukemia, and B16 melanoma). Due to poor solubility in water and rapid biliary excretion, none of the chartreusins found any clinical application.[2] Elsamicin A[3] and IST-622,[4] a semi-synthetic derivative, which have improved water solubility due to the amino sugar moiety are currently undergoing phase II clinical trials in Japan for the treatment of patients with breast cancer.[5]

Structurally allied chrymutasin[6] A (**2**), on the contrary, has not received any attention even though it showed stronger antitumor activities than chartreusin (**1**). Neither, has it been the subject of any synthetic research activity. In view of the sustained interest[4a] in chartreusin (**1**) and its striking similarities with chrymutasins, we decided to develop a diversity-oriented synthetic approach[7] for the titled molecules and analogs. Our interest in this area was reinforced by the fact that the extended aromatic structures have found important commercial applications in electro-luminescence, field-effect transistors (FET), organic light emitting diodes (OLED), and photovoltaic devices[8] as well as in the synthesis of axially chiral biaryl natural products.[9]

We focused our study on the aglycones, since the intercalation of aglycones is known to be the main source of free energy of binding in any intercalated drug–DNA complex.[10] In a recent communication,[11] we reported a tandem annulation route to benzonaphthopyranones. Herein, we present a detailed account of the study leading to the first synthesis of *O*-methylhayumicinone (**67**).

2. Synthetic strategy

Chartreusin (**1**) and chrymutasin A (**2**), albeit structurally very similar, differ markedly in the constitution of the B-rings.

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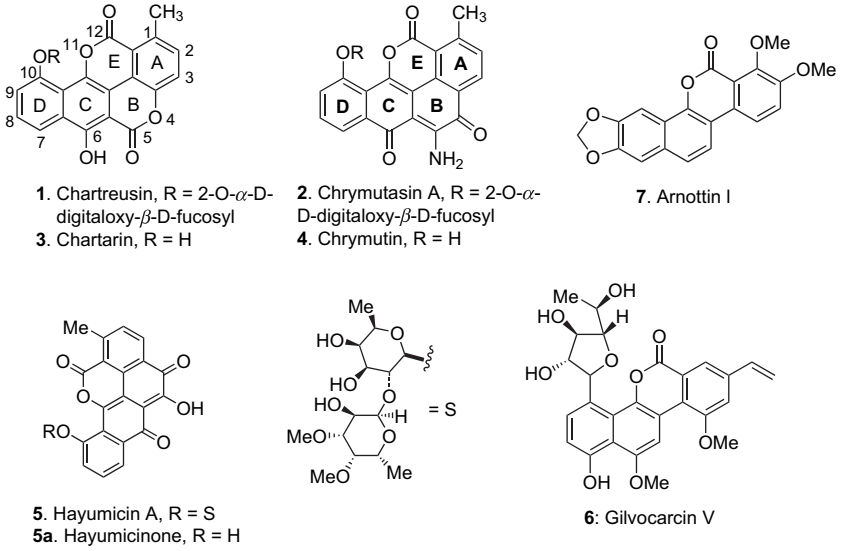
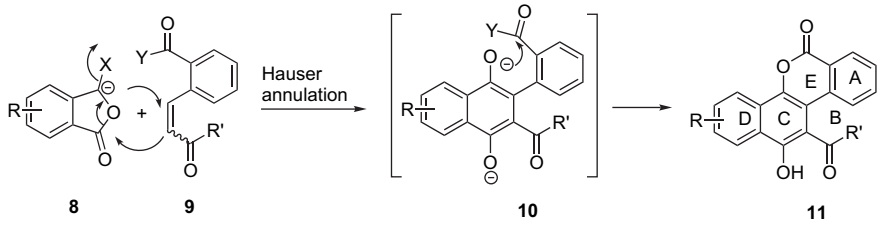


Figure 1. Structures of benzonaphthopyranone antibiotics.



Scheme 1. Tandem annulation strategy for the synthesis of benzonaphthopyranones.

Yet, they possess a similar bioactivity profile, implying the allowance of structural modification/diversity in the B-ring part of the molecules. Consequently, we formulated a tandem annulation strategy (Scheme 1) for the synthesis of B-ring analogs by involving the Hauser annulation.[12] The aryloxy anion of the intermediate **10**, generated by the initial annulation of compound **8** with acceptor **9**, was envisaged to undergo intramolecular nucleophilic attack to the pendant ester in the acceptor **9**, providing in situ formation of the lactone ring of the product **11**. This synthetic approach proved to be successful for the construction of both the C and E rings in one-pot in a regiospecific manner.[11] The A, B, and D rings were derivable from the isobenzofuranones and the Michael acceptors with a preset substitution pattern.

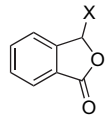
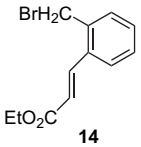
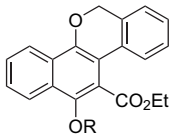
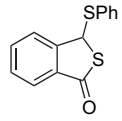
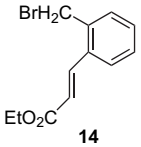
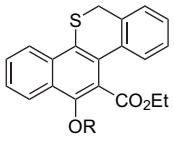
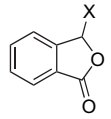
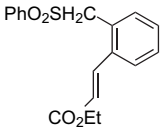
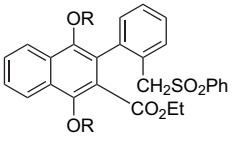
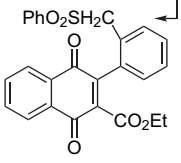
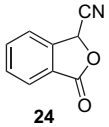
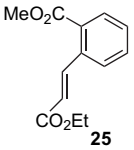
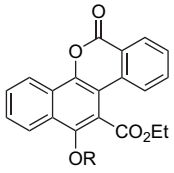
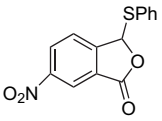
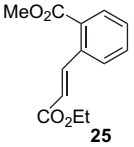
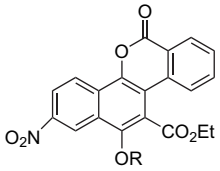
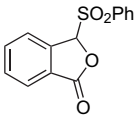
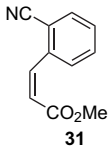
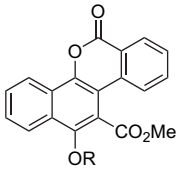
3. Results and discussion

3.1. Model study on the synthesis of benzo[d]naphtho-[1,2-b]pyran-6-ones

The tandem strategy was first examined with the cinnamate **14**,[13] prepared in two steps from *o*-tolualdehyde by Wittig reaction with $Ph_3P{=}CHCO_2Et$ followed by benzylic bromination (NBS/Bz_2O_2, heat). Annulation of **14** with isobenzofuranone **12** in the presence of lithium *tert*-butoxide at −60 °C afforded the desired doubly annulated product **15** in 65% yield (entry 1, Table 1). When isobenzofuranone **13** was treated with cinnamate **14** under similar conditions as above, it expectedly gave benzonaphthopyran **15** (63%), which was duly characterized as its *O*-methyl derivative **16**. For the preparation of the thiopyran analog of **16**, Michael acceptor **14** was annulated with 3-phenylthio-3*H*-benzo[*c*]thiophen-1-one (**17**)[14] under the conditions described above to give **18** in 63% yield (entry 2). It was primarily characterized by ^{1}H NMR data and for further characterization compound **18** was subjected to acetylation with Ac_2O/Et_3N/DMAP (4-*N*,*N*-dimethylaminopyridine) in CH_2Cl_2 to give **19** in 91% yields.

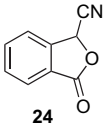
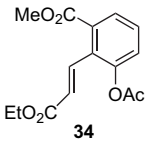
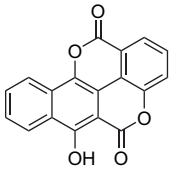
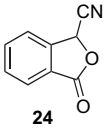
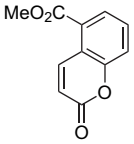
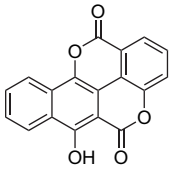
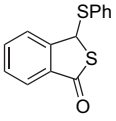
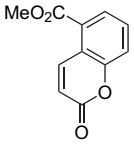
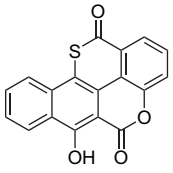
Next, we applied the annulation to a cinnamate derivative with a poor nucleofuge at the *ortho*-position, i.e., **20**. It reacted with phthalide **12**[15] in the presence of lithium *tert*-butoxide in dry THF at −60 °C forming mono annulation product arylnaphthoquinol **21** in 85% yield (entry 3). The same compound was obtained in 81% yield when sulfone phthalide **13**[16,12b,12c] was condensed with the cinnamate **20**. The structure of arylnaphthoquinol **21** was established by ^{1}H NMR data. It was also characterized as methyl ether **22**, prepared by methylation of **21** with Me_2SO_4/K_2CO_3 in 92% yield. Two 3H singlets at δ 4.01 and 3.36 in the ^{1}H NMR spectrum clearly indicated the formation of dihydroxyarylnaphthoquinol **21**. The compound **21** was further transformed to **23** by oxidation with ceric ammonium nitrate (CAN) in acetonitrile. The annulated product **22** can be viewed as a potential intermediate for an

Table 1
Annulation between 3-substituted phthalides and Michael acceptors

Entry	Isobenzofuranones	Michael acceptors	Benzonaphthopyranes
1	 **12**: X = SPh **13**: X = SO_2Ph	 **14**	 **15**: R = H, 65% **16**: R = Me — 89%[a]
2	 **17**	 **14**	 **18**: R = H, 63% **19**: R = $COCH_3$ — 91%[b]
3	 **12**: X = SPh **13**: X = SO_2Ph	 **20**	 **21**: R = H, 85% **22**: R = Me — 92%[a], 83%[c]  **23**
4	 **24**	 **25**	 **26**: R = H, 81% **27**: R = Me — 92%[a]
5	 **28**	 **25**	 **29**: R = H, 86% **30**: R = Me — 90%[a]
6	 **13**	 **31**	 **32**: R = H, 83% **33**: R = Me — 92%[a]

(*continued*)

Table 1 (*continued*)

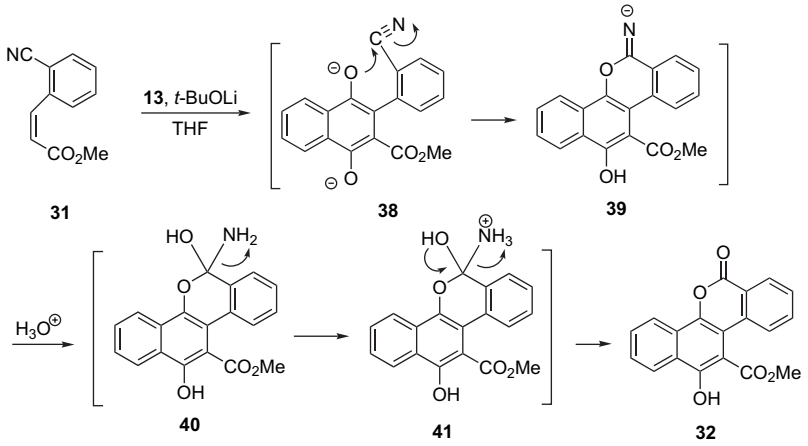
Entry	Isobenzofuranones	Michael acceptors	Benzonaphthopyranes
7	 **24**	 **34**	 **35** (76%)
8	 **24**	 **36**	 **35** (91%)
9	 **17**	 **36**	 **37** (71%)

[a] Me_2SO_4/K_2CO_3, acetone.
[b] Ac_2O/Et_3N/DMAP, dichloromethane.
[c] CAN.

entry to angucyclines[17] through anionic intramolecular cyclization.

For the fabrication of a benzonaphthopyranone, structurally akin to the target molecule, the ester appended cinnamate **25**[18] was prepared in two steps from commercially available phthalaldehydic acid by methylation (DBU/MeI, rt) followed by Wittig reaction with $Ph_3P{=}CHCO_2Et$. LiO^tBu promoted annulation of cinnamate **25** with cyanophthalide **24**[19] under the conditions described previously gave compound **26** (81%) resembling the gilvocarcin nucleus (entry 4). This product was characterized as its *O*-methyl derivative **27**. Nitro substituted isobenzofuranone **28** was similarly condensed with **25** to provide benzonaphthopyranone **29** as a yellow solid in 86% yield (entry 5). The nitro group attached to the A-ring of benzo[*d*]naphtho[1,2-*b*]pyran-6-one **29** can, in principle, be transformed to an array of substituents providing newer analogs of benzonaphthopyranones. Methylation (Me_2SO_4/K_2CO_3) of **29** routinely provided **30** in 90% yield.

When Michael acceptor **31**, prepared from the corresponding cinnamic acid,[20] was subjected to annulation reaction with sulfone phthalide **13**, benzo[*d*]naphtho[1,2-*b*]pyran-6-one **32** was formed in 83% yield (entry 6). It was fully characterized by analysis of IR, NMR, and mass spectral data, and its conversion to *O*-methyl derivative **33**. The formation of **32** can be explained by the mechanism shown in Scheme 2. The aryloxy anion intermediate **38** formed after initial annulation underwent intramolecular cyclization through nucleophilic attack of O^- group to the cyano group to form **39** followed by **40**, which, probably during acidic work-up underwent hydrolysis to provide **32**. It may be concluded that the tandem annulation route to benzonaphthopyranone is applicable to



Scheme 2. Mechanism for the formation of benzonaphthopyranone **32**.

a Michael acceptor with a cyano appendage. The monoannulated product corresponding to the dianion **38**, i.e., the protonated form of **38** was not isolated.

For the synthesis of the pentacyclic model compound **35**, representing the core structure of chartarin (**3**), annulation reaction between **24** and **34** was conducted under the conditions used for the preceding examples. In one-pot operation, *three new rings* were formed in one-pot to afford triply annulated product **35** in 76% yield (entry 7). It is important to note that the phenolic acetate group in **34** did not impede the annulation. The desired core structure of chartarin (**3**) was obtained instead of B-ring *seco* derivative. The expected doubly annulated product with an intact phenolic acetate group was not isolated. In a similar vein, we examined the annulation of coumarin **36**, prepared according to the literature procedure[21] from 3-hydroxybenzoic acid through a regioselective Duff reaction as a key step. Its reaction with 3-cyano-1(3*H*)-isobenzofuranone (**24**) in the presence of lithium *tert*-butoxide provided, as expected, the doubly annulated pentacyclic product **35** (entry 8). In order to examine whether the reaction can be applied to the preparation of E-ring thio analog of chartreusin, we considered the annulation between phthalide **17** and coumarin **36** (entry 9). Under the conditions as described above, it provided pentacyclic **37** as a yellow solid. Both the pentacyclic compounds **35** and **37** have diminished solubility in organic solvents compared to the tetracyclic compound **26**.

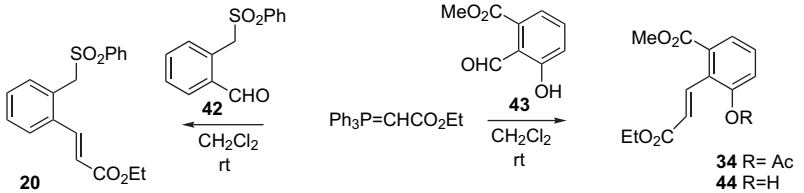
3.2. Preparation of synthons *20* and *44*

Both the Michael acceptors **20** and **34** were prepared by a Wittig reaction with freshly prepared $Ph_3P{=}CHCO_2Et$ in CH_2Cl_2 (Scheme 3). Sulfone aldehyde **42**, available from our recently reported[22] six-step synthesis from methyl *o*-toluate was reacted with the Wittig reagent in CH_2Cl_2 to give unsaturated ester **20** in 94% yield.

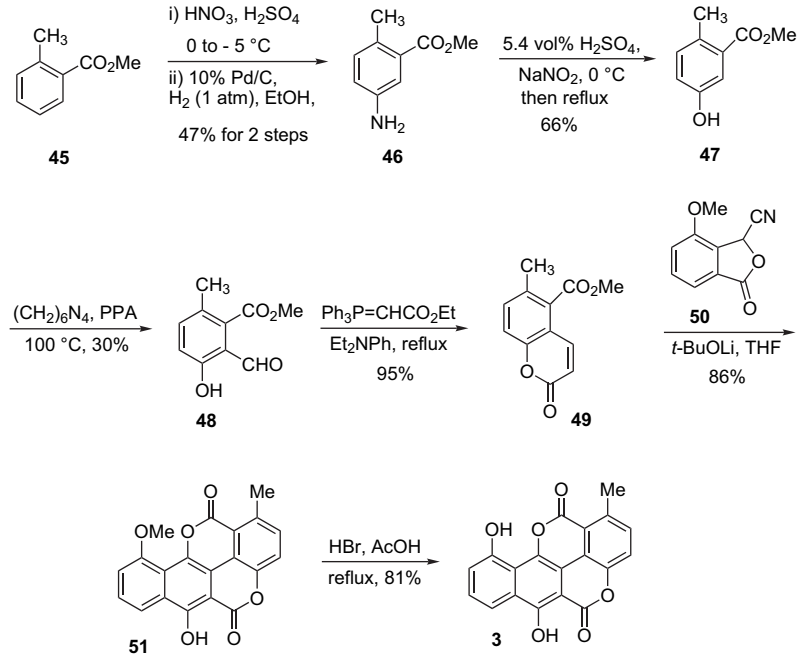
Similarly, methyl 2-formyl-3-hydroxybenzoate[21] **43** was reacted with $Ph_3P{=}CHCO_2Et$ in CH_2Cl_2 at room temperature to give cinnamate **44** in 94% yield, which on acetylation with Ac_2O/Et_3N/DMAP provided **34** in 96% yield (Scheme 3).

3.3. Total synthesis of chartarin (*3*)

For the total synthesis of chartarin (**3**), the required coumarin **49** was prepared as depicted in Scheme 4. Although the synthesis looked straightforward at the outset, it required lot of experimentation and optimization due to the non-availability of detailed procedures. The synthesis was begun with nitration of methyl *o*-toluate (**45**). Treatment of **45** with a mixture of concentrated H_2SO_4 and concentrated HNO_3 provided a mixture of methyl 2-methyl-5-nitrobenzoate and the corresponding *ortho*-isomer, which were separated by fractional crystallization from a MeOH/H_2O system. The yields of the products were 50% and 30%, respectively. Reduction of nitro group in the *para*-isomer to amine group was performed by hydrogenation in the presence of 10% Pd–C in MeOH to give methyl 5-amino-2-methylbenzoate (**46**)[23] in 94% yield. Diazotization of the amino group in **46** with $NaNO_2/H_2SO_4$, followed by reflux in H_2O furnished the phenol **47**[24] in 66% yield. Duff reaction of **47** with $(CH_2)_6N_4$/PPA (polyphosphoric acid) at 100 °C afforded ester **48** in 30% yield. The ^1H NMR data of **48** was in conformity with its structure. Two 1H doublets at δ 7.36 and 6.98 with coupling constants J=8.7 Hz



Scheme 3. Synthesis of compounds **20** and **44**.



Scheme 4. Total synthesis of chartarin **3**.

corresponding to the aromatic hydrogens were in support of the desired formylation. Treatment of **48** with $Ph_3P{=}CHCO_2Et$ in Et_2NPh at reflux for 20 min, followed by usual work-up gave coumarin ester **49** in 95% yield. The structure of **49** was elucidated on the basis of IR, NMR, and MS (mass spectral) data. The ^3J coupling constants of two H atoms of the lactone ring in **49** were in accordance with the structure.

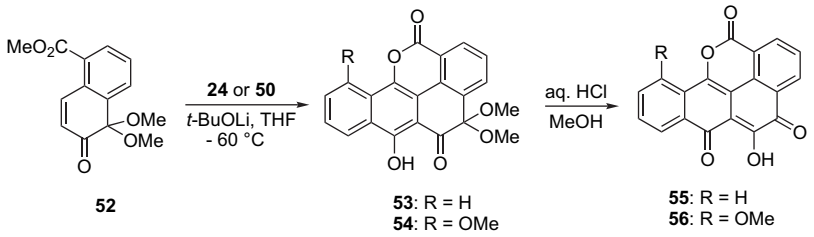
Annulation of 4-methoxycyanophthalide **50**[19] with coumarin **49** in the presence of ^{t}BuOLi under typical conditions followed by usual work-up gave **51** as a yellow solid in 86% yield (Scheme 4). Unlike the pentacyclic compounds **35** and **37**, this compound is fairly soluble in common organic solvents. It could be purified by column chromatography (silica gel) followed by recrystallization from ethyl acetate/petroleum ether. ^{1}H NMR spectrum of this compound showed a broad singlet at δ 11.57 for the *peri*-hydroxy group (6-OH). In the aromatic region, it revealed four 1H doublets at δ 8.06, 7.54, 7.46, and 7.19, and a 1H triplet at δ 7.59. These data were indicative of two aromatic rings, one of which is 1,2,3-trisubstituted and the other is a 1,2,3,4-tetrasubstituted ring system. ^{13}C NMR, IR, and MS data of this sample also matched the structure. HBr-promoted demethylation of **51** provided chartarin (**3**) in 81% yield. The ^{1}H NMR spectrum (200 MHz) of **3** recorded in DMSO-d_6 was not well resolved. However, it compared well with the reported[3b] one. For further verification, its ^{1}H NMR spectrum was recorded in $CDCl_3$ on a 500 MHz spectrometer. The spectrum was well resolved and the data were in conformity with reported values.

Although the concept of condensation of a coumarin with a 3-substituted isobenzofuranone to give the corresponding benzo[*b*]naphtho[*d*]pyran-6-one was originally introduced by Hauser and Combs in the total synthesis of chartarin,[16] the present strategy provided a significantly shorter route. The pentacyclic framework as in **51** was fabricated in one-pot operation. The key to our success in this area was the choice of cyanophthalide **24** instead of phthalide sulfone **13** for the crucial condensation reaction with coumarin **49**.

3.4. Model studies of chrymutasin and hayumicin aglycones

Following the total synthesis of chartarin (**3**), we deployed the tandem annulation strategy to the synthesis of chrymutasins and hayumicins, which could be considered as B-ring carbon analogs of chartreusins. As the initial target, we chose model compound **55**, embodying the entire chromophoric part of hayumicin aglycone (**5a**). We were apprehensive that the reaction between **24** and the required naphthoquinone monoketal **52**[25a] might lead to the formation of hydroxymethoxyanthraquinone in accordance with our reported results.[25] Nevertheless, cyanophthalide **24** was reacted with Michael acceptor **52** in the presence of ^{t}BuOLi in THF to give pentacyclic compound **53** as a yellow solid in 87% yield. It may be noted that phthalide sulfone **13** was not compatible to react with the naphthoquinone monoketal **52**. The ^{1}H NMR spectrum of **53** exhibited a 6H singlet at δ 3.41, characteristic of two chemically equivalent OCH_3 groups supporting the monoketal structure of **53**. It also showed a sharp singlet at δ 13.48 corresponding to the hydrogen-bonded OH group. Acid catalyzed deketalization of ketal **53** furnished the model compound **55** in 98% yield.

Similarly, methoxycyanophthalide **50** was reacted with quinone monoketal **52** in the presence of ^{t}BuOLi in THF at -60 °C to give pentacyclic monoketal **54** in 92% yield as a yellow solid. The signals at δ 13.54 (OH), 4.12 (3H,



Scheme 5. Synthesis of hayumicinone analogs.

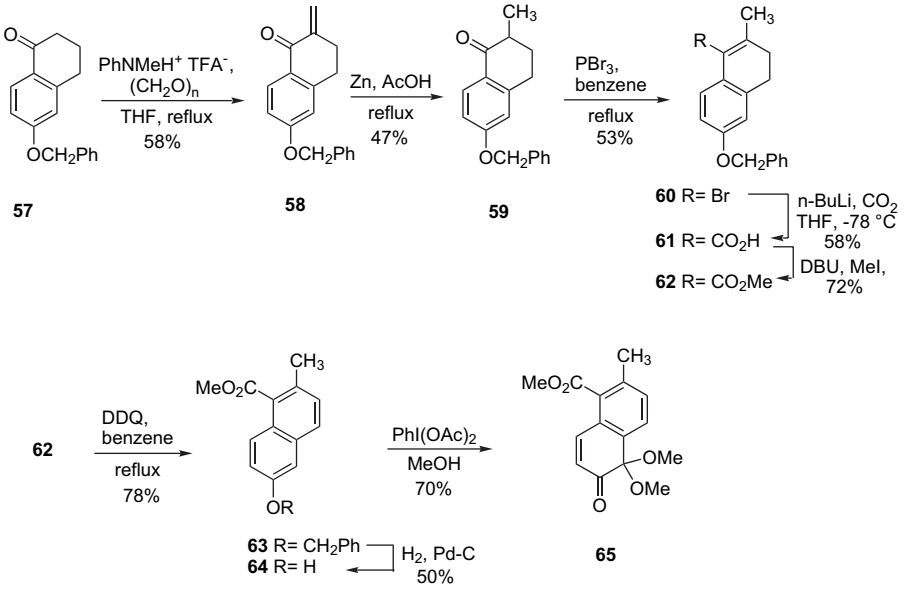
OCH_3), and 3.40 (6H, $2\times OCH_3$) in ^1H NMR spectrum were in agreement with the structure of the compound. Acid catalyzed deketalization of **54** provided hayumicinone analog **56** in 98% yield (Scheme 5). Like compound **55**, it was poorly soluble in common organic solvents. In ^1H NMR spectrum, it exhibited a sharp singlet at δ 14.52 for the hydroxy group (5-OH). In the aromatic region, it revealed four 1H doublets at δ 8.71, 8.64, 8.20, and 7.34 and two 1H triplets at δ 7.77 and 7.69 corresponding to two aromatic rings, which are 1,2,3-trisubstituted ring systems.

4. Extension to the synthesis of *O*-methylhayumicinone (67)

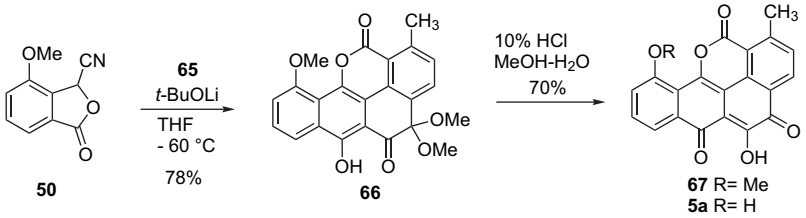
For the synthesis of hayumicinone **5a** by extension of the above methodology, naphthoquinone monoketal **65** was required. With the synthesis of **52** reported in the literature that of structurally analogous ketal **65** appeared to be straightforward. However, it necessitated rigorous studies. It was partly because of our keenness to utilize readily available 6-methoxytetralone. At the initial stages, we examined, *without success*, several approaches, which included (i) Friedel–Crafts reaction of anisole with 3-methylfuran-2-carboxylic acid, (ii) Michael-initiated ring closure reaction of dimethyl methoxyhomophthalate, (iii) reduction of *N*,*N*-diethyl 2-formyl-6-methoxynaphthalene-1-carboxamide, and (iv) elaboration of 6-methoxytetralone through cyanohydrin formation, Shapiro reaction, and nitromethane addition. Eventually, a eight-step synthesis of the naphthoate **65** from **57**, depicted in Scheme 6, was executed.

6-Benzyloxytetralone (**57**), prepared by O-benzylation[26] of 6-hydroxy-α-tetralone was methylenated with paraformaldehyde and *N*-methylanilinium trifluoroacetate to give **58**. Zn/AcOH reduction of **58** followed by reaction with PBr_3 furnished alkenyl bromide **60**, which was homologated via lithiation and reaction with carbon dioxide to give acid **61** in moderate overall yield. This was then methylated with DBU/CH_3I[27] to give ester **62**. DDQ-promoted aromatization of **62**, followed by reductive debenzylation with H_2/Pd–C provided naphthoate **64**. As expected, oxidation of **64** with $PhI(OAc)_2$ in methanol at 0 °C resulted in the formation of naphthoquinone monoketal **65** in 70% yield.

With both **65** and **50** in hand, we explored their condensation chemistry for the synthesis of hayumicinone (**5a**). Treatment of the quinone monoketal **65** with cyanophthalide **50** in the presence of LiO^tBu afforded the desired pentacyclic annulation product (**66**) in 78% yield, which characteristically gave a ^1H NMR signal at δ 13.71 for the hydrogen-bonded



Scheme 6. Synthesis of *o*-naphthoquinone monoketal **65**.



Scheme 7. Synthesis of *O*-methylhayumicinone.

proton and IR signal at 1737 cm^{-1} for lactone carbonyl. Deketalization of **66** with aq HCl solution in methanol furnished hayumicinone **67** in yield via keto–enol transposition. The possibility of **67** existing in the isomeric *ortho*-quinone structure was ruled out on the basis of calculated minimized energy (MM2). However, the final O-demethylation of **67** remained to be accomplished (Scheme 7). The preliminary attempts with HBr/AcOH were unsuccessful.

5. Conclusion

In conclusion, a tandem annulation (formation of more than one ring in one-pot) has been introduced for the one-pot regiospecific fabrication of a variety of benzonaphthopyranones from readily accessible starting materials. This strategy has been utilized in the total synthesis of chartarin (**3**) and *O*-methylhayumicinone (**67**) from **57**. Work is in progress for incorporation of the peripheral amino group toward completion of the synthesis of chrymutin (**4**).

6. Experimental

6.1. General experimental

Melting points are uncorrected. IR spectra were recorded on a Thermo Nicolet Nexus 870 FT-IR spectrophotometers using KBr pellet. ^{1}H and ^{13}C NMR spectra of the samples in the indicated solvents were recorded on 200 MHz, 300 MHz or 400 MHz spectrometer (Brücker) as solution in $CDCl_3$ or DMSO-d_6 or mixture of $CDCl_3$ and DMSO-d_6 with residual $CHCl_3$ as the internal standard. Chemical shifts are expressed in δ unit and coupling constant in hertz. Mass spectra were taken using a VG Autospec M mass spectrometer. Elemental analyses were carried out by using an elemental analyzer VARIO EL instrument. Dry solvents used for reactions were purified, before use, according to the standard protocols. All solvents for chromatography were distilled prior to use. Columns were prepared with silica gel (60–120 or 230–400 mesh).

6.2. General procedure for annulation reaction

To a stirred solution of lithium *tert*-butoxide (9.84 mmol) in THF (40 mL) at −60 °C (chloroform/liquid N_2 bath) under an inert atmosphere was added a solution of a phthalide (3.28 mmol) in THF (5 mL). The resulting yellowish solution was stirred at −60 °C for 25 min, after which a solution of a Michael acceptor (1.0–1.5 equiv unless otherwise stated) in THF (5 mL) was added to it. The cooling bath was removed after about 1 h at −60 °C and the reaction mixture was brought to room temperature over a period of 1 h and further stirred for 2–6 h. The reaction was then quenched with 10% NH_4Cl (15 mL) and the resulting solution was concentrated. Generally, a bright yellow solid appeared, which was filtered and washed with 1:1 mixture (20 mL) of diethyl ether and petroleum ether. Otherwise, the residue was diluted with ethyl acetate (50 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×25 mL). The combined extracts were washed with H_2O (15 mL), brine (15 mL), dried (anhydrous Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel or by recrystallization to get a pure product.

6.3. General procedure of O-methylation of phenolic compounds

A hydroxy compound (3.0 mmol) was dissolved in dry acetone (20 mL) under N_2-atmosphere. To this solution were added dry K_2CO_3 (15 mmol) and Me_2SO_4 [6 mmol; freshly washed with cold water (10 mL), saturated $NaHCO_3$ solution (15 mL), brine (15 mL), and dried over anhydrous K_2CO_3]. After 2 h of reflux, on completion of the reaction, the inorganic salts were filtered and the filtrate was concentrated. The residue was diluted with ethyl acetate (15 mL), treated with Et_3N (6 mmol) at room temperature and stirred for 30 min. The reaction mixture was then diluted with ethyl acetate (50 mL), washed with 5% aq HCl solution (15 mL) and water (15 mL) and subjected to usual work-up (drying over anhydrous Na_2SO_4 and concentrating under reduced pressure) to get a crude residue, which was further purified by recrystallization or by column chromatography on silica gel to give a pure methoxy compound.

6.4. Chartarin (3)[3b]

Compound **53** (100 mg, 0.29 mmol) was dissolved in a solution of acetic acid (5.0 mL) and 42% aq HBr (5.0 mL). The mixture was heated at reflux for 8 h. After cooling the reaction mixture, the brown resulting solid was separated by filtration and further purified by repeated washing with petroleum ether to furnish **3** as an amorphous solid (78 mg, 81%). Mp: 280 °C

(sublimed) (lit.[3b] mp: 308–309 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.59 (s, 1H), 8.63 (s, 1H), 8.10 (d, 1H, J=8.2 Hz), 7.64 (t, 1H, J=8.0 Hz), 7.59 (d, 1H, J=8.3 Hz), 7.52 (d, 1H, J=8.4 Hz), 7.34 (d, 1H, J=7.7 Hz), 2.91 (s, 3H).

6.5. Ethyl 12-hydroxy-6H-dibenzo[c,h]chromene-11-carboxylate (*15*)

This compound was prepared as a greenish yellow liquid in 65% yield by the reaction between **12** and **14**, according to the general procedure described in Section 6.2. It was also prepared in 61% yield by the reaction between **13** and **14**. The crude product was purified by column chromatography on silica gel (R_f 0.70, 1:5 ethyl acetate/petroleum ether) to furnish pure **15**. ν_{max} ($CHCl_3$, cm^{-1}): 3437, 1724, 1655 (s), 1438, 1391 (s), 1320, 1229, 1154, 1084, 1030, 938, 758, 617; ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.33 (s, 1H), 8.39 (dd, 1H, J=7.8, 1.7 Hz), 8.21 (dd, 1H, J=7.3, 1.5 Hz), 7.69–7.53 (m, 2H), 7.34–7.14 (m, 4H), 5.18 (s, 2H), 4.34 (q, 2H, J=7.1 Hz), 1.20 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.3, 156.0, 145.5, 130.8, 130.2, 129.4 (CH), 128.2, 127.2 (CH), 127.1 (CH), 126.9 (CH), 126.4 (CH), 125.6, 124.3 (CH), 124.1 (CH), 122.0 (CH), 114.8, 69.3 (CH_2), 61.2 (CH_2), 13.7 (CH_3) (signal of one aromatic carbon was not observed). Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 75.20; H, 4.89.

6.6. Ethyl 12-methoxy-6H-dibenzo[c,h]chromene-11-carboxylate (*16*)

This compound was prepared as a white solid in 89% yield from **15**, following the general procedure of methylation described in Section 6.3. The crude product was purified by column chromatography on silica gel (R_f 0.40, 1:10 ethyl acetate/petroleum ether) to furnish pure **16** as a white solid. Mp: 98–100 °C; ν_{max} (KBr, cm^{-1}): 1727 (s), 1634, 1452, 1387, 1346, 1304, 1267, 1228 (s), 1185, 1082 (s), 1011, 936, 857, 759, 654; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.30–8.25 (m, 1H), 8.11–8.05 (m, 1H), 7.60–7.42 (m, 3H), 7.38–7.20 (m, 3H), 5.20 (s, 2H), 4.44 (q, 2H, J=7.1 Hz), 4.06 (s, 3H), 1.35 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.3, 149.1, 148.3, 131.6, 129.7, 128.3, 127.9, 127.3, 127.2, 127.1, 126.8, 124.7, 124.0, 122.8, 122.6, 121.2, 115.1, 69.2, 63.7, 61.5, 14.0; MS EI (70 eV): 334 (M+), 319, 305, 291, 275, 261, 247, 231, 217, 202, 189 (100%). Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.73; H, 5.29.

6.7. Ethyl 12-hydroxy-6H-dibenzo[c,h]thiochromene-11-carboxylate (*18*)

This compound was prepared as a solid in 63% yield by the reaction between **14** and **17**, according to the general procedure described in Section 6.2. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.72 (s, 1H), 8.44 (d, 1H, J=8.2 Hz), 8.06 (d, 1H, J=9.0 Hz), 7.92 (d, 1H, J=7.9 Hz), 7.70–7.10 (m, 5H), 4.63 (q, 2H, J=7.2 Hz), 4.11 (s, 2H), 1.50 (t, 3H, J=7.2 Hz).

6.8. Ethyl 12-acetoxy-6H-dibenzo[c,h]thiochromene-11-carboxylate (*19*)

To a stirred solution of hydroxy compound **18** (200 mg, 0.60 mmol) in CH_2Cl_2 (10 mL) were added acetic anhydride (120 mg, 1.20 mmol), Et_3N (120 mg, 1.20 mmol), and DMAP (10 mg). The reaction mixture was stirred at 25 °C for 4 h. The resulting reaction mixture was partitioned between CH_2Cl_2 (100 mL) and H_2O (50 mL) and the organic layer was washed with dilute HCl (20 mL), brine (20 mL), dried (anhydrous Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (R_f 0.60, 1:1 ethyl acetate/petroleum ether) to furnish **19** in 91% yield (200 mg) as a white solid. Mp: 134–137 °C; ν_{max} (KBr, cm^{-1}): 1773 (s), 1724 (s), 1626, 1582, 1460, 1365, 1298, 1239, 1199 (s), 1153, 1068, 1019, 945, 860, 753, 715; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.02 (d, 1H, J=8.2 Hz), 7.84 (d, 1H, J=8.2 Hz), 7.68–7.50 (m, 4H), 7.38–7.30 (m, 2H), 4.58 (q, 2H, J=7.1 Hz), 4.18 (s, 2H), 2.48 (s, 3H), 1.46 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.9, 166.6, 144.5, 143.3, 140.3, 139.0, 134.9, 131.3, 127.9 (CH), 126.7 (CH), 126.6 (CH), 126.5 (CH), 125.3, 124.6 (CH), 124.3 (CH), 122.8 (CH), 121.6 (CH), 118.8, 61.7 (CH_2), 35.3 (CH_2), 20.5 (CH_3), 14.1 (CH_3); MS EI (70 eV): 378 (M^+), 346, 336, 318, 304 (100%), 290, 272, 262, 258, 230, 202. Anal. Calcd for $C_{22}H_{18}O_4S$: C, 69.82; H, 4.79. Found: C, 70.05; H, 4.63.

6.9. Ethyl 3-(2-phenylsulfonylmethylphenyl)acrylate (*20*)

To a solution of 2-(phenylsulfonylmethyl)benzaldehyde (**42**) (900 mg, 3.46 mmol) in dry CH_2Cl_2 (30 mL) was added freshly prepared $Ph_3P{=}CHCO_2Et$ (1.45 g, 4.16 mmol). The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and successively washed with H_2O (30 mL), brine (30 mL), dried (anhydrous Na_2SO_4), and concentrated. Purification of the crude residue by chromatography on silica gel (R_f 0.70, 3:7 ethyl acetate/petroleum ether) gave **20** (1.07 g, 94%) as a white solid. Mp: 110–112 °C; ν_{max} (KBr, cm^{-1}): 2981, 2934, 1706, 1629, 1483, 1443, 1374, 1311, 1181, 1130, 1080, 1024, 987, 873, 761, 686, 615; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60–7.34 (m, 9H), 7.4 (d, 1H, J=15.6 Hz), 5.96 (d, 1H, J=15.6 Hz), 4.46 (s, 2H), 4.22 (q, 2H, J=7.1 Hz), 1.35 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.7, 139.8, 137.6, 135.0, 133.7, 132.8, 129.8, 129.3, 128.9, 128.7, 127.5, 126.7, 120.8, 60.3, 59.4, 14.3. Anal. Calcd for $C_{18}H_{18}O_4S$: C, 65.43; H, 5.49. Found: C, 65.49; H, 5.45.

6.10. Ethyl 3-(2-phenylsulfonylmethylphenyl)-1,4-dihydroxynaphthalene-2-carboxylate (*21*)

This compound was prepared as a white solid in 85% yield by the reaction between **12** and **20** according to the general procedure described in Section 6.2. It was also obtained from the reaction between **13** and **20** in 81% yield. The crude product was purified by column chromatography on silica gel (R_f 0.60, 1:3 ethyl acetate/petroleum ether) to furnish **21** as

a white solid. Mp: 116–119 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.34 (s, 1H), 8.46 (d, 1H, J=8.4 Hz), 8.26 (d, 1H, J=8.4 Hz), 7.70–7.20 (m, 11H), 4.22 (s, 2H), 3.91 (q, 2H, J=7.2 Hz), 0.69 (t, 3H, J=7.2 Hz, 3H).

6.11. Ethyl 3-(2-phenylsulfonylmethylphenyl)-1,4-dimethoxynaphthalene-2-carboxylate (**22**)

This compound was prepared as a white solid in 92% yield from **21**, following the general procedure of methylation described in Section 6.3. It was purified by column chromatography on silica gel (R_f 0.55, 1:3 ethyl acetate/petroleum ether) to furnish **22** as a white solid. Mp: 96–98 °C; ν_{max} (KBr, cm^{-1}): 1726 (s), 1630, 1590, 1448, 1402, 1357, 1307 (s), 1229, 1147, 1083, 1011, 966, 860, 755, 693; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.20–8.13 (m, 1H), 8.10–8.02 (m, 1H), 7.85–7.78 (m, 1H), 7.74–7.46 (m, 5H.), 7.42–7.28 (m, 5H), 4.38 (d, 2H, J=4.2 Hz), 4.01 (s, 3H), 3.94 (q, 2H, J=7.1 Hz), 3.36 (s, 3H), 0.88 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.6, 149.9, 149.2, 139.7, 136.6, 133.1, 130.9, 130.0, 129.3, 128.7, 128.4, 128.2, 128.1, 127.8, 127.5, 127.0, 125.7, 122.9, 63.6, 61.5, 61.1, 59.4, 13.5 (signals of 3 aromatic carbons were not observed). Anal. Calcd for $C_{26}H_{26}O_6S$: C, 68.55; H, 5.34. Found: C, 68.59; H, 5.25.

6.12. Ethyl 3-(2-benzenesulfonylmethylphenyl)-1,4-naphthoquinone-2-carboxylate (**23**)

To a solution of arylnaphthoquinol **21** (600 mg, 1.30 mmol) in CH_3CN (10 mL) was added aqueous solution of ceric ammonium nitrate (1.78 mg, 3.25 mmol in 10 mL H_2O) and stirring was continued at room temperature for 1.5 h. The resulting mixture was concentrated and after the usual work-up, the residue was purified by column chromatography (R_f 0.60, 3:7 ethyl acetate/petroleum ether) to give **23** (495 mg, 83%) as a yellow solid. Mp: 133–134 °C; ν_{max} (KBr, cm^{-1}): 1734 (s), 1663 (s), 1597, 1450, 1379, 1287 (s), 1229, 1143, 1080, 1012, 935, 891, 856, 756, 605; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.20–8.12 (m, 2H), 7.86–7.72 (m, 2H), 7.60–7.10 (m, 8H), 6.80 (d, 1H, J=7.0 Hz), 4.90 (d, 1H, J=14.5 Hz), 4.12 (d, 1H, J=14.5 Hz), 4.10 (q, 2H, J=7.1 Hz), 0.94 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 183.2, 181.8, 163.9, 144.5, 139.0, 137.5, 134.6, 134.1, 133.7, 132.6, 132.4, 132.2, 131.5, 130.8, 129.3, 128.9, 128.7, 128.2, 127.2, 126.9, 126.6, 62.0, 60.9, 13.7; HRMS ESI (70 eV) for $C_{26}H_{21}O_6S$ $[M+H]^+$ calcd: 461.1059, found: 461.1070.

6.13. Ethyl 12-hydroxy-6-oxo-6H-dibenzo[c,h]chromene-11-carboxylate (**26**)

This compound was prepared as a white crystalline solid in 81% yield by the reaction between **24** and **25**, according to the general procedure described in Section 6.2. The crude product was purified by column chromatography on silica gel (R_f 0.70, 1:5 ethyl acetate/petroleum ether) to furnish **26**. Mp: 111–114 °C; ν_{max} (KBr, cm^{-1}): 3437, 1743 (s), 1654, 1595, 1481, 1446, 1374, 1322, 1277, 1238, 1160, 1090, 1023, 958, 853, 791, 756, 696; ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.92 (s, 1H), 8.52 (d, 1H, J=8.3 Hz), 8.42 (d, 2H, J=7.8 Hz), 7.83–7.53 (m, 5H), 4.39 (q, 2H, J=7.1 Hz), 1.21 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.6, 161.0, 156.7, 142.0, 134.9, 132.8 (CH), 130.5 (CH), 129.7 (CH), 128.2 (CH), 127.6 (CH), 126.7, 125.6, 124.1 (CH), 122.4 (CH), 121.8, 110.9, 101.8, 62.0 (CH_2), 13.7 (CH_3) (one aromatic carbon signal was not observed); MS EI (70 eV): 334 (M^+), 288 (100%), 260, 232, 204, 176. Anal. Calcd for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22. Found: C, 71.90; H, 4.17.

6.14. Ethyl 12-methoxy-6-oxo-6H-dibenzo[c,h]chromene-11-carboxylate (**27**)

This compound was prepared as a white solid in 92% yield from **26**, following the general procedure of methylation described in Section 6.3. The residue was purified by column chromatography on silica gel (R_f 0.40, 1:10 ethyl acetate/petroleum ether) to furnish **27**. Mp: 159–161 °C; ν_{max} (KBr, cm^{-1}): 1719 (s), 1607, 1480, 1455, 1361, 1311, 1281, 1233, 1192, 1083 (s), 1017, 998, 939, 847, 795, 757, 696; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.65–8.58 (m, 1H), 8.49 (dd, 1H, J=7.8, 1.4 Hz), 8.14–8.06 (m, 1H), 7.91 (d, 1H, J=8.2 Hz), 7.78 (dt, 1H, J=7.6, 1.4 Hz), 7.74–7.55 (m, 3H), 4.57 (q, 2H, J=7.1 Hz), 4.06 (s, 3H), 1.43 (t, 3H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 160.5, 150.7, 144.3, 134.6, 133.9, 130.8, 128.8, 128.6, 128.3, 127.8, 125.2, 123.8, 123.0, 122.3, 121.5, 120.3, 110.1, 64.0, 62.3, 13.9; MS EI (70 eV): 348 (M+), 303, 291 (100%), 275, 261, 231, 201, 176. Anal. Calcd for $C_{21}H_{16}O_5$: C, 72.41; H, 4.63. Found: C, 72.46; H, 4.60.

6.15. Ethyl 12-hydroxy-2-nitro-6-oxo-6H-dibenzo[c,h]chromen-11-carboxylate (**29**)

This compound was prepared as a yellow solid in 86% yield by the reaction between **28** and **25** according to the general procedure described in Section 6.2. The crude product was purified by column chromatography on silica gel (R_f 0.60, 1:5 ethyl acetate/petroleum ether) to furnish **29**. Mp: 225–227 °C; ν_{max} (KBr, cm^{-1}): 3380, 1754 (s), 1679 (s), 1625, 1598, 1529, 1483, 1423, 1378, 1344 (s), 1319, 1263, 1238, 1199, 1120, 1068, 1024, 968, 844, 765, 740, 703; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.88 (s, 1H), 9.25 (d, 1H, J=2.1 Hz), 8.58 (d, 1H, J=9.0 Hz), 8.46–8.35 (m, 2H), 7.71 (dt, 1H, J=7.5, 1.5 Hz), 7.63–7.40 (m, 2H), 4.36 (q, 2H, J=7.1 Hz), 1.15 (t, 3H, J=7.1 Hz); ^{13}C NMR (200 MHz, $CDCl_3$): δ 170.0, 160.1, 156.6, 146.8, 141.1, 133.9, 133.1, 130.0, 129.5, 129.2, 127.9, 124.9, 124.2, 123.7, 122.3, 120.8, 114.8, 104.1, 62.6, 13.6. HRMS ESI (70 eV) for $C_{20}H_{14}NO_7$ $[M+H]^+$ calcd: 380.0770, found: 380.0751.

6.16. Ethyl 12-methoxy-2-nitro-6-oxo-6H-dibenzo[c,h]chromen-11-carboxylate (**30**)

This compound was prepared as a pale yellow solid in 90% yield from **29**, following the general procedure of methylation

described in Section 6.3. The crude product was purified by column chromatography on silica gel (R_f 0.50, 1:5 ethyl acetate/petroleum ether) to furnish **30**. Mp: 246–248 °C; ν_{max} (KBr, cm^{-1}): 1753 (m), 1722 (s), 1601, 1529, 1477, 1444, 1342 (s), 1272, 1248 (m), 1225, 1117, 1091, 1064, 1012, 978, 667; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.03 (d, 1H, J=2.1 Hz), 8.79 (d, 1H, J=9.2 Hz), 8.54 (dd, 1H, J=7.6, 1.4 Hz), 8.44 (dd, 1H, J=9.2, 2.1 Hz), 7.98 (d, 1H, J=8.1 Hz), 7.85 (dt, 1H, J=7.8, 1.4 Hz), 7.71 (dt, 1H, J=7.6, 1.4 Hz), 4.60 (q, 2H, J=7.2 Hz), 4.13 (s, 3H), 1.44 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 159.8, 151.7, 147.3, 143.9, 135.0, 133.1, 131.1, 130.1, 127.6, 127.3, 125.3, 124.3, 122.8, 122.0, 121.8, 119.2, 113.9, 65.0, 62.7, 14.0; HRMS ESI (70 eV) for $C_{21}H_{16}NO_7$ $[M+H]^+$ calcd: 394.0927, found: 394.0920.

6.17. Methyl 12-hydroxy-6-oxo-6H-dibenzo[c,h]chromene-11-carboxylate (*32*)

This compound was prepared as a white solid in 83% yield by the reaction between **13** and **31** according to the general procedure described in Section 6.2. The residue was purified by column chromatography on silica gel (R_f 0.50, 1:1 ethyl acetate/petroleum ether) to furnish **32**. Mp: 229–233 °C; ν_{max} (KBr, cm^{-1}): 3422, 1735 (s), 1657, 1615, 1478, 1441, 1366, 1336, 1274, 1237, 1168, 1086, 1030, 993, 880, 842, 792, 753, 696; ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.78 (s, 1H), 8.50 (d, 1H, J=8.2 Hz), 8.41 (d, 2H, J=8.0 Hz), 7.82–7.48 (m, 5H), 3.86 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.9, 160.9, 156.6, 142.0, 134.9, 133.0, 130.5, 129.8, 128.3, 128.2, 127.1, 126.8, 125.6, 124.2, 122.4, 121.8, 110.8, 101.5, 52.2; HRMS ESI (70 eV) for $C_{19}H_{13}O_5$ $[M+H]^+$ calcd: 321.0763, found: 321.0758.

6.18. Methyl 12-methoxy-6-oxo-6H-dibenzo[c,h]chromene-11-carboxylate (*33*)

This compound was prepared as a white solid in 92% yield from **32**, following the general procedure described in Section 6.3. The crude product was purified by column chromatography on silica gel (R_f 0.55, 1:1 ethyl acetate/petroleum ether) to furnish **33**. Mp: 195–197 °C; ν_{max} (KBr, cm^{-1}): 1724 (s), 1602, 1485, 1441, 1360, 1311, 1281, 1234, 1086, 1031, 995, 760; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.70–8.62 (m, 1H), 8.51 (d, 1H, J=7.7 Hz), 8.18–8.10 (m, 1H), 7.84–7.58 (m, 5H), 4.08 (s, 3H), 4.07 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.8, 160.5, 150.9, 144.4, 134.8, 133.9, 130.9, 128.9, 128.7, 128.4, 127.9, 125.4, 123.6, 123.1, 122.4, 121.7, 120.0, 110.2, 64.1, 53.0; HRMS ESI (70 eV) for $C_{20}H_{15}O_5$ $[M+H]^+$ calcd: 335.0920, found: 335.0915.

6.19. Methyl 3-acetoxy 2-(2-ethoxycarbonyl-vinyl)-benzoate (*34*)

This compound was prepared as a white solid in 96% yield from **44**, following the procedure for the preparation of compound **22**. The crude product was purified by column chromatography on silica gel (R_f 0.60, 1:3 ethyl acetate/petroleum ether) to furnish **34**. Mp: 58–60 °C; ν_{max} (KBr, cm^{-1}): 1759, 1722 (s), 1645, 1458, 1369, 1311, 1277, 1227, 1195, 1172, 1025, 912, 758; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, 1H, J=16.3 Hz), 7.84 (d, 1H, J=7.6 Hz), 7.42 (t, 1H, J=7.6 Hz), 7.26 (d, 1H, J=7.6 Hz), 6.15 (d, 1H, J=16.3 Hz), 4.26 (q, 2H, J=7.1 Hz), 3.89 (s, 3H), 2.27 (s, 3H), 1.33 (t, 3H, J=7.1 Hz); MS EI (70 eV): 292 (M^+), 250, 233, 219, 204, 187, 177 (100%), 145. Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.74; H, 5.49.

6.20. 6-Hydroxy-benzo[h]chromeno[5,4,3-cde]chromene-5,12-dione (*35*)

This compound was prepared as a yellow solid in 91% yield by the condensation between **24** and **34**, according to the general procedure described in Section 6.2. The crude product was purified by column chromatography on silica gel (R_f 0.40, 1:1 ethyl acetate/petroleum ether) to furnish **35**. Mp: >400 °C; ν_{max} (KBr, cm^{-1}): 3496, 1754 (s), 1683 (s), 1612 (s), 1502, 1378 (m), 1330, 1259, 1205, 1143, 1085, 1070 (m), 914, 752 (s); ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.42 (s, 1H), 8.57 (t, 2H, J=8.4 Hz), 8.27 (dd, 1H, J=6.5, 2.5 Hz), 7.91 (dt, 1H, J=7.7, 1.3 Hz), 7.81–7.60 (m, 3H); MS ESI (70 eV): $[M+H]^+$, 305.07. Anal. Calcd for $C_{18}H_8O_5$: C, 71.06; H, 2.65. Found: C, 71.26; H, 2.59. The poor solubility of this compound in deuterated solvent prevented us from recording ^{13}C NMR data.

6.21. 6-Hydroxy-4-oxa-11-thia-benzo[def]chrysene-5,12-dione (*37*)

This compound was prepared as a yellow solid in 71% yield by the reaction between **17** and **36** according to the general procedure of annulation described in Section 6.2. The crude product was purified by column chromatography on silica gel (R_f 0.50, 1:1 ethyl acetate/petroleum ether) to furnish **37**. ν_{max} (KBr, cm^{-1}): 3433, 1678 (s), 1647 (m), 1626, 1597, 1502, 1371, 1344, 1317, 1246 (m), 1157, 1101, 1047, 890, 808, 765, 669; ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.77 (s, 1H), 8.66 (dd, 1H, J=8.3, 1.6 Hz), 8.37–8.32 (m, 1H), 8.22 (d, 1H, J=8.3 Hz), 7.87 (dt, 1H, J=1.3, 8.3 Hz), 7.84–7.73 (m, 3H); MS EI (70 eV): 320 (M^+, 100%), 292, 273, 256, 236, 208, 172. Anal. Calcd for $C_{18}H_8O_4S$: C, 67.49; H, 2.52. Found: C, 67.72; H, 2.47. The poor solubility of this compound in deuterated solvent prevented us from recording ^{13}C NMR data.

6.22. Methyl 2-(2-ethoxycarbonylvinyl)-3-hydroxybenzoate (*44*)

This compound was prepared as a white solid in 94% yield from **43**, following the procedure for the preparation of compound **14**. The crude product was purified by column chromatography on silica gel (R_f 0.55, 1:3 ethyl acetate/petroleum ether) to furnish pure compound **44**. Mp: 120–123 °C; ν_{max} (KBr, cm^{-1}): 3354, 1718 (s), 1680 (s), 1624, 1595, 1460,

1436, 1373, 1338, 1294 (s), 1196, 1170, 1136, 1010, 987, 765. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, 1H, J=16.3 Hz), 7.44 (d, 1H, J=8.1 Hz), 7.25 (t, 1H, J=8.1 Hz), 7.11 (d, 1H, J=8.1 Hz), 6.66 (d, 1H, J=16.3 Hz), 4.29 (q, 2H, J=7.2 Hz), 3.90 (s, 3H), 1.35 (t, 3H, J=7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.6, 168.3, 156.0, 139.8, 132.4, 129.7, 123.1, 122.0, 121.3, 120.0, 61.0, 52.5, 14.1. Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.50; H, 5.56.

6.23. Methyl 5-amino-2-methylbenzoate (**46**)[23]

To a well-stirred solution of methyl *o*-toluate (**45**) (6.0 g. 40.0 mmol) at 0–5 °C was added dropwise a solution of nitrating agent (a mixture of 4.0 mL concentrated H_2SO_4 and 4.0 mL concentrated HNO_3, cooled to 0–5 °C). The resulting reaction mixture was further stirred for 2 h at this temperature. The mixture was then poured into 100 g of crushed ice and stirred for few minutes. A white solid appeared, which was filtered and washed with H_2O and dried under vacuum. ^{1}H NMR of the crude solid indicated the presence of methyl 2-methyl-5-nitrobenzoate and its corresponding *ortho*-isomer in 5:3 ratio. Methyl 2-methyl-5-nitrobenzoate was separated by fractional crystallization from MeOH and H_2O system to give it as a white solid. This solid was dissolved in dry ethanol (50 mL) was hydrogenated in the presence of 10% Pd–C (250 mg) at atmospheric pressure during 16 h. The catalyst was removed by filtration and the filtrate was concentrated. After chromatographic purification on silica gel (R_f 0.50, 1:1 ethyl acetate/petroleum ether), compound **46** (3.10 g, 47%) was obtained as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25 (d, 1H, J=2.6 Hz), 7.00 (d, 1H, J=8.0 Hz), 6.74 (dd, 1H, J=8.0, 2.6 Hz), 3.86 (s, 3H), 2.45 (s, 3H).

6.24. Methyl 5-hydroxy-2-methylbenzoate (**47**)

To a stirred solution of methyl 5-amino-2-methylbenzoate (**46**) (4.5 g, 27.27 mmol) in a mixture of H_2O (75 mL) and concentrated H_2SO_4 (4.4 mL) was added dropwise $NaNO_2$ solution (1.88 g, 27.27 mmol in H_2O (10 mL)) at 0–5 °C. At the end of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature and then heated at reflux for 0.5 h. On cooling, crystals deposited were collected by filtration and recrystallized from ethyl acetate/petroleum ether system to give **47** (2.95 g, 66%) as a white solid (R_f 0.40, 3:7 ethyl acetate/petroleum ether). Mp: 75–76 °C (lit.[24] mp: 74–76 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40 (d, 1H, J=2.7 Hz), 7.09 (d, 1H, J=8.3 Hz), 6.91 (dd, 1H, J=8.3, 2.7 Hz), 3.87 (s, 3H), 2.49 (s, 3H).

6.25. Methyl 2-formyl-3-hydroxy-6-methylbenzoate (**48**)

Hexamethylenetetramine (700 mg, 5 mmol) was added to a stirred solution of methyl 5-hydroxy-2-methylbenzoate (**47**) (830 mg, 5 mmol) in 80% polyphosphoric acid (4 mL) at 100 °C and the reaction mixture was stirred for 45 min. After cooling, the mixture was diluted with cold water (100 mL) and extracted with ethyl acetate (3×50 mL). The combined extracts were washed with brine, dried (anhydrous Na_2SO_4), and concentrated. Purification of the crude product by column chromatography on silica gel (R_f 0.50, 1:10 ethyl acetate/petroleum ether) provided **48** (290 mg, 30%) as a white solid. Mp: 71–73 °C; ν_{max} (KBr, cm^{-1}): 3414, 1720, 1658, 1472, 1437, 1298, 1225, 1185, 1045, 998, 945, 882, 833, 731; ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.55 (s, 1H), 9.91 (s, 1H), 7.36 (d, 1H, J=8.7 Hz), 6.98 (d, 1H, J=8.7 Hz), 3.97 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 194.9 (CH), 167.8, 160.4, 139.0 (CH), 136.0, 126.7, 119.5 (CH), 116.7, 52.6 (OCH_3), 18.6 (CH_3). Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.98; H, 5.09.

6.26. Methyl 6-methylcoumarin-5-carboxylate (**49**)

(Carboethoxymethylene)triphenylphosphorane (765 mg, 2.2 mmol) was added to a solution of methyl 2-formyl-3-hydroxy-6-methylbenzoate (**48**) (388 mg, 2 mmol) in Et_2NPh (10 mL), and the resulting reaction mixture was heated at reflux for 20 min. After cooling, the mixture was diluted with water (30 mL) and extracted with ethyl acetate (3×40 mL). The combined organic extracts were washed with 5% HCl (20 mL), brine (20 mL), dried (anhydrous Na_2SO_4), and concentrated. The residue was column chromatographed on silica gel (R_f 0.50, 1:4 ethyl acetate/petroleum ether) to provide **49** (415 mg, 95%) as a white solid. Mp: 90–93 °C; ν_{max} (KBr, cm^{-1}): 1752 (s), 1722 (s), 1628, 1583, 1438, 1380, 1292 (m), 1252 (m), 1182, 1115, 1047, 1006, 928, 889, 822; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.83 (d, 1H, J=10.0 Hz), 7.39 (d, 1H, J=8.6 Hz), 7.31 (d, 1H, J=8.6 Hz), 6.45 (d, 1H, J=10.0 Hz), 3.99 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.4, 159.8, 152.1, 140.6 (CH), 133.8 (CH), 132.4, 130.5, 118.4 (CH), 117.3 (CH), 116.2, 52.5 (CH_3), 19.6 (CH_3); MS EI (70 eV): 218 (M^+, 100%), 187, 159, 131. Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.21; H, 4.47.

6.27. 6-Hydroxy-10-methoxy-1-methylbenzo[h]chromeno-[5,4,3-cde]chromene-5,12-dione (**51**)

This compound was prepared as a yellow crystalline solid in 86% yield by the reaction between **49** and **50** according to the general procedure described in Section 6.2. The crude product was purified by column chromatography on silica gel (R_f 0.50, 1:1 ethyl acetate/petroleum ether) to furnish **51**. Mp: 237–239 °C; ν_{max} (KBr, cm^{-1}): 3440, 1739 (s), 1697 (s), 1585, 1500, 1450, 1376 (m), 1319, 1255 (m), 1155 (m), 1043, 773; ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.57 (s, 1H), 8.06 (d, 1H, J=8.4 Hz), 7.59 (t, 1H, J=8.1 Hz), 7.54 (d, 1H, J=8.4 Hz), 7.46 (d, 1H, J=8.4 Hz), 7.19 (d, 1H, J=7.8 Hz), 4.09 (s, 3H), 2.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 159.5, 157.6, 157.2, 146.7, 140.3, 139.3, 132.9 (CH), 128.5 (CH), 127.1, 121.1 (CH), 120.3, 119.0, 117.9, 116.5 (CH), 111.7 (CH), 108.6, 96.7, 56.7 (CH_3), 22.6 (CH_3); MS EI (70 eV): 348 (M^+), 333, 320, 305, 284, 273, 256, 236, 214, 198, 172, 69, 54 (100%). Anal. Calcd for $C_{20}H_{12}O_6$: C, 68.97; H, 3.47. Found: C, 69.21; H, 3.32.

6.28. 6-Hydroxy-4,4-dimethoxy-4H-11-oxa-benzo[def]chrysene-5,12-dione (**53**)

This compound was prepared as a yellow solid in 87% yield by the condensation between **24** and **52** according to the general procedure described in Section 6.2. The crude product was purified by column chromatography on silica gel (R_f 0.60, 1:1 ethyl acetate/petroleum ether) to furnish **53**. Mp: 175–177 °C; ν_{max} (KBr, cm^{-1}): 3434, 1733 (s), 1624 (m), 1578 (m), 1496 (m), 1454 (m), 1380 (m), 1319, 1275 (m), 1220, 1159, 1070 (s), 981 (m), 768; ^1H NMR (200 MHz, $CDCl_3$): δ 13.48 (s, 1H), 8.51–8.44 (m, 3H), 8.16 (dd, 1H, J=7.6, 1.1 Hz), 7.83 (dt, 1H, J=7.7, 1.2 Hz), 7.73 (t, 1H, J=7.8 Hz), 7.68 (dt, 1H, J=7.6, 1.1 Hz), 3.41 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.6, 160.7, 160.0, 139.0, 134.3, 132.9, 131.7, 131.3, 130.5, 129.1, 128.2, 127.9, 125.5, 124.7, 122.0, 120.7, 108.4, 104.2, 95.1, 52.2; MS EI (70 eV): 362 (M^+), 331 (100%), 315, 302, 288, 273, 257, 232, 204, 176, 150, 144. Anal. Calcd for $C_{21}H_{14}O_6$: C, 69.61; H, 3.89. Found: C, 69.72; H, 3.82.

6.29. 6-Hydroxy-10-methoxy-4,4-dimethoxy-4H-11-oxa-benzo[def]chrysene-5,12-dione (**54**)

This compound was prepared as a yellow solid in 87% yield by the condensation between **52** and **50**, according to the general procedure of annulation described in Section 6.2. The crude product was purified by column chromatography on silica gel (R_f 0.60, 1:3 ethyl acetate/petroleum ether) to furnish **54**. Mp: 176–178 °C; ν_{max} (KBr, cm^{-1}): 3438, 1735 (s), 1639, 1602, 1582, 1511, 1488, 1457, 1427, 1382, 1344, 1313, 1268, 1214, 1201, 1103, 1085, 1070, 1037, 1006, 827, 808, 757, 748; ^1H NMR (300 MHz, $CDCl_3$): δ 13.54 (s, 1H), 8.48 (dd, 1H, J=7.8, 1.1 Hz), 8.15 (dd, 1H, J=8.7, 1.1 Hz), 8.12 (d, 1H, J=8.1 Hz), 7.72 (t, 1H, J=7.8 Hz), 7.58 (t, 1H, J=8.1 Hz), 7.24 (d, 1H, J=8.1 Hz), 4.12 (s, 3H), 3.40 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.8, 160.4, 160.3, 157.4, 140.6, 134.1, 132.6, 131.2, 131.0, 129.0, 128.8, 128.2, 120.3, 119.6, 116.8, 113.0, 108.5, 104.9, 95.2, 56.6, 52.3; HRMS ESI (70 eV) for $C_{22}H_{17}O_7$ $[M+H]^+$ calcd: 393.0974, found: 393.0970.

6.30. 5-Hydroxy-4H-benzo[2,3]phenanthro[4,5-bcd]pyran-4,6,12-trione (**55**)

To a well-stirred solution of a ketal **53** (725 mg, 2 mmol) in methanol (10 mL) at room temperature was added 10% HCl solution (10 mL) and stirring was continued for 1 h. A solid precipitate appeared. The resulting precipitate was collected by filtration and thoroughly washed with MeOH/H_2O to give **55** (620 mg, 98%) as an amorphous brown-red solid. Mp: 370–372 °C; ν_{max} (KBr, cm^{-1}): 3452, 3085, 1747 (s), 1689, 1637, 1606, 1589, 1569, 1512, 1494, 1463, 1440, 1390, 1348, 1299, 1280, 1205, 1137, 1074, 998, 889, 846, 802, 759, 682; ^1H NMR (200 MHz, $CDCl_3$): δ 14.32 (s, 1H), 8.71 (dd, 1H, J=7.8, 1.2 Hz), 8.65 (dd, 1H, J=7.8, 1.1 Hz), 8.56 (dd, 1H, J=7.8, 1.1 Hz), 8.52 (dd, 1H, J=7.8, 1.1 Hz), 7.92 (dt, 1H, J=7.8, 1.1 Hz), 7.79 (t, 1H, J=7.8 Hz), 7.77 (dt, 1H, J=7.8, 1.1 Hz); MS ESI (70 eV): 316 (M+), 288, 273, 256, 236, 232, 208. Anal. Calcd for $C_{19}H_8O_5$: C, 72.16; H, 2.55. Found: C, 71.96; H, 2.41. The poor solubility of this compound in deuterated solvent prevented us from recording ^{13}C NMR data.

6.31. 5-Hydroxy-10-methoxy-4H-benzo[2,3]phenanthro-[4,5-bcd]pyran-4,6,12-trione (**56**)

This compound was prepared as a brown solid in 98% yield from **54**, following the procedure for the preparation of compound **55**. The solid precipitate obtained after reaction was collected by filtration and thoroughly washed with MeOH/H_2O to give pure **56**. Mp: 375–377 °C; ν_{max} (KBr, cm^{-1}): 3436, 1741 (s), 1687, 1633, 1591, 1490, 1456, 1384, 1348, 1324, 1265 (s), 1105, 1070, 1039, 1002, 808, 746, 671; ^1H NMR (500 MHz, $CDCl_3$): δ 14.52 (s, 1H), 8.71 (d, 1H, J=7.4 Hz), 8.64 (d, 1H, J=7.5 Hz), 8.20 (d, 1H, J=7.8 Hz), 7.77 (t, 1H, J=8.3 Hz), 7.69 (t, 1H, J=8.4 Hz), 7.34 (d, 1H, J=7.7 Hz), 4.14 (s, 3H); MS ESI (70 eV): $[M+H]^+$ 347.0500, $[M-CO_2]$ 302.1913. Anal. Calcd for $C_{20}H_{10}O_6$: C, 69.37; H, 2.91. Found: C, 69.45; H, 2.84. The poor solubility of this compound in deuterated solvents prevented us from recording ^{13}C NMR data.

6.32. 6-Benzyloxy-2-methylene-3,4-dihydro-2H-naphthalen-1-one (**58**)

To a stirred solution of *N*-methylanilinium trifluroacetate (210 mg, 0.95 mmol) in THF (10 mL) at room temperature, was added paraformaldehyde (110 mg, 1.2 mmol), followed by a solution of **57** (200 mg, 0.79 mmol) in THF (2 mL) over a period of 0.5 h. The resulting solution was heated at reflux for about 6 h. After completion of the reaction, the reaction mixture was cooled and diluted with ether (50 mL). The ether layer was washed with saturated aqueous sodium bicarbonate solution (2×10 mL) and water (2×10 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. Column chromatography of the residue afforded naphthalen-1-one **58** as a low melting solid (120 mg, 58%). R_f 0.65 (1:3 ethyl acetate/petroleum ether); ν_{max} (KBr, cm^{-1}): 3029, 2935, 1945, 1594, 1301, 1232, 1103, 991, 802, 694; ^1H NMR (200 MHz, $CDCl_3$): δ 8.07 (d, 1H, J=8.7 Hz), 7.34–7.40 (m, 5H), 6.91 (dd, 1H, J_1=2.5 Hz, J_2=8.7 Hz), 6.77 (d, 1H, J=2.3 Hz), 6.16 (s, 1H), 5.39 (d, 1H, J=1.5 Hz), 5.10 (s, 2H), 2.94 (t, 2H, J=5.7 Hz), 2.82 (t, 2H, J=5.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 186.3, 162.8, 146.6, 143.4, 136.2, 130.4, 128.6, 128.2, 127.4, 126.9, 121.0, 114.0, 113.5, 70.0, 31.7, 30.0; HRMS ESI (70 eV) for $C_{18}H_{17}O_2$ $[M+H]^+$ calcd: 265.1229, found: 265.1225.

6.33. 6-Benzyloxy-2-methyl-3,4-dihydro-2H-naphthalen-1-one (**59**)

To a stirred solution of **58** (100 mg, 0.38 mmol) in acetic acid (4 mL) was added Zn dust (74.3 mg, 1.04 mmol) in portions over a period of 5 min. The resulting mixture was heated

at reflux for 1.5 h. After completion of the reaction, the reaction mixture was cooled and diluted with ether (50 mL). The ether layer was washed with aqueous sodium bicarbonate solution (2×10 mL) and water (2×10 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. Column chromatography of the residue afforded naphthalen-1-one **59** as a yellow oil (50 mg, 47%). R_f 0.65 (1:4 ethyl acetate/petroleum ether); ν_{max} (KBr, cm^{-1}): 3064, 2931, 1600, 1454, 1375, 1249, 1159, 1025, 696; ^1H NMR (200 MHz, $CDCl_3$): δ 8.01 (d, 1H, J=8.7 Hz), 7.31–7.44 (m, 5H), 6.89 (dd, 1H, J_1=2.4 Hz, J_2=8.7 Hz), 6.76 (d, 1H, J=2.3 Hz), 5.11 (s, 2H), 2.92–3.00 (m, 2H), 2.49–2.58 (m, 1H), 2.10–2.22 (m, 1H), 1.82–1.89 (m, 1H), 1.23 (d, 3H, J=6.81 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 199.5, 162.5, 146.6, 136.3, 129.8, 128.6, 128.2, 127.4, 126.2, 113.7, 113.4, 70.0, 42.2, 31.4, 29.1, 15.5; HRMS ESI (70 eV) for $C_{18}H_{19}O_2$ $[M+H]^+$ calcd: 267.1385, found: 267.1383.

6.34. 7-Benzyloxy-4-bromo-3-methyl-1,2-dihydro-naphthalene (*60*)

To a stirred solution of **59** (100 mg, 0.38 mmol) in dry benzene (4 mL), phosphorus tribromide (0.05 mL, 153 mg, 0.56 mmol) was added dropwise over a period of 5 min. The resulting mixture was heated at reflux for 2 h. After completion of the reaction, the reaction mixture was cooled and diluted with ether (50 mL). The ether layer was washed with water (2×10 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. Column chromatography of the residue afforded 1,2-dihydro-naphthalene **60** as a yellow oil (65 mg, 53%). R_f 0.70 (1:4 ethyl acetate/petroleum ether); ν_{max} (KBr, cm^{-1}): 3421, 2925, 1598, 1494, 1259, 1024, 798, 696; ^1H NMR (200 MHz, $CDCl_3$): δ 7.32–7.53 (m, 6H), 6.73–6.83 (m, 2H), 5.06 (s, 2H), 2.76 (t, 2H, J=7.4 Hz), 2.37 (t, 2H, J=7.6 Hz), 2.08 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 157.9, 137.0, 136.9, 134.2, 128.5, 127.9, 127.7, 127.6, 127.4, 117.6, 113.9, 111.9, 70.0, 31.4, 28.2, 24.2; HRMS ESI (70 eV) for $C_{18}H_{18}BrO$ $[M+H]^+$ calcd: 329.0541, found: 329.0526.

6.35. 6-Benzyloxy-2-methyl-3,4-dihydro-naphthalene-1-carboxylic acid (*61*)

A stirred solution of **60** (100 mg, 0.30 mmol) in dry THF (5 mL) was cooled to −78 °C. To it *n*-butyllithium (0.24 mL, 1.6 M, 0.39 mmol) was added dropwise and stirred for 1 h. Then dry CO_2 was passed through this solution for 1 h at −78 °C. Afterward, the reaction mixture was stirred at room temperature for 3 h under a CO_2 atmosphere. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (50 mL). The organic layer was washed with hydrochloric acid (15 mL) and water (2×10 mL). This was dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. Column chromatography of the residue afforded carboxylic acid **61** as a white solid (52 mg, 58%). R_f 0.20 (2:1 ethyl acetate/petroleum ether); mp: 98–99 °C; ν_{max} (KBr, cm^{-1}): 2861, 1689, 1500, 1427, 1326, 1251, 1122, 1010, 811, 698; ^1H NMR (200 MHz, $CDCl_3$): δ 7.22–7.42 (m, 6H), 6.75–6.84 (m, 2H), 5.05 (s, 2H), 2.76 (t, 2H, J=7.4 Hz), 2.32 (t, 2H, J=7.9 Hz), 2.14 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.5, 157.7, 141.4, 137.1, 136.5, 128.6, 127.9, 127.4, 126.2, 125.8, 125.0, 114.5, 112.2, 70.0, 30.9, 28.1, 21.8; HRMS ESI (70 eV) for $C_{19}H_{17}O_3$ $[M-H]^+$ calcd: 293.1178, found: 293.1165.

6.36. 6-Benzyloxy-2-methyl-3,4-dihydro-naphthalene-1-carboxylic acid methyl ester (*62*)

To a stirred solution of **61** (100 mg, 0.34 mmol) in acetonitrile (3 mL) was added DBU (0.05 mL, 51.7 mg, 0.34 mmol) and the reaction stirred for 10 min. Then iodomethane (0.1 mL, 241.5 mg, 1.7 mmol) was added to this mixture and stirring continued for 4 h at room temperature. The reaction mixture was then diluted with water and extracted with ether (2×50 mL). The organic layer was washed successively with hydrochloric acid (5 mL), water (10 mL), saturated aqueous solution of sodium thiosulfate (5 mL), and brine. The organic layer was dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. Column chromatography of the residue afforded ester **62** as a yellow oil (100 mg, 96%). R_f 0.70 (1:4 ethyl acetate/petroleum ether); ν_{max} (KBr, cm^{-1}): 3490, 2948, 1724, 606, 1500, 1257, 1018, 804, 698; ^1H NMR (200 MHz, $CDCl_3$): δ 7.30–7.45 (m, 5H), 6.95–7.03 (m, 1H), 6.71–6.79 (m, 2H), 5.04 (s, 2H), 3.86 (s, 3H), 2.77 (t, 2H, J=7.5 Hz), 2.28 (t, 2H, J=8.1 Hz), 2.0 (s, 3H), ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.7, 157.7, 137.9, 137.0, 136.2, 128.5, 127.9, 127.4, 127.3, 125.2, 125.1, 114.5, 112.1, 69.9, 51.6, 30.0, 28.0, 21.3; HRMS ESI (70 eV) for $C_{20}H_{21}O_3$ $[M+H]^+$ calcd: 309.1491, found: 309.1478.

6.37. 6-Benzyloxy-2-methyl-naphthalene-1-carboxylic acid methyl ester (*63*)

To a stirred solution of **62** (80 mg, 0.26 mmol) in dry benzene (5 mL), DDQ (120 mg, 0.52 mmol) was added and the reaction heated at reflux for 12 h. After completion of the reaction the mixture was cooled and filtered. Then the filtrate was concentrated and column chromatography of the crude gave methyl ester (**63**) as oil (62 mg, 78%). R_f 0.70 (1:3 ethyl acetate/petroleum ether); ν_{max} (KBr, cm^{-1}): 2962, 1724, 1600, 1411, 1261, 1020, 800, 698; ^1H NMR (200 MHz, $CDCl_3$): δ 7.23–7.48 (m, 10H), 5.17 (s, 2H), 4.03 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.2, 156.3, 136.7, 132.8, 131.1, 129.9, 129.9, 128.6, 128.0, 127.5, 126.1, 125.6, 120.0, 107.5, 70.0, 52.1, 19.9; HRMS ESI (70 eV) for $C_{20}H_{19}O_3$ $[M+H]^+$ calcd: 307.1334, found: 307.1348.

6.38. 6-Hydroxy-2-methyl-naphthalene-1-carboxylic acid methyl ester (*64*)

To a stirred solution of **63** (100 mg, 0.33 mmol) in dry methanol (5 mL), were added formic acid (2 drops) and Pd–C (50 mg). The resulting mixture was stirred under H_2 atmosphere for 6 h. After completion of the reaction the mixture

was filtered through Celite. The filtrate was concentrated and column chromatography of the crude gave methyl ester **64** as an oil (35 mg, 70%). R_f 0.50 (1:3 ethyl acetate/petroleum ether); ν_{max} (KBr, cm^{-1}): 2962, 1704, 1513, 1263, 1097, 802, 663; ^1H NMR (200 MHz, $CDCl_3$): δ 7.58–7.73 (m, 2H), 7.26 (d, 1H, J=3.2 Hz), 7.06–7.14 (m, 2H), 4.03 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.0, 153.4, 132.9, 130.8, 129.5, 128.8, 128.3, 126.1, 125.1, 119.0, 109.8, 52.3, 19.8; HRMS ESI (70 eV) for $C_{13}H_{13}O_3$ $[M+H]^+$ calcd: 217.0865, found: 217.0865.

*6.39. 5,5-Dimethoxy-2-methyl-6-oxo-5,6-dihydro-naphthalene-1-carboxylic acid methyl ester (**65**)*

A stirred solution of **64** (100 mg, 0.46 mmol) in dry methanol (3 mL) under nitrogen atmosphere was cooled to 0 °C. To it iodobenzenediacetate (327.9 mg, 1.02 mmol) was added and the mixture stirred for 2 h at 0 °C. Then the mixture was slowly warmed to room temperature. The reaction mixture was then extracted with ether (2×50 mL). The organic layer was then washed successively with sodium bicarbonate saturated solution (5 mL) and brine. Then the organic layer was dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. Column chromatography of the residue afforded ester **65** as yellow oil (90 mg, 70%), which tends to decompose on standing. R_f 0.55 (1:3 ethyl acetate/petroleum ether): ν_{max} (KBr, cm^{-1}): 1718, 1680, 1452, 1387, 1276, 1250, 1190, 1146, 1076; ^1H NMR (200 MHz, $CDCl_3$): δ 7.66 (d, 1H, J=7.9 Hz), 7.24–7.36 (m, 2H), 6.14 (d, 1H, J=10.6 Hz), 3.97 (s, 3H), 3.26 (s, 6H), 2.31 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 194.9, 168.7, 140.1, 137.1, 135.9, 133.6, 131.6, 129.2, 128.6, 126.1, 95.3, 52.4, 51.9, 51.9, 19.7.

*6.40. 6-Hydroxy-4,4,10-trimethoxy-1-methyl-4H-11-oxa-benzo[def]chrysene-5,12-dione (**66**)*

This compound was prepared as a yellow solid in 78% yield by condensation between **65** and **50** according to the general procedure of annulation described in Section 6.2. The crude product was purified by column chromatography on silica gel (R_f 0.60, 1:1 ethyl acetate/petroleum ether) to furnish **66**. Mp: 115–116 °C; ν_{max} (KBr, cm^{-1}): 2964, 2362, 1737, 1629, 1456, 1261, 1076, 800; ^1H NMR (200 MHz, $CDCl_3$): δ 13.71 (s, 1H), 8.14 (d, 1H, J=8.3 Hz), 8.01 (d, 1H, J=7.9 Hz), 7.48–7.65 (m, 2H), 7.20–7.31 (m, 1H), 4.16 (s, 3H), 3.38 (s, 6H), 2.94 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.8, 160.6, 159.8, 157.5, 145.8, 133.5, 133.4, 132.1, 130.2, 128.8, 128.3, 119.7, 118.7, 117.8, 116.9, 116.4, 113.2, 105.0, 95.3, 64.1, 56.6, 56.2, 23.5; HRMS ESI (70 eV) for $C_{23}H_{19}O_7$ $[M+H]^+$ calcd: 407.1131, found: 407.1141.

*6.41. 5-Hydroxy-10-methoxy-1-methyl-11-oxa-benzo[def]chrysene-4,6,12-trione (**67**)*

To a well-stirred solution of ketal **66** (100 mg, 0.25 mmol) in methanol (5 mL) at room temperature was added 10% HCl solution (5 mL) and stirring was continued for 1 h. A solid precipitate appeared. The precipitate was collected by filtration and thoroughly washed with $MeOH/H_2O$ to give **67** (62 mg, 98%) as an amorphous deep violet solid: mp: >300 °C; ν_{max} (KBr, cm^{-1}): 3438, 2362, 1731, 1596, 1459, 1272, 1072, 798, 470; ^1H NMR (200 MHz, $CDCl_3$): δ 14.8 (s, 1H), 8.51 (d, 1H, J=7.98 Hz), 8.16 (dd, 1H, J_1=8.28 Hz, J_2=0.92 Hz), 7.32–7.72 (m, 3H), 4.12 (s, 3H), 2.99 (s, 3H); HRMS ESI (70 eV) for $C_{21}H_{13}O_6$ $[M+H]^+$ calcd: 361.0712, found: 361.0730. The poor solubility of this compound in deuterated solvent prevented us from recording ^{13}C NMR data.

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