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Synthesis of chlorine-containing angucycline BE-23254 and its analogs

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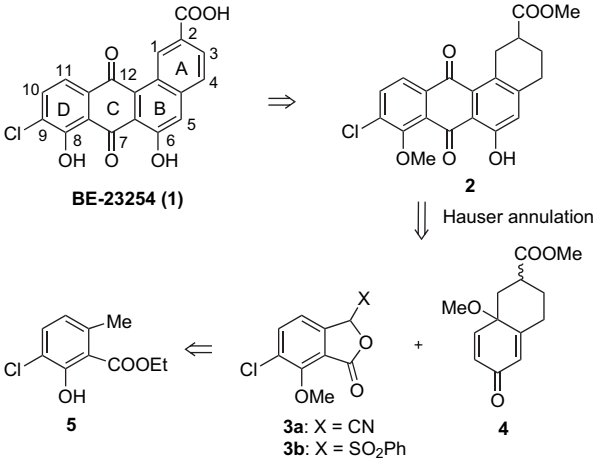
Abstract—The total synthesis of BE-23254, an unusual angucycline antibiotic is reported. This is achieved by adopting a Hauser annulation and a DDQ-promoted aromatization as the key steps. The strategy has been generalized for the synthesis of several analogs of the target molecule. A regioselective preparation of chlorine-containing phenols is also described.

1. Introduction

Angucyclines and angucyclinones are a large group of quinonoid natural products characterized by a benz[*a*]anthraquinone or a variant thereof as the core structure originating from a decaketide chain precursor.[1,2] This class of compounds often displays a broad spectrum of biological activities, which include antiviral and antitumor activities, cytotoxic activity against various cancer cell lines, inhibition of angiogenesis and platelet aggregation, and inhibitory activity against the pentagastrin-stimulated acid secretion. BE-23254 (**1**), an unusual angucycline antibiotic with aromatic A ring was isolated by Okabe et al.[3] in 1992 from *Streptomyces* sp. A 23254. It was reported to possess activity against the human colon cancer DLD-1 (IC_{50} 0.75 μg mL^{-1}). It is structurally unique in that it is the only member of angucyclines to contain a chlorine atom at the C-9 position of the ring skeleton. The methyl group at C-3, which is present in almost all other angucyclines numbering about 150, is absent in BE-23254 (**1**). In addition, the presence of a carboxylic acid at the C-2 position of BE-23254 is a rare structural feature of angucycline antibiotics. These unusual structural features coupled with its bioactivity prompted us to execute a short and efficient total synthesis of the molecule that has been the subject of a recent communication[4] from our laboratory. We now report a full account of the investigation and the synthesis of analogs of the target molecule.

2. Synthetic strategy

During the past two decades, a good number of methodologies have been developed and employed for the total synthesis of angucycline targets.[5] While the Diels–Alder strategy has been very successful for the total syntheses of complex angucyclines, we introduced the notion of employing Hauser annulation[6a] as a complementary means.[6] We were particularly attracted by the unambiguous regiochemical integrity of the methodology in addition to the mildness of the reaction conditions. The retrosynthetic disconnections for BE-23254 (**1**) featuring a Hauser annulation are shown in Scheme 1. It was planned to condense naphthalenone **4** (AB ring synthon) with the isobenzofuranones **3a** and **3b** (D ring synthons) for the regiospecific fabrication of the tetracyclic framework **2**. DDQ-promoted aromatization of



Scheme 1. Retrosynthetic plan for BE-23254 (**1**).

Keywords: Angucyclines; Hauser annulation; Naphthalenone; Chlorinative aromatization.
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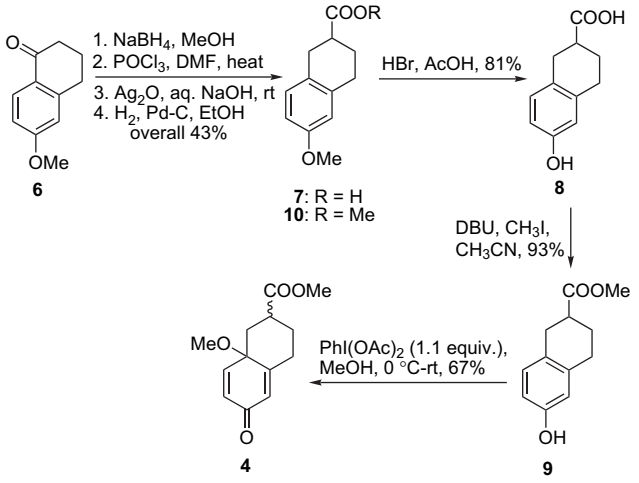
the nonaromatic A ring of the product **2** was expected to furnish the complete chromophoric structure of the target molecule.

3. Results and discussion

3.1. Synthesis of naphthalenone 4 (AB ring synthon)

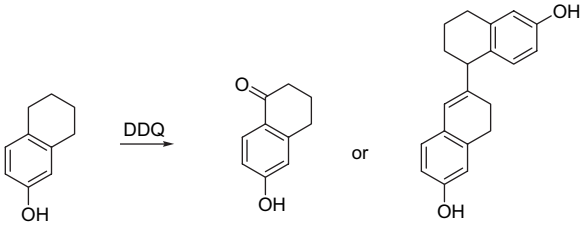
We began the synthesis of hitherto unreported naphthalenone **4** (Scheme 2) starting from commercially available 6-methoxytetralone (**6**) through compound **7**. Compound **7** was prepared from compound **6** in four steps in 43% overall yield by the reported sequence[7] of reactions. The IR and NMR spectroscopic data of all the intermediate compounds were in agreement with the reported[7] values. It was then demethylated by treatment with HBr–AcOH under reflux conditions to give the hydroxyacid **8**[8] in 81% yield. In order to protect the acid functionality, the acid **8** was selectively esterified with DBU–MeI[9] in acetonitrile to afford compound **9**. Doubly methylated compound **10** was also isolated as a co-product when a slight excess of MeI was used. Compound **9** on treatment with 1.1 equiv of phenyliodonium diacetate (PIDA) in MeOH at 0 °C to rt furnished the naphthalenone **4** in 67% yield together with a small amount of unknown byproducts. The structure of this compound was established by analysis of its IR, ^{1}H NMR, and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **4** showed two doublets at δ 6.64 and 6.21 and one doublet of doublets at δ 6.63 corresponding to olefinic protons at C-8, C-5, and C-7, respectively, along with other characteristic signals.



Scheme 2. Synthesis of naphthalenone **4**.

3.2. Model synthetic study of benz[*a*]anthraquinones

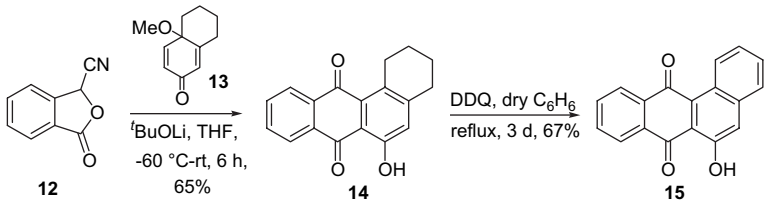
At the outset, the synthesis of compound **15** representing the chromophoric part of BE-23254 (**1**) was chosen for the model study. We were apprehensive that compound **14** might undergo benzylic oxidation or oxidative dimerization under the influence of DDQ, which is known to cause such reactions[10] with structurally similar hydroxytetralin **11** (Eq. 1). Yet, the easy accessibility of compound **14** led us to examine Scheme 3. Isobenzofuranone **12**[11] was annulated with naphthalenone **13** in the presence of ^{t}BuOLi in dry THF at −60 °C and benz[*a*]anthraquinone **14** with a nonaromatic A ring was obtained in 65% yield. This was then subjected to aromatization by DDQ in dry benzene under reflux for 3 days to furnish benz[*a*]anthraquinone **15** in 67% yield (Scheme 3). Comparison of its ^{1}H NMR and ^{13}C NMR spectroscopic data with the literature[12] data confirmed the structure.



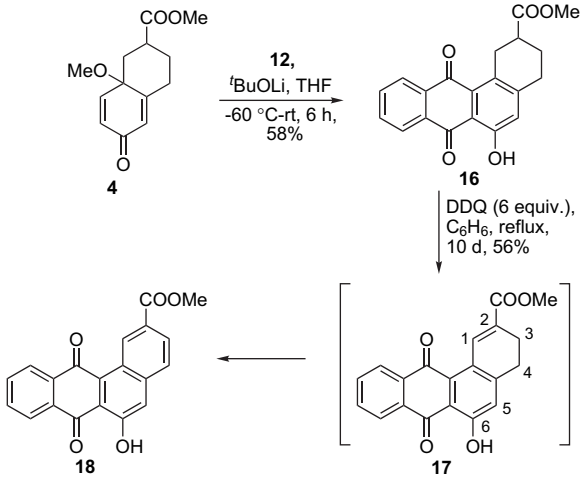
(1)

We then proceeded to execute the crucial annulation reaction of cyanophthalide **12** with naphthalenone **4** to install the carboxylic acid group at C-2 (AB ring synthon). Annulation of naphthalenone **4** with cyanophthalide **12** was carried out in the presence of ^{t}BuOLi, which has proved to be the best base for such purposes, in THF at −60 °C ($CHCl_3$/liq. N_2 bath) under an inert atmosphere. After usual work-up of the reaction mixture and chromatographic purification of the crude product, compound **16** was obtained in an unoptimized yield of 58%. It is noteworthy that the ester functionality in **4** did not interfere with the annulation process. For aromatization, compound **16** was treated with DDQ (6.0 equiv) in dry benzene at reflux for 10 days. Monitoring the course of the reaction required recording ^{1}H NMR spectra of the reaction mixture at regular intervals because TLC experiments were not useful. Formation of an inseparable mixture of didehydro intermediate **17** and the desired product **18** was revealed by analysis of the ^{1}H NMR spectra. The formation of didehydro intermediate **17** was ascertained by appearance of two triplets at δ 2.63 and 2.92 for two CH_2 groups at C-4 and C-3, respectively, two singlets: one at δ 8.87 for =CH at C-1 and other at δ 13.48 for hydrogen bonded –OH group at C-6. Although it was possible to record the ^{1}H NMR spectrum of **18** in $CDCl_3$, its ^{13}C NMR spectrum could not be recorded due to its poor solubility in common deuterated solvents (e.g., $CDCl_3$, CD_3OD, acetone-d_6, DMSO-d_6). This compound was further characterized by analysis using IR spectroscopy and HRMS.

With the two successes (Schemes 3 and 4), we next examined annulation of the naphthalenone **4** with isobenzofuranones **19** and **20**. This model study entails the differences in the isobenzofuranone parts. Isobenzofuranones **19** and **20** were prepared from ethyl 2-hydroxy-5-methylbenzoate (**26**), which, in turn, was obtained in two steps starting from ethyl acetoacetate and crotonaldehyde according to the published procedure.[13] Transformation of compound **26** to **19** and **20** were achieved in four steps by literature methods.[11,14] Annulation reaction between **20** and **4** in the presence of ^{t}BuOLi under the typical conditions used previously, afforded the angucycline analog **21** in 69% yield (Scheme 5) after chromatographic purification. This was aromatized by DDQ oxidation to give compound **22**, which was demethylated by treatment with anhydrous $AlCl_3$ in CH_2Cl_2 to furnish compound **23**. Compounds **22** and **23** were primarily characterized by IR, ^{1}H NMR, and mass



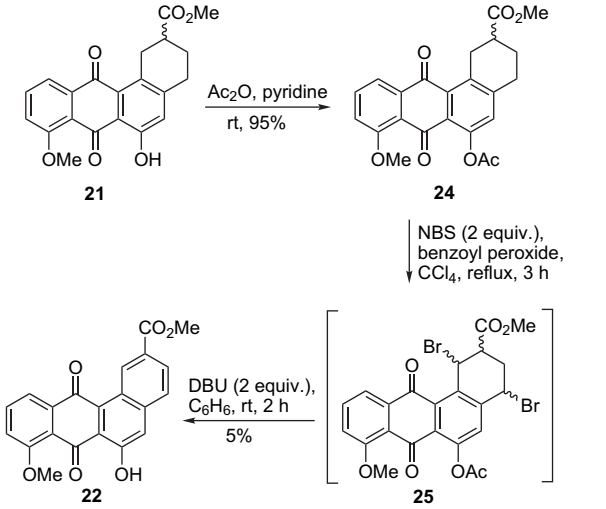
Scheme 3. Synthesis of model compound **15**.



Scheme 4. Synthesis of model compound **18**.

spectral data. The poor solubility of the compounds in common deuterated solvents precluded recording of ^{13}C NMR spectra. The ^1H NMR spectrum of compound **23** showed two sharp singlets at δ 12.10 and 11.80 characteristics of two H-bonded OH groups present at C-6 and C-8 positions. In the aromatic region it showed two sharp singlets, one at δ 10.15, characteristic of the proton at C-1 and the other at δ 7.67 for the aromatic proton at C-5. It may be noted that the use of sulfone phthalide **19** in the above reaction with naphthalenone **4** provided no annulation product, i.e., **21**. Naphthalenone **4** could be recovered in a substantial amount from the reaction, whereas sulfone phthalide **19** was destroyed during the reaction. The failure of the reaction is presumably due to a steric interaction between the sulfone group of phthalide and the OMe group at C-4a position of the naphthalenone.

In order to find a suitable substitute for the DDQ-promoted aromatization, which typically gave nearly 50% yields of the aromatized products for compounds **14**, **16**, and **21**, we examined a sequence of NBS bromination and HBr elimination. This sequence was applied to compound **21** (Scheme 6).

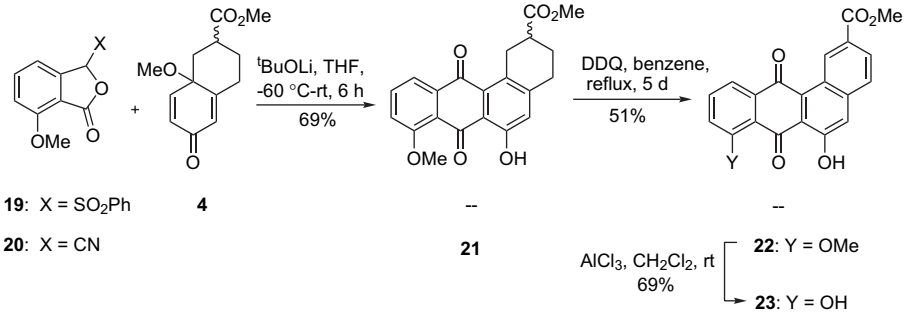


Scheme 6. Bromination and HBr elimination approach for aromatization study.

Compound **24**, prepared by acetylation of **21**, was brominated with NBS (2 equiv) in the presence of benzoyl peroxide and the resulting crude brominated product **25** was treated with DBU (2 equiv). However, the yield of the expected aromatized product **22** was very low (5%).

3.3. Synthesis of isobenzofuranones 3a and 3b (D ring synthons)

For the synthesis of key isobenzofuranones **3a** and **3b** (D ring synthons), the phenolic ester **26** was chosen as the starting material, since it had all the necessary substituents except the chlorine, and it was easily accessible.[13] We studied its direct chlorination with different chlorinating agents, while we were aware that methods for selective *ortho*



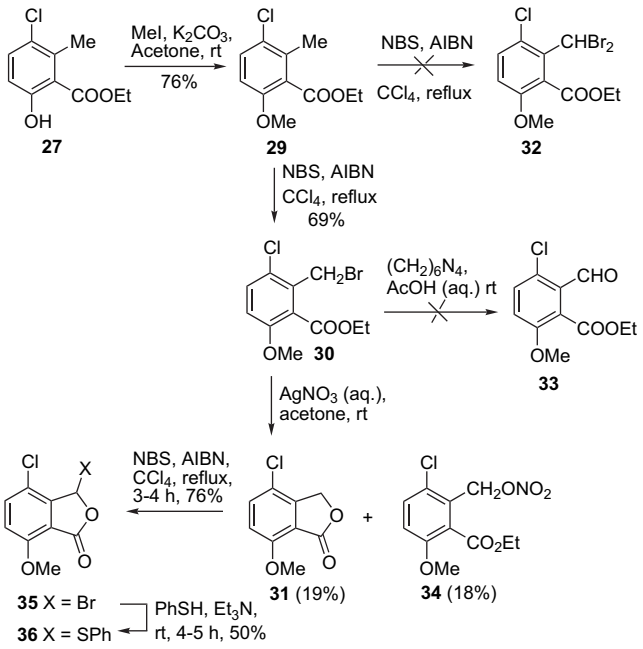
Scheme 5. Synthesis of dechloro analog of BE-23254 (**1**).

Table 1. Product distribution of chlorination of phenol **26**

Entry	Reagents and conditions	Yield of **5** (%)	Yield of **27** (%)	Yield of **28** (%)
1	Cl_2 (excess), AcOH, rt	—	—	79
2	SO_2Cl_2, 100 °C, 3 h	—	—	65
3	NCS (1.1 equiv), CCl_4, reflux, 4–5 h	11	53	—
4	NCS (1.1 equiv), AcOH, reflux, 4–5 h	Trace	35	—
5	NaOCl (1.1 equiv), AcOH, reflux, 4–5 h	Trace	15	49
6	Cl_2 (1.2 equiv), AcOH, rt	—	47	21
7	Cl_2 (1.2 equiv), AcOH, rt (inverse addition)	—	74	—

chlorination of substituted phenols are rare in the literature.[15] Initially, the phenolic ester was subjected to chlorination by passing chlorine gas through a stirred solution of the phenol **26** dissolved in AcOH (entry 1, Table 1; Scheme 7). It was difficult to control the absorption of the required amount of chlorine gas. As a result, an excess of chlorine gas was absorbed and only the dichlorophenol **28** was obtained in 79% yield as a white solid after column chromatographic purification. The same dichloro compound **28** was also obtained in 65% yield by heating the phenolic ester **26** with sulfuryl chloride (1.5 equiv). Alternatively, the chlorination at C-3 position of compound **26** was tried with NCS (1.1 equiv) in CCl_4, NCS (1.1 equiv) in AcOH, and aq NaOCl in AcOH. However, in each of these cases, an inseparable mixture of monochloro compounds **5**, **27**, and dichloro compound **28** was obtained in different ratios. In another mode, the phenol **26** was added to a solution of chlorine gas (1.2 equiv) dissolved in acetic acid (entry 6) and a 2:1 mixture of monochlorophenol **27** and dichlorophenol **28** was obtained in 68% yield. The monochloro compound **27** was obtained as the sole chlorinated product in 74% yield on addition of chlorine (1.2 equiv) in acetic acid to a stirred solution of the phenolic ester **26** taken in acetic acid (entry 7). The structure of product **27** was confirmed by analysis of ^{1}H NMR, ^{13}C NMR, and NOE spectra and also by a number of chemical transformations (Scheme 8). In the NOE spectrum of **27**, irradiation of the Me-signal at δ 2.62 produced no NOE enhancement of the Ar-H signal at δ 6.79.

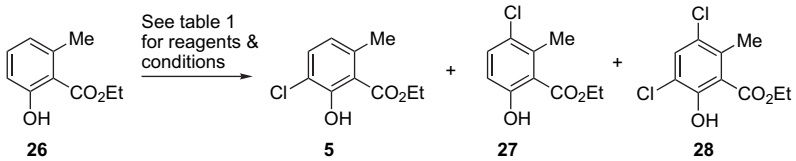
The chlorophenol **27** was methylated with methyl iodide in the presence of K_2CO_3 and the methoxy compound **29**, when reacted with NBS (2.2 equiv) and AIBN in CCl_4, gave monobromo derivative **30**, instead of dibromo compound **32** (Scheme 8). The monobromo compound **30** was then subjected to Sommelet reaction with urotropine in acetic acid, but aldehyde **33** was not formed. Alternatively, compound **30** was treated with aqueous silver nitrate solution. After stirring at room temperature for 2 h, a mixture of chlorophthalide **31**[16] and nitrite **34** was obtained. The two products



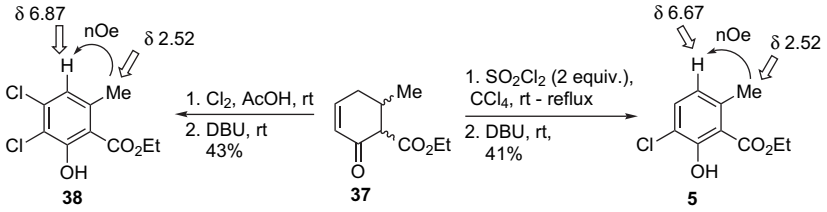
Scheme 8. Chemical transformations of monochlorophenol **27**.

were separated by column chromatography. The chlorophthalide **31** was then transformed into phenylthiophthalide **36** by reaction with NBS (1.1 equiv) followed by the treatment of the resulting bromophthalide **35** with a 1:1 mixture of thiophenol and triethylamine in chloroform at room temperature.

The above unwanted results on chlorination of phenolic ester **26** led us to select cyclohexenone **37** as the alternative starting material, the immediate precursor of the phenolic ester **26**. In the first attempt on the way to compound **5**, excess of chlorine gas was passed through a solution of cyclohexenone ester **37** taken in AcOH during 2 h at room temperature and the resulting crude product was treated with DBU (2 equiv) to afford the dichloro compound **38** in 43% yield (Scheme 9). The structure of this product was confirmed by analysis of its NMR and NOE spectra. In the NOE spectrum, irradiation of the Me-signal at δ 2.52 produced NOE enhancement of the Ar-H signal at δ 6.87. This indicated that the Ar-H and the Me group are present on vicinal carbon atoms of compound **38**. Finally, the problem of preparing monochloro compound **5** was solved by sulfuryl chloride promoted chlorination of cyclohexenone **37**. Its reaction with sulfuryl chloride (2 equiv) followed by treatment with DBU (3 equiv) at room temperature afforded, after usual work-up, the desired chloro compound **5** in 41% yield (Scheme 9). The structure of this product was confirmed by analysis of its NMR and NOE spectra. In the NOE spectrum, irradiation of the Me-signal at δ 2.52 produced NOE



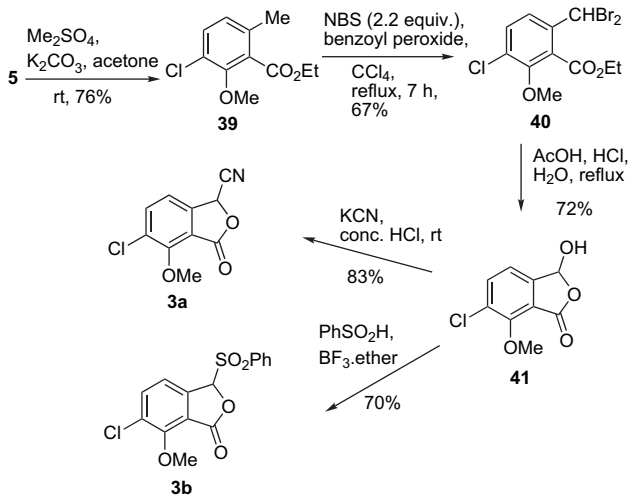
Scheme 7. Product distribution of chlorination of phenol **26**.



Scheme 9. Chlorination study on cyclohexenone **37**.

enhancement of the Ar-H signal at δ 6.67. This observation indicated that the Ar-H and the benzylic CH_3 group are present on vicinal carbon atoms of compound **5**.

Chlorophenol **5** was then transformed into isobenzofuranones **3a** and **3b** in four steps (Scheme 10). The phenolic OH group of compound **5** was methylated (Me_2SO_4, K_2CO_3) to give ester **39**, which was subjected to benzylic bromination with NBS (2.2 equiv) to furnish compound **40**. Dibromo compound **40** was hydrolyzed with a refluxing mixture of AcOH, HCl, and H_2O to produce corresponding phthalaldehydic acid **41**. This five-step synthesis of **41** appears to be competitive to its earlier synthesis.[17] Two key



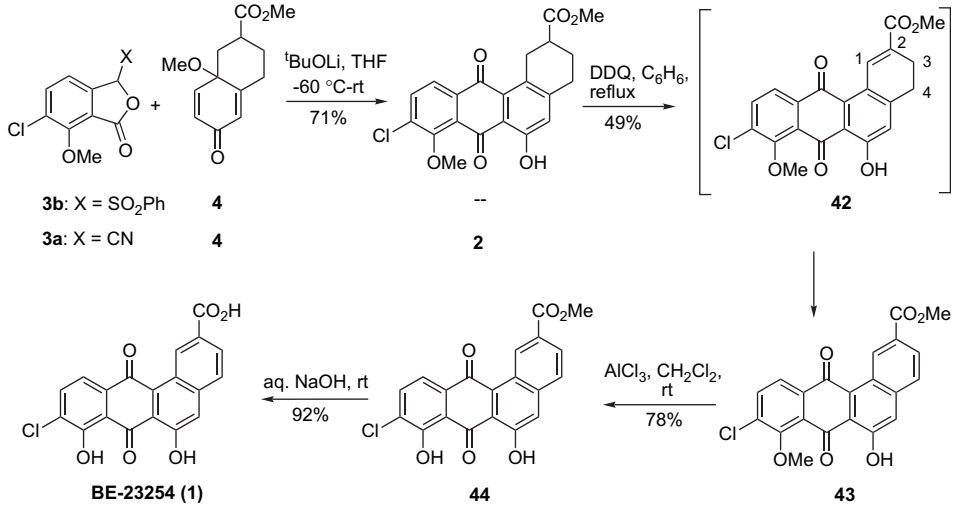
Scheme 10. Synthesis of isobenzofuranones **3a** and **3b**.

synthons **3a** and **3b** were then prepared according to the general procedures reported for the preparation of cyanophthalides[11] and phenylsulfone phthalides.[18] Reaction of phthalaldehydic acid **41** with KCN in the presence of concd HCl afforded cyanophthalide **3a** in 83% yield. Its structure was established by analysis of IR, NMR (^1H and ^{13}C), and mass spectral data. Similarly, the corresponding sulfone phthalide **3b** was prepared in 70% yield from phthalaldehydic acid **41** by its reaction with phenylsulfinic acid in the presence of $BF_3\cdot$etherate.

3.4. Total synthesis of BE-23254 (1)

3-Phenylsulfonylphthalides are generally preferred to the 3-cyanophthalides as the Hauser-donors due to difficulties in the preparation of the latter. Consequently, we first attempted to condense sulfone phthalide **3b** with naphthalenone **4** (Scheme 11). Their reaction in the presence of lithium *tert*-butoxide from −60 to 0 °C, followed by stirring overnight at room temperature and routine work-up did not yield the expected annulation product **2**. Naphthalenone **4** could be recovered from the reaction in a substantial amount, whereas sulfone phthalide **3b** was destroyed during the reaction. This failure with the sulfone phthalide was apprehended on the basis of the experiment described for **19** (Scheme 5). However, this experiment was performed to reinforce our explanation that this failure was due to the steric effect. The polar effect of the chlorine atom has little influence on the failure.

Alternatively, reaction of cyanophthalide **3a** with naphthalenone **4** in the presence of ^{t}BuOLi at −60 °C followed by stirring at room temperature for 6 h provided the



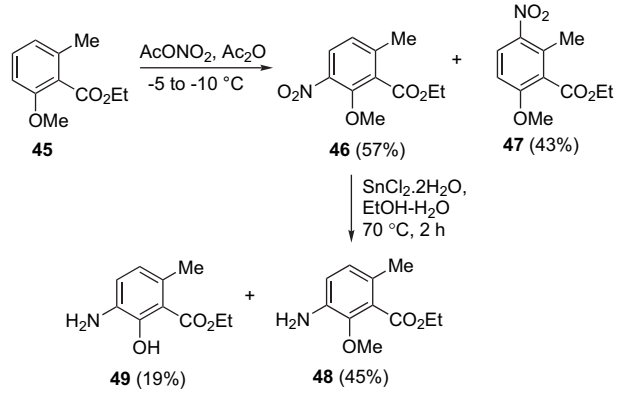
Scheme 11. Total synthesis of BE-23254 (**1**).

tetrahydrobenz[*a*]anthraquinone **2** in 71% yield, which was characterized by analysis of IR, NMR (^{1}H and ^{13}C), and mass spectral data. The ^{1}H NMR spectrum of the compound **2** showed three sharp singlets: at δ 13.00 (H-bonded OH group at C-6), 4.01 (OCH_3), and 3.74 ($COOCH_3$). In the aromatic region, it revealed two one-hydrogen doublets at δ 7.99 and 7.82, and one singlet at δ 7.06 for hydrogen at C-5. The nonequivalent protons of the CH_2 group at C-1 appeared as doublet of doublets at δ 3.61 and 3.30. Each proton was equally splitted by the other (J_{gem}=18.6 Hz) and unequally by the neighboring proton (i.e., α to ester functionality) at C-2 (J_{vic}=10.0 and 5.6 Hz). IR, ^{13}C NMR, and mass spectral data of this compound were also in accordance with the structure. Aromatization of the A-ring in **2** was effected by DDQ in refluxing benzene to provide **43** in 49% yield. This reaction required careful monitoring by ^{1}H NMR spectra of the interrupted reaction mixtures because the reaction progressed through the formation of inseparable mixtures of didehydro intermediate **42** and the desired product **43**. Prolonged refluxing seemed to destroy the aromatized product **43** into an unidentified product. Formation of the didehydro intermediate **42** was ascertained by the appearance of two triplets at δ 2.89 and 2.60 for two CH_2 groups at C-4 and C-3, respectively, and two singlets: one at δ 8.70 for C-1 hydrogen and other at δ 13.43 for hydrogen bonded –OH group. Demethylation of compound **43** was done by treatment with anhydrous $AlCl_3$ in CH_2Cl_2 at room temperature to afford **44** in 78% yield. Base (NaOH) catalyzed hydrolysis of **44** yielded the natural product BE-23254 (**1**) in 92% yield. All the A-ring aromatic compounds of this series (**1**, **43**, and **44**) were characterized by analysis of IR, ^{1}H NMR, and HRMS spectra. ^{13}C NMR spectra of compounds **1**, **43**, and **44** could not be recorded due to their poor solubility in common deuterated solvents including pyridine-d_5.

3.5. Synthesis of fluoro analog of BE-23254

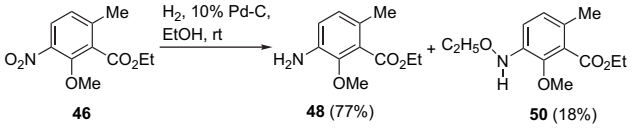
As a matter of course, our next effort was directed at synthesizing a fluorine-containing analog of BE-23254 (**1**). It is well established that the selective introduction of a fluorine atom or a fluorinated residue into a biologically active molecule is an effective means for modifying its physicochemical properties and consequently its physiological behavior.[19]

For the synthesis of the required fluoro cyanophthalide **55**, we commenced with anisic ester **45**, obtained from phenolic ester **25**. Considering the fact that acetyl nitrate is orthoselective,[20] anisic ester **45** was treated with acetyl nitrate[21] at −5 to −10 °C in acetic anhydride (Scheme 12). It yielded a mixture of *ortho*- and *para*-nitro anisic esters **46** and **47** in 57 and 43% yield, respectively. These were separated by column chromatography and characterized by analysis of their IR and NMR (^{1}H and ^{13}C) spectra. Both the compounds **46** and **47** showed the same coupling pattern in their ^{1}H NMR spectrum but they were distinguished by comparing the chemical shift of the methyl groups at C-6. In compound **46**, the methyl group appeared at δ 2.36, while that in compound **47** appeared at δ 2.48 as it is closer to the electron withdrawing nitro group. These data are comparable to that of the corresponding methyl esters.[22] Ester **46** was then transformed to the corresponding amine **48** by treatment with stannous chloride dihydrate in ethanol at 70 °C in accordance with the literature procedure.[23] The amine **48** was obtained in 45% yield along with hydroxy amine compound **49** in 19% yield.



Scheme 12. Synthesis of amine **48**.

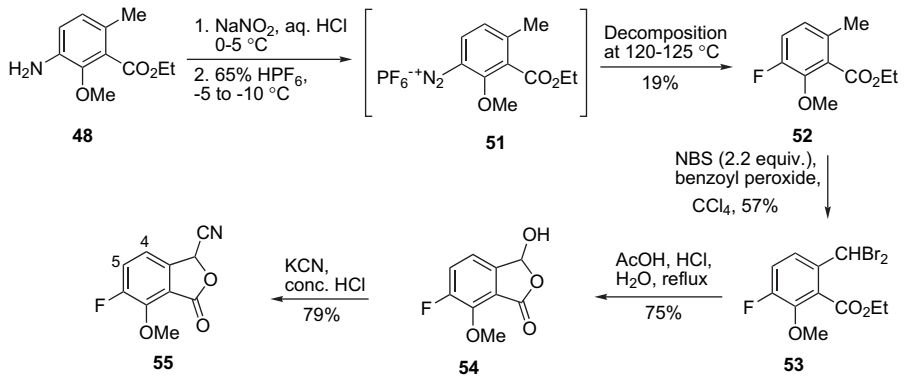
In order to avoid the formation of **49** and thereby increase the yield of **48**, we submitted compound **46** to hydrogenation over 10% Pd–C[24] in absolute ethanol at room temperature. In this case (Scheme 13), the amine **48** was obtained in 77% yield with the side product **50** in 18% yield.



Scheme 13. Reduction of nitro compound **46** to amine **48**.

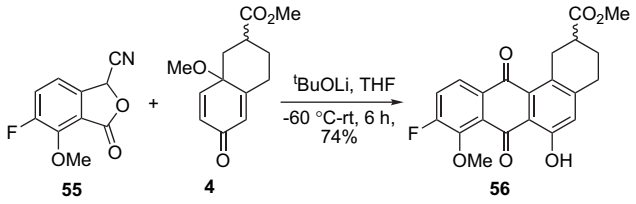
The required fluorophthalide **55** was synthesized from amine **48** in five steps (Scheme 14). Amine **48** was treated with $NaNO_2$ and HCl followed by cold HPF_6 solution to obtain the corresponding phosphorus hexafluoride salt **51**, which was filtered, dried, and without purification decomposed at 120–125 °C.[25] After the decomposition was complete, the residue was processed in usual manner to yield fluoro compound **52**, after purification, in overall 19% yield. Compound **52** was then subjected to benzylic bromination with NBS (2.2 equiv) to furnish dibromo compound **53**, which was then hydrolyzed with a refluxing mixture of AcOH, HCl, and H_2O to yield corresponding phthalaldehydic acid **54** in 75% yield. Finally, the cyanophthalide **55** was prepared according to the general procedure.[11] Reaction of phthalaldehydic acid **54** with KCN in the presence of concd HCl afforded, after column chromatographic purification, the cyanophthalide **55** in 79% yield. Structures of the compounds **52**–**55** were established by the analysis of IR, NMR (^{1}H and ^{13}C), and mass spectral data. The ^{1}H NMR spectra of compounds **54** and **55** had a pair of double doublets corresponding to C-4 and C-5 hydrogens due to coupling with each other and with fluorine at C-6. In addition, these also showed a doublet for the methoxy group at C-7 due to its coupling with the fluorine.

Treatment of naphthalenone **4** with the anion of fluorophthalide **55** (Scheme 15) generated with lithium *tert*-butoxide in THF at −60 °C ($CHCl_3$/liq. N_2 bath) under N_2 atmosphere provided tetracyclic compound **56**. The structure of the annulated product **56** was characterized by examination of



Scheme 14. Synthesis of fluoro cyanophthalide **55**.

IR, NMR, and mass spectral data. Its ^{1}H NMR spectrum showed a sharp singlet at δ 13.02 for the H-bonded hydroxyl group at C-6. In the aromatic region, it revealed two double doublets at δ 8.02 ($J_{H-F(o)}$=10.1 Hz and $J_{H-H(o)}$=8.7 Hz) and 7.45 ($J_{H-F(m)}$=5.0 Hz and $J_{H-H(o)}$=8.7 Hz) corresponding to C-10 and C-11 hydrogens. The singlet at δ 7.06 corresponds to hydrogen at C-5. In addition, it also exhibited a doublet at δ 4.08 (J_{OMe-F}=3.3 Hz) for the methoxy group at C-8 due to its coupling with fluorine and another singlet at δ 3.74 for carbomethoxy group. Due to the inefficiency in the conversion of **48**→**52**, further investigations with **56** on the way to obtain fluoro analog of BE-23254 (**1**) were stalled.



Scheme 15. Annulation of cyanophthalide **55** with naphthalenone **4**.

4. Conclusions

In conclusion, we have presented a regiospecific total synthesis of BE-23254 (**1**) starting from commercially available 6-methoxytetralone, and showcased the applicability and brevity of Hauser annulation–DDQ-promoted aromatization strategy in the synthesis of angucyclines. Use of the strategy has culminated in the synthesis of several angucycline analogs, namely **15**, **18**, **22**, and fluoro analog **56**. We have also executed a new regiospecific preparation of *ortho*-chlorinated phenols based on chlorinative aromatization of a cyclohexenone derivative (Scheme 9). It would be interesting to examine the biological activities of the newly prepared A-ring nonaromatic benz[*a*]anthraquinone derivatives like **2**, **14**, **16**, **21**, and **56**.

5. Experimental

5.1. General

^{1}H NMR spectra were recorded on a 200, 300, or a 500 MHz spectrometer (Brücker) as solution in ^2H-chloroform or mixture of ^2H-chloroform and CCl_4, or in mixture of ^2H-chloroform and DMSO-d_6 with TMS as an internal standard. Chemical shifts are expressed in δ unit and ^{1}H–^{1}H coupling constants in hertz. ^{13}C NMR spectra were recorded on a 50, 75, or a 125 MHz spectrometer (Brücker) instrument with solution of compounds in ^2H-chloroform, mixture of ^2H-chloroform and CCl_4, and mixture of ^2H-chloroform and DMSO-d_6. IR spectra were recorded on a Thermo Nicolet Nexus 870 FTIR spectrometer using KBr pellets. EIMS (70 eV) spectra were taken using a VG Autospec M mass spectrometer. Elemental analyses were carried out by using an elemental analyzer VARIO EL instrument. All solvents for chromatography (column and preparative layer chromatography) were distilled prior to use. In most of the column chromatographic separations, ethyl acetate, chloroform, and petroleum ether (60–80 °C) were used as eluants. Columns were prepared with silica gel (60–120 mesh). For preparative thin layer chromatographic (PLC) separations, the layer was prepared over a glass plate using water gel. The mixture of silica gel-GF_{254} and silica gel-G was used for the PLC plate preparation. The phrase 'usual work-up' or 'worked up in usual manner' refers to washing of the organic phase with water and brine, drying (Na_2SO_4), filtration, and concentration under reduced pressure. Solid compounds were recrystallized from ethyl acetate–petroleum ether or otherwise mentioned.

5.2. General procedure for annulation reaction

To a stirred solution of lithium *tert*-butoxide (9.84 mmol) in THF (40 mL) at −60 °C (chloroform/liq. 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 30 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. 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 in vacuo. 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 brine, H_2O, dried (Na_2SO_4), and

concentrated. The crude product was purified by column chromatography or by recrystallization to get a pure product.

5.3. General procedure for DDQ oxidation

To a stirred solution of 1,2,3,4-tetrahydrobenz[*a*]anthraquinone compound (280 mmol) in dry benzene (10 mL) under an inert atmosphere was added DDQ (6 equiv). The resulting mixture was refluxed with stirring for 3–12 days under inert atmosphere. The progress of the reaction was monitored by ^{1}H NMR spectroscopy and disappearance of the signals in the aliphatic region was followed. TLC was not useful for the purpose because of the formation of the inseparable mixtures of didehydro compound and final aromatized product at the intermediate stage of the reaction. After completion of the reaction, benzene was removed under reduced pressure. The aromatized product was purified by column chromatography using mixtures of $CHCl_3$ and petroleum ether (5:1) as eluant.

5.4. General procedure for O-demethylation of phenolic ether

To a stirred solution of a methoxy compound (0.105 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C under Ar-atmosphere was added anhydrous $AlCl_3$ (5 equiv). After 1 h of stirring at 0 °C, the reaction mixture was allowed to come to room temperature and stirring was continued for additional 6 h. The reaction mixture was quenched with 2 M HCl (4 mL). Usual work-up of the organic extract afforded a solid that was further purified by column chromatography (3:1 mixture of $CHCl_3$/petroleum ether).

5.5. General procedure of O-methylation of phenolic compounds

A phenolic compound (3.0 mmol) was dissolved in dry acetone (15 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, saturated $NaHCO_3$ solution, brine, and then dried over anhydrous K_2CO_3). After 2 h of reflux, on completion of the reaction, inorganic salts were filtered and the filtrate was concentrated. The residue was diluted with ether, 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 water and 5% HCl, and subjected to usual work-up to get a crude residue, which was further purified by recrystallization or by column chromatography to give a pure methoxy compound.

5.5.1. BE-23254 (1). To a stirred solution of ester compound **44** (20 mg, 0.05 mmol) in methanol (5 mL), 20% aq solution of NaOH (2 mL) was added. The resulting pink colored solution was allowed to stir overnight. Then the reaction mixture was acidified with dilute HCl and extracted with ethyl acetate (3×30 mL). Usual work-up of the organic extract afforded a red solid that was further purified by column chromatography (3:1 $CHCl_3$/petroleum ether). Yield: 92%; mp: 324–326 °C; ν_{max} (KBr, cm^{-1}): 3409, 1705, 1618, 1425, 1233, 1050, 759; ^{1}H NMR (200 MHz, pyridine-d_5): δ 10.9 (s, 1H), 8.55 (d, 1H, J=8.3 Hz), 7.90–7.81 (m, 4H); MS *m*/*z* (EI): 368 (M$^+$), 354, 323, 256, 236, 194, 152, 137, 129, 111, 97, 83, 69; HRMS *m*/*z* (ESI) calcd for $C_{19}H_9{}^{35}ClO_6$ (M$^+$−H): 367.0009; found: 367.0026.

5.5.2. Methyl 9-chloro-6-hydroxy-8-methoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione-2-carboxylate (2). This compound was prepared as a yellow solid by annulation of 6-chloro-7-methoxy cyanophthalide (**3a**) with Michael acceptor **4** following the general procedure in Section 5.2. Yield: 71%; mp: 135–136 °C; ν_{max} (KBr, cm^{-1}): 3408, 1733, 1634, 1273, 1025, 763, 697; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 13.00 (s, 1H), 7.99 (d, 1H, J=8.0 Hz), 7.82 (d, 1H, J=8.0 Hz), 7.06 (s, 1H), 4.01 (s, 3H), 3.74 (s, 3H), 3.61 (dd, 1H, J=5.6 and 18.6 Hz), 3.30 (dd, 1H, J=10.0 and 18.6 Hz), 2.94–2.89 (m, 2H), 2.80–2.68 (m, 1H), 2.21–2.12 (m, 1H), 2.03–1.90 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 187.8, 183.7, 175.4, 160.7, 156.1, 147.8, 136.5, 135.8, 135.2, 131.8, 129.9, 126.2, 124.5, 124.2, 116.4, 61.6, 51.9, 39.8, 30.9, 29.9, 24.1; MS *m*/*z* (EI): 400 (M$^+$), 369, 340, 326, 322, 297, 284, 256, 236, 197; HRMS *m*/*z* (ESI) calcd for $C_{21}H_{13}{}^{35}ClO_6$ (M$^+$+H): 401.0792; found: 401.0755.

5.5.3. 6-Chloro-3-cyano-7-methoxyphthalide (3a). To a solution of KCN (1.25 g, 19.2 mmol) in water (5 mL) was added phthalaldehydic acid **41** (0.5 g, 2.78 mmol). The clear reddish solution was stirred for 10 min at room temperature and cooled to 0 °C. After addition of ice (~5 g), concentrated HCl (4 mL) was added and the resulting clear colorless solution was removed from the ice bath and stored at room temperature for 5 h. A white precipitate deposited. This was filtered, dried, and recrystallized from ethyl acetate to give a white crystalline solid (430 mg, 1.92 mmol). Yield: 83%; mp: 90–91 °C; ν_{max} (KBr, cm^{-1}): 1788, 1601, 1390, 1024, 768; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.84–7.80 (d, 1H, J=8.0 Hz), 7.33–7.28 (d, 1H, J=8.0 Hz), 6.97 (s, 1H), 4.21 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 163.8, 155.5, 141.6, 137.5, 130.3, 117.4, 116.6, 113.2, 64.6, 62.9; MS *m*/*z* (EI): 223 (M$^+$), 205, 194, 177, 167, 149, 137, 100, 75; HRMS *m*/*z* (ESI) calcd for $C_{10}H_6N{}^{35}ClO_3$ (M$^+$+H): 224.0114; found: 224.0106.

5.5.4. 3-Benzenesulfonyl-6-chloro-7-methoxy-3*H*-isobenzofuran-1-one (3b). This compound was prepared from compound **41** following the procedure of Mal et al.[18] To a stirred mixture of phthalaldehydic acid **41** (200 mg, 0.93 mmol) and a freshly prepared benzenesulfinic acid (400 mg, 2.82 mmol) in dry dichloromethane (5 mL) at room temperature under Ar-atmosphere was added 4–5 drops of boron trifluoride diethyl etherate. The mixture was stirred for about 12 h. A pale yellow solid separated on addition of ice-cold water (15 mL) into the reaction mixture. It was filtered and recrystallized from ethyl acetate–hexane to give sulfone phthalide **3b** as white crystalline solid (220 mg, 0.65 mmol). Yield: 70%, mp: 138–139 °C; ν_{max} (KBr, cm^{-1}): 1781, 1596, 1469, 1348, 1155, 1004, 835, 719, 682, 593; ^{1}H NMR (200 MHz, $CDCl_3$): 7.84–7.48 (m, 7H), 6.07 (s, 1H), 4.01 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 164.2, 155.2, 139.5, 137.1, 135.0, 140, 130.5, 129.7, 129.3, 120.1, 118.3, 89.5, 62.0; HRMS *m*/*z* (ESI) calcd for $C_{15}H_{11}{}^{35}ClO_5S$ (M$^+$+H): 339.0094; found: 339.0107.

5.5.5. Methyl 1,2,3,4-tetrahydro-4a-methoxy-6-oxonaphthalene-2-carboxylate (4). To a stirred solution of

compound **9** (300 mg, 1.46 mmol) in methanol (10 mL) at 0 °C under N_2 atmosphere was portionwise added PIDA (560 mg, 1.74 mmol). The temperature was held at 0 °C for about 30 min. Then the mixture was allowed to come to ambient temperature during a period of 1 h. Bulk of methanol was removed under reduced pressure and the residue upon quick silica gel filtration afforded compound **4** as waxy solid. Yield: 65%; ν_{max} (KBr, cm^{-1}): 1735, 1667, 1636, 1441, 1305, 1207, 1085, 987, 891; ^1H NMR (200 MHz, $CDCl_3$): 6.64 (d, 1H, J=10.0 Hz), 6.63 (dd, 1H, J=1.9 and 10.0 Hz), 6.21 (d, 1H, J=1.4 Hz), 3.65 (s, 3H), 3.02 (s, 3H), 2.53–2.20 (m, 5H), 1.60–1.41 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 185.8, 174.6, 160.5, 149.8, 131.3, 127.1, 72.7, 51.82, 51.7, 40.5, 37.5, 31.0, 29.9. No attempt was made for preparing an analytical sample due to its propensity to decomposition on silica gel chromatography or standing.

5.5.6. Ethyl 3-chloro-2-hydroxy-6-methylbenzoate (5). To the stirred solution of cyclohexenone **37** (4.22 g, 23.2 mmol) in CCl_4 at 0 °C was added SO_2Cl_2 (3.8 mL, 46.9 mmol) dropwise. The reaction mixture was allowed to stir for additional half an hour at room temperature. Thereafter, it was heated at reflux for 4 h. After completion of the reaction, the product was extracted with dichloromethane, dried over sodium sulfate, and solvent was then removed. The crude residue was then dissolved in benzene (10 mL) and treated with 3 equiv of DBU with occasional stirring at room temperature for about 4–5 h. Benzene was removed under reduced pressure. Finally, the mixture was extracted with ethyl acetate (3×25 mL) and washed with cold 10% aq HCl (15 mL). The extract was worked up in usual manner to give the desired product, which was further purified by column chromatography using petroleum ether and ethyl acetate (15:1) to afford a pure product **5** as white solid (2.04 g). Yield: 41%; mp: 55–56 °C; ν_{max} (KBr, cm^{-1}): 3442, 1663, 1424, 1256, 1205, 802; ^1H NMR (200 MHz, $CDCl_3$+CCl_4): 11.97 (s, 1H), 7.37 (d, 1H, J=8.0 Hz), 6.67 (d, 1H, J=8.0 Hz), 4.50 (q, 2H, J=7.0 Hz), 2.52 (s, 3H), 1.44 (t, 3H, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 172.4, 158.1, 140, 134, 122.8, 120, 113.6, 62.1, 23.8, 14.1; HRMS m/z (ESI) calcd for $C_{10}H_{11}{}^{35}ClO_3$ (M^++H): 215.0475; found: 215.0461.

5.5.7. 1,2,3,4-Tetrahydro-6-methoxynaphthalene-2-carboxylic acid (7). This compound was prepared following the procedure reported by Reddy and Rao[7] in four steps starting from 6-methoxytetralone (**6**) . White solid. Yield: 91%, mp: 146–147 °C (lit.[7] mp: 152 °C). ν_{max} (KBr, cm^{-1}): 2947, 1694, 1431, 1302, 1264, 959; ^1H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 6.86 (1H, d, J=8.0 Hz), 6.57–6.46 (m, 2H), 5.15 (br s, 1H), 2.80–2.66 (m, 4H), 2.60–2.43 (m, 1H), 2.12–1.99 (m, 1H), 1.74–1.60 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$+DMSO-d_6): δ 176.6, 156.7, 136.1, 129.0, 126.4, 112.5, 111.3, 54.3, 39.1, 30.0, 27.9, 24.9; HRMS m/z (ESI) calcd for $C_{12}H_{14}O_3$ (M^++H): 207.1021; found: 207.1014.

5.5.8. 6-Hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (8). A mixture of naphthalene-2-carboxylic acid **7** (2.5 g, 12.13 mmol), 20 mL of hydrobromic acid (48% aq solution), and 20 mL of acetic acid was heated at reflux for 3–4 h. After completion of the reaction, acetic acid was removed. Usual work-up of the residue furnished the desired product **8** as a white solid. This was recrystallized from ethyl acetate and petroleum ether. Yield: 81%; mp: 137–138 °C; ν_{max} (KBr, cm^{-1}): 3257, 1691, 1608, 1456, 1239, 942; ^1H NMR (200 MHz, DMSO-d_6+$CDCl_3$): δ 7.72 (d, 1H, J=8.0 Hz), 6.46–6.38 (m, 2H), 3.91 (br s, 1H), 2.75–2.39 (m, 5H), 2.04–1.94 (m, 1H), 1.72–1.59 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.9, 154.2, 136, 129.0, 124.9, 114.3, 112.7, 39.3, 30.1, 27.8, 25.0.

5.5.9. Methyl 6-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (9). This was prepared in accordance with the procedure[9] of Mal. To a solution of 1,2,3,4-tetrahydro-6-hydroxynaphthalene-2-carboxylic acid (1.00 g, 7.81 mmol) and DBU (1.20 g, 7.88 mmol) in acetonitrile (15 mL) cooled to 0 °C was slowly added methyl iodide (0.5 mL, 8.1 mmol) over 5 min. The resulting solution was stirred for 30 min at 0 °C and then for 2 h at room temperature. Solvent was removed under reduced pressure and the residue was diluted with water (30 mL). The aqueous solution was extracted with ether (3×25 mL). The combined organic layer was washed with $NaHCO_3$ solution (20 mL), brine, and concentrated. Purification of the crude residue by column chromatography (3:7 mixture of ethyl acetate–petroleum ether) gave compound **9** as a white solid. Yield: 96%; mp: 90–91 °C; ν_{max} (KBr, cm^{-1}): 3439, 1701, 1619, 1587, 1499, 1266, 1221, 1145, 1009, 808, 584; ^1H NMR (200 MHz, $CDCl_3$): δ 6.93 (d, 1H, J=8.2 Hz), 6.65 (dd, 1H, J=2.0 and 8.2 Hz), 6.59 (d, 1H, J=2.0 Hz), 3.74 (s, 3H), 2.95–2.89 (m, 2H), 2.82–2.63 (m, 3H), 2.22–2.10 (m, 1H), 1.89–1.75 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.6, 153.9, 136.9, 129.0, 126.6, 115.1, 113.4, 51.9, 40.2, 30.9, 28.5, 25.7; HRMS m/z (ESI) calcd for $C_{12}H_{14}O_3$ (M^+−H): 205.0779; found: 205.0788.

5.5.10. Methyl 1,2,3,4-tetrahydro-6-methoxynaphthalene-2-carboxylate (10). This product was obtained as a side product during the esterification of compound **8** with DBU–MeI in acetonitrile. Colorless liquid. Yield: 5%; ν_{max} (KBr, cm^{-1}): 1734, 1613, 1502, 1443, 1265, 1227, 1166, 1035, 821; ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 6.98 (d, 1H, J=8.3 Hz), 6.64 (dd, 1H, J=2.1 and 8.3 Hz), 6.57 (d, 1H, J=2.1 Hz), 3.76 (s, 3H), 3.72 (s, 3H), 2.84 (m, 4H), 2.68 (m, 1H), 2.18 (m, 1H), 1.85 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 175.3, 157.6, 136.3, 129.6, 126.6, 113.1, 112.0, 54.8, 51.3, 39.9, 30.7, 28.6, 25.6.

5.5.11. 6-Hydroxybenz[*a*]anthracene-7,12-dione (15). This compound was prepared from **14** according to the general procedure in Section 5.3. Red solid. Yield: 67%; mp: 203 °C (lit.[12] mp: 201–204 °C); ν_{max} (KBr, cm^{-1}): 3429, 1641, 1589, 1442, 1379, 1307; ^1H NMR (300 MHz, $CDCl_3$): δ 12.46 (s, 1H), 9.49–9.46 (m, 1H), 8.30–8.28 (m, 2H), 7.82 (m, 2H), 7.88–7.77 (m, 1H), 7.74–7.69 (s, 1H), 7.58–7.52 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.1, 185.4, 156.8, 139.2, 135.0, 133.6, 132.0, 129.9, 129.5, 128.9, 128.5, 127.9, 127.3, 127.2, 126.4, 126.2, 121.1, 119.5.

5.5.12. Methyl 6-hydroxy-1,2,3,4-tetrahydrobenz[*a*]-anthracene-7,12-dione-2-carboxylate (16). This compound was prepared as a yellow solid by annulation of cyanophthalide **12** with Michael acceptor **4** following the general procedure of annulation in Section 5.2. Yield: 58%;

mp: 196–197 °C; ν_{max} (KBr, cm^{-1}): 3435, 1739, 1660, 1634, 1587, 1456, 1360, 1283, 1250, 1176, 1017, 795, 722; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 13.03 (s, 1H), 8.40–8.09 (m, 2H), 7.92–7.60 (m, 2H), 7.04 (s, 1H), 3.75 (s, 3H), 3.64–3.61 (m, 1H), 3.40–3.25 (m, 1H), 2.96–2.89 (m, 2H), 2.79–2.65 (m, 1H), 2.15–2.10 (m, 1H), 2.05–1.92 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 188.7, 175.4, 160.9, 148.1, 135.5, 134.5, 133.4, 132.3, 130.5, 130.1, 127.3, 126.2, 124.1, 121.3, 115.7, 51.9, 39.9, 31.0, 30.0, 24.1; HRMS *m/z* (ESI) calcd for $C_{20}H_{16}O_5$ (M^++H): 337.1017; found: 337.1021.

5.5.13. Methyl 6-hydroxybenz[*a*]anthracene-7,12-dione-2-carboxylate (18). This compound was prepared from **16** according to the general procedure in Section 5.3. Red solid. Yield: 56%; mp: 262–263 °C; ν_{max} (KBr, cm^{-1}): 3444, 1720, 1639, 1587, 1533, 1662, 1319, 1275, 1216, 748; ^{1}H NMR (200 MHz, $CDCl_3$): 12.56 (s, 1H), 10.19 (s, 1H), 8.36–8.25 (m, 2H), 8.14 (dd, 1H, *J*=2.0 and 8.0 Hz), 7.91–7.69 (m, 4H), 4.02 (s, 3H); HRMS *m/z* (ESI) calcd for $C_{20}H_{12}O_5$ (M^++H): 333.0763; found: 333.0761.

5.5.14. Methyl 6-hydroxy-8-methoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione-2-carboxylate (21). This compound was prepared by annulation of cyanophthalide **20** with Michael acceptor **4** following the general procedure in Section 5.2. Orange solid. Yield: 69%; mp: 174–175 °C; ν_{max} (KBr, cm^{-1}): 3432, 1730, 1632, 1582, 1466, 1361, 1290, 1229, 1174, 1031, 1065, 948, 919, 838, 785; ^{1}H NMR (200 MHz, $CDCl_3$): δ 13.23 (s, 1H), 7.86 (d, 1H, *J*=7.8 Hz), 7.72 (dd, 1H, *J*=7.8 and 8.2 Hz), 7.30 (d, 1H, *J*=8.2 Hz), 7.03 (s, 1H), 4.01 (s, 3H), 3.70 (s, 3H), 3.68–3.56 (m, 1H), 3.38–3.24 (m, 1H), 2.97–2.85 (m, 2H), 2.80–2.65 (m, 1H), 2.20–1.80 (m, 2H).

5.5.15. Methyl 6-hydroxy-8-methoxybenz[*a*]anthracene-7,12-dione-2-carboxylate (22). This compound was prepared from **21** according to the general procedure in Section 5.3. Red solid. Yield: 51%; mp: 266–267 °C; ν_{max} (KBr, cm^{-1}): 3414, 1710, 1643, 1452, 1286, 1255, 1221, 1033, 939, 763. ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.67 (s, 1H), 9.98 (s, 1H), 8.06 (d, 1H, *J*=9.0 Hz), 7.90 (d, 1H, *J*=7.7 Hz), 7.72 (m, 2H), 7.60 (s, 1H), 7.31 (d, 1H, *J*=8.1 Hz), 4.04 (s, 3H), 3.95 (s, 3H); HRMS *m/z* (ESI) calcd for $C_{21}H_{14}O_6$ (M^++H): 363.0869; found: 363.0872.

5.5.16. Methyl 6,8-dihydroxybenz[*a*]anthracene-7,12-dione-2-carboxylate (23). This compound was prepared as a brick red solid by $AlCl_3$ catalyzed demethylation of compound **22** following the procedure adopted for compound **43**. Yield: 69%; mp: 278–279 °C; ν_{max} (KBr, cm^{-1}): 3410, 1716, 1633, 1590, 1457, 1409, 1309, 1223, 1106, 1081, 758; ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.10 (1H, s), 11.80 (s, 1H), 10.15 (s, 1H), 8.13 (d, 1H, *J*=8.6 Hz), 7.85 (d, 1H, *J*=7.6 Hz), 7.79–7.68 (m, 2H), 7.67 (s, 1H), 7.31 (d, 1H, *J*=8.3 Hz), 4.02 (s, 3H); HRMS *m/z* (ESI) calcd for $C_{20}H_{12}O_6$ (M^++H): 349.0712; found: 349.0721.

5.5.17. Methyl 6-acetoxy-8-methoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione-2-carboxylate (24). Phenolic compound **20** (100 mg, 0.27 mmol) was dissolved in a mixture of distilled acetic anhydride (0.5 mL) and pyridine (1.5 mL). The resulting solution was allowed to stir for about 6 h at ambient temperature and then poured into crushed ice (25 g) and extracted with ether (3×15 mL). The extract was washed several times with $CuSO_4$ solution followed by usual work-up gave a crude product. This was purified by column chromatography (ethyl acetate–petroleum ether) to furnish **24** as a yellow solid. Mp: 168–169 °C; ν_{max} (KBr, cm^{-1}): 1768, 1727, 1668, 1587, 1469, 1369, 1257, 1031, 944, 790, 759, 678, 584; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74–7.58 (m, 3H), 7.09 (s, 1H), 4.07 (s, 3H), 3.73 (s, 3H), 3.68–3.58 (m, 1H), 3.43–3.29 (m, 1H), 2.97–2.89 (m, 2H), 2.78–2.68 (m, 1H), 2.47 (s, 3H), 2.17–2.03 (m, 1H), 1.98–1.86 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 185.7, 181.9, 175.3, 170.1, 159, 147.3, 144.1, 136.8, 136.1, 134.5, 132.6, 129.8, 126.5, 122.1, 119.1, 117.1, 56.6, 51.9, 39.7, 31, 29.4, 24.1, 21.2; HRMS *m/z* (ESI) calcd for $C_{23}H_{20}O_7$ (M^++H): 409.1229; found: 409.1239.

5.5.18. Ethyl 3-chloro-6-hydroxy-2-methylbenzoate (27). To a stirred solution of ethyl 2-hydroxy-6-methylbenzoate (**26**) (1 g, 5.55 mmol) in acetic acid (5 mL) was added dropwise a solution of chlorine (0.470 g, 6.62 mmol) in acetic acid (3 mL) and stirring was continued for additional 2 h. The solution was evaporated to dryness and the residue was extracted with ethyl acetate (2×25 mL) and usual work-up of the extract furnished the product **27**, which was further purified by column chromatographic separation using petroleum ether–ethyl acetate (10:1). White solid. Yield: 75%; mp: 54–55 °C; ν_{max} (KBr, cm^{-1}): 3439, 1664, 1597, 1452, 1382, 1320, 1293, 1213, 1023, 914; ^{1}H NMR (200 MHz, $CDCl_3$): 10.95 (s, 1H), 7.38 (d, 1H, *J*=10.0 Hz), 6.79 (d, 1H, *J*=10.0 Hz), 4.44 (q, 2H, *J*=7.0 Hz), 2.62 (s, 3H), 1.43 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 170.7, 160.6, 137.6, 134.7, 125.8, 122.6, 116.4, 62.0, 19.4, 14.0; HRMS *m/z* (ESI) calcd for $C_{10}H_{11}{}^{35}ClO_3$ (M^++H): 215.0475; found: 215.0466.

5.5.19. Ethyl 3,5-dichloro-2-hydroxy-6-methylbenzoate (28). To a stirred solution of phenolic ester **26** (1.5 g, 8.3 mmol) in acetic acid, excess of chlorine gas (generated by dropwise addition of concd HCl to solid $KMnO_4$) was absorbed at room temperature for 2 h. After completion of the reaction, acetic acid was removed under reduced pressure and the residue was extracted with ethyl acetate (3×20 mL) and usual work-up of the combined extract furnished crude product **28**, which was purified by column chromatography. Yield: 79%; ν_{max} (KBr, cm^{-1}): 3408, 1577, 1453, 1387, 1319, 1287, 1278, 1031, 957, 808, 670; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 11.31 (s, 1H), 7.53 (s, 1H), 4.53–4.40 (q, 2H, *J*=7.2 Hz), 2.56 (s, 3H), 1.48–1.40 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 170.4, 156.1, 136.6, 134.3, 125.7, 120.4, 115.6, 62.7, 19.3, 14.1; HRMS *m/z* (ESI) calcd for $C_{10}H_{10}{}^{35}Cl_2O_3$ (M^++H): 249.0035; found: 249.0039.

5.5.20. Ethyl 3-chloro-6-methoxy-2-methylbenzoate (29). This compound was prepared from ethyl 3-chloro-6-hydroxy-2-methylbenzoate (**27**) following the general procedure in Section 5.5. Colorless liquid. Yield: 76%; ν_{max} (KBr, cm^{-1}): 2988, 1733, 1566, 1468, 1261, 1024, 808; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.30 (d, 1H, *J*=8 Hz), 6.70 (d, 1H, *J*=8 Hz), 4.40 (q, 2H, *J*=7 Hz), 3.79 (s, 3H), 2.81 (s, 3H), 1.37 (t, 3H, *J*=7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 167.4, 154.7, 133.8, 130.3, 126.3, 125.7, 109.8, 61.4, 56.0, 17.0, 14.1.

5.5.21. Ethyl 2-bromomethyl-3-chloro-6-methoxybenzoate (30). Benzylic bromination was performed using 1.1 equiv of NBS following the procedure adopted for the preparation of compound **40** from **39**. ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.37 (d, 1H, J=8.8 Hz), 6.83 (d, 1H, J=8.8 Hz), 4.53 (s, 2H), 4.48 (q, 2H, J=7.2 Hz), 3.83 (s, 3H), 1.42 (t, 3H, J=7.2 Hz).

5.5.22. 4-Chloro-7-methoxyphthalide (31). An aqueous solution of silver nitrate (0.270 g, 1.6 mmol) was added to 50% ethanolic solution of ethyl 2-bromomethyl-3-chloro-6-methoxybenzoate (**30**) (0.410 g, 1.33 mmol). The resulting mixture was then stirred at room temperature for about 4–5 h. Solid materials were filtered off and the filtrate was evaporated. The residue on usual work-up furnished a crude mixture of products **31** and **34**. Phthalide **31** was separated by column chromatographic separation using petroleum ether and ethyl acetate (3:1). White solid. Yield: 19%; mp: 163–164 °C (lit.[16] mp: 167–168 °C); ν_{max} (KBr, cm^{-1}): 1759, 1485, 1288, 1028, 819; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.54 (d, 1H, J=8.6 Hz), 6.92 (d, 1H, J=8.6 Hz), 5.20 (s, 2H), 3.99 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 167.3, 157.4, 146.6, 135.2, 118.9, 115.2, 112.4, 67.4. 56.1; HRMS m/z (ESI) calcd for $C_9H_7{}^{35}ClO_3$ (M^+−H): 197.0005; found: 197.0004.

5.5.23. Ethyl 3-chloro-6-methoxy-2-nitrooxymethylbenzoate (34). This was obtained as a co-product in the reaction of ethyl 2-bromomethyl-3-chloro-6-methoxybenzoate (**30**) with aq silver nitrate as described above. Colorless liquid. Yield: 18%; ν_{max} (KBr, cm^{-1}): 1730, 1639, 1275, 851; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.40 (d, 1H, J=8.8 Hz), 6.91 (d, 1H, J=8.8 Hz), 5.59 (s, 2H), 4.39 (q, 2H, J=7.2 Hz), 3.84 (s, 3H), 1.37 (t, 3H, J=7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 165.6, 155.4, 131.4, 128.0, 126.6, 113.7, 68.8, 61.7, 56.1, 29.6, 14.0.

5.5.24. 3-Bromo-4-chloro-7-methoxyphthalide (35). Benzylic bromination of compound **31** was performed using 1.2 equiv of *N*-bromosuccinimide according to the procedure adopted for compound **39**. Light brown colored liquid. Crude yield: 75% (as judged by NMR); ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.63 (d, 1H, J=8.8 Hz), 7.23 (s, 1H), 7.02 (d, 1H, J=8.8 Hz), 4.02, (s, 3H).

5.5.25. 4-Chloro-3-phenylthio-7-methoxyphthalide (36). To a stirred solution of 3-bromo-4-chloro-7-methoxyphthalide (**35**) (20 mg, 0.072 mmol) in dry chloroform, triethylamine (0.072 mmol) and thiophenol (0.072 mmol) were added and the resulting mixture was stirred for 4–5 h. After completion of the reaction, it was diluted with diethyl ether (15 mL), washed with 5% NaOH (15 mL) solution, and worked up in usual manner. Crude product **36** was purified by column chromatography. Yield: 50%; mp: 117–118 °C; ν_{max} (KBr, cm^{-1}): 1754, 1590, 1473, 1442, 1281, 1199, 1160, 1046, 946; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.52–7.43 (m, 3H), 7.26–7.19 (m, 3H), 6.82 (d, 1H, J=8.6 Hz), 6.50 (s, 1H), 3.90 (s, 3H).

5.5.26. Ethyl 3,4-dichloro-2-hydroxy-6-methylbenzoate (38). Excess chlorine gas was passed through a stirred solution of ethyl 6-methyl-2-oxo-3-cyclohexenecarboxylate (**37**) (1.00 g, 5.46 mmol) in acetic acid during half an hour and stirring was continued for additional 2 h. Acetic acid was removed in vacuo. The product was extracted with ethyl acetate (3×15 mL). The extract was dried over Na_2SO_4 and solvent was removed. The residue was then dissolved in CCl_4 (10 mL) and treated with 2 equiv of DBU with stirring at room temperature. Stirring was continued for 5–6 h. The reaction mixture was extracted with ethyl acetate (3×10 mL) and washed with cold 10% aq HCl. The extract was worked up in usual manner to give a crude product, which was purified by column chromatography to get pure **38**. White solid. Yield: 43%; mp: 98–99 °C; ν_{max} (KBr, cm^{-1}): 3445, 1657, 1387, 1259, 1193, 860, 800. ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 12.33 (s, 1H), 6.87 (s, 1H), 4.46 (q, 2H, J=7.2 Hz), 2.52 (s, 3H), 1.44 (t, 3H, J=7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 171.2, 159.7, 140.0, 138.2, 134.0, 123.6, 111.7, 62.4, 23.8, 14.1; HRMS m/z (ESI) calcd for $C_{10}H_{10}{}^{35}Cl_2O_3$ (M^++H): 249.0035; found: 249.0037.

5.5.27. Ethyl 3-chloro-2-methoxy-6-methylbenzoate (39). This compound was prepared as a colorless liquid from phenolic ester **5** (2.11 g, 9.84 mmol) following the general procedure in Section 5.5. Yield: 68%; ν_{max} (KBr, cm^{-1}): 1731, 1461, 1272, 1107, 807; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.27 (d, 1H, J=8.0 Hz), 6.88 (d, 1H, J=8.0 Hz), 4.41 (q, 2H, J=7.0 Hz), 3.90 (s, 3H), 2.28 (s, 3H), 1.39 (t, 3H, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 166.8, 152.9, 134.9, 130.9, 130.6, 126.3, 125.1, 61.7, 61.1, 18.8, 14.2.

5.5.28. Ethyl 3-chloro-2-methoxy-6-dibromomethylbenzoate (40). A mixture of compound **39** (1.17 g, 5.12 mmol) and NBS (2.00 g, 11.2 mmol) in CCl_4 (15 mL) containing a catalytic amount of benzoyl peroxide was heated at reflux for 1 h while irradiated by a 100 W electric bulb. At the end of the reaction, the mixture was chilled (ice bath) and filtered. Removal of solvent from the filtrate furnished the crude dibromo compound **40**. This was further purified by column chromatography separation. Light yellow colored liquid. Yield: 67%; ν_{max} (KBr, cm^{-1}): 1720, 1461, 1268, 938, 692; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.72 (d, 1H, J=8.0 Hz), 7.51 (d, 1H, J=8.0 Hz), 6.75 (s, 1H), 4.46 (q, 2H, J=7.0 Hz), 3.91 (s, 3H), 1.44 (t, 3H, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 165.0, 152.2, 138.5, 132.4, 131.7, 129.2, 126.2, 62.2, 62.0, 35.4, 14.1.

5.5.29. 6-Chloro-3-hydroxy-7-methoxyphthalide (41). A mixture of dibromo compound **40** (2.20 g, 5.7 mmol), concd hydrochloric acid (3 mL), acetic acid (3 mL), and water (10 mL) was heated at reflux for 4 h. The solution was concentrated to dryness under reduced pressure and the concentrate was extracted with saturated sodium bicarbonate solutions, which on acidification (10% aq HCl), extraction into ethyl acetate layer, and usual work-up of the organic phase furnished compound **41** as a crystalline solid. The undissolved part of the residue was further hydrolyzed by repeating the procedure described above to furnish **41** as a crystalline solid. Yield: 72%; mp: 147–148 °C (lit.[17] mp: 159–163 °C); ν_{max} (KBr, cm^{-1}): 1741, 1633, 1383; ^{1}H NMR (200 MHz, DMSO-d_6+$CDCl_3$): 7.60 (d, 1H, J=8.0 Hz), 7.16 (d, 1H, J=8.0 Hz), 6.42 (s, 1H), 5.16 (br s, 1H), 4.05 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$): 165.2, 153.9, 147.8, 136.1, 128.7, 119.2, 118.5, 96.5, 62.2; MS m/z (EI): 214 (80) M^+, 203, 196, 184, 178, 169, 156, 139, 126, 110, 99, 77.

5.5.30. Methyl 9-chloro-6-hydroxy-8-methoxybenz[*a*]-anthracene-7,12-dione-2-carboxylate (43). This compound was prepared from compound **2** according to the general procedure in Section 5.3. Red solid. Yield: 49%; mp: 234–235 °C; ν_{max} (KBr, cm^{-1}): 3426, 1725, 1644, 1570, 1459, 1314, 1265, 1222, 1019, 760; ^1H NMR (200 MHz, $CDCl_3$): δ 12.42 (s, 1H), 10.04 (s, 1H), 8.12 (d, 1H, J=8.4 Hz), 8.08 (d, 1H, J=8.6 Hz), 7.86 (d, 1H, J=8.4 Hz), 7.75 (d, 1H, J=8.6 Hz). 7.68 (s, 1H), 4.06 (s, 3H), 4.01 (s, 3H); HRMS *m/z* (ESI) calcd for $C_{21}H_{13}{}^{35}ClO_6$ (M^++H): 397.0479; found: 397.0468.

5.5.31. Methyl 9-chloro-6,8-dihydroxy-benz[*a*]anthracene-7,12-dione-2-carboxylate (44). To a stirred solution of compound **43** (40 mg, 0.105 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C under Ar-atmosphere was added anhydrous $AlCl_3$ (5 equiv). After 1 h of stirring at 0 °C, the reaction mixture was allowed to come to room temperature and stirring was continued for additional 6 h. The reaction mixture was quenched with 2 M HCl (4 mL). Usual work-up of the organic extract afforded a solid, which was purified by column chromatography ($CHCl_3$–petroleum ether, 3:1) to give **44** as a red solid. Yield: 78%; mp: 273–274 °C; ν_{max} (KBr, cm^{-1}): 3407 (br s), 1713, 1627, 1419, 1282, 1224, 1128, 1080, 994, 761; ^1H NMR (200 MHz, $CDCl_3$): δ 12.34 (s, 1H), 11.90 (s, 1H), 10.15 (s, 1H), 8.14 (dd, 1H, J=1.5 and 8.7 Hz), 7.83 (s, 2H), 7.76 (d, 1H, J=8.7 Hz), 7.71 (s, 1H), 4.02 (s, 3H); MS *m/z* (EI): 382 (100) M^+, 351 (64), 323 (39), 256, 236, 175, 137, 123, 103, 91, 80, 69, 54; HRMS *m/z* (ESI) calcd for $C_{20}H_{11}{}^{35}ClO_6$ (M^+−H): 381.0166; found: 381.0150.

5.5.32. Ethyl 2-methoxy-6-methyl-3-nitrobenzoate (46). Acetyl nitrate was prepared by dropwise addition of fuming HNO_3 (0.270 mg, 3 mmol) with rapid stirring to 1.5 mL of acetic anhydride taken in a flask at 0–10 °C. After 15 min, the resulting solution was added to a stirred solution of ethyl 2-methoxy-6-methylbenzoate (460 mg, 2.8 mmol) in acetic anhydride (4 mL) at temperature between 0 and −10 °C. Stirring was continued at this temperature for about 1 h and then allowed to come to room temperature. The mixture was then poured into 10 mL of cold water and triturated with saturated solution of $NaHCO_3$ solution and then extracted with ether (3×20 mL). Usual work-up of the combined extracts furnished a light yellow liquid. The crude product was purified by column chromatography to give compound **46** as a yellow liquid. Yield: 57%; ν_{max} (KBr, cm^{-1}): 1730, 1592, 1526, 1351, 1273, 1120, 1066; ^1H NMR (200 MHz, $CDCl_3$): 7.85 (d, 1H, J=8.4 Hz), 7.06 (d, 1H, J=8.4 Hz), 4.42 (q, 2H, J=7.1 Hz), 3.87 (s, 3H), 2.36 (s, 3H), 1.39 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 165.7, 150.7, 142.6, 140.8, 131.4, 125.8, 125.5, 63.3, 61.5, 19.0, 13.8.

5.5.33. Ethyl 6-methoxy-2-methyl-3-nitrobenzoate (47). This was obtained as a co-product during the nitration (described above) of ethyl 2-methoxy-6-methylbenzoate by acetyl nitrate. Light yellow solid. Yield: 43%; mp: 70 °C; ν_{max} (KBr, cm^{-1}): 1730, 1603, 1583, 1513, 1471, 1347, 1261, 1110, 1070, 1027, 824, 650; ^1H NMR (200 MHz, $CDCl_3$): δ 8.07 (d, 1H, J=9.2 Hz), 6.83 (d, 1H, J=9.2 Hz), 4.41 (q, 2H, J=6.9 Hz), 3.90 (s, 3H), 2.48 (s, 3H), 1.37 (t, 3H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): 166.2, 159.3, 142.6, 132.5, 127.7, 126.3, 108.5, 61.7, 56.2, 16.9, 13.9.

5.5.34. Ethyl 3-amino-6-methoxy-2-methylbenzoate (48). To a solution of nitro compound **46** (1.5 g, 6.24 mmol) in ethanol (25 mL), 20 mg of 10% Pd–C was added. The solution was then deoxygenated under vacuum and was allowed to absorb hydrogen gas from a balloon. The mixture was stirred at rt for 5–6 h under hydrogen atmosphere. After completion of the reaction, the catalyst was removed by filtration and solvent was removed under vacuum. The crude product was purified by column chromatographic separation using a 1:5 mixture of ethyl acetate and petroleum ether as eluant. Colorless liquid. Yield: 77%; ν_{max} (KBr, cm^{-1}): 3447, 3369, 1718, 1652, 1550, 1506, 1495, 1264, 1058, 817; ^1H NMR (200 MHz, $CDCl_3$): δ 6.80–6.76 (d, 1H, J=8.4 Hz), 6.74–6.70 (d, 1H, J=8.4 Hz), 4.46–4.35 (q, 2H, J=7.0 Hz), 3.80 (s, 3H), 2.20 (s, 3H), 1.42–1.35 (t, 3H, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 167.9, 143.4, 137.4, 128.1, 125.6, 124.2, 116.7, 60.6, 60.0, 17.8, 13.7.

5.5.35. Ethyl 3-amino-2-hydroxy-6-methylbenzoate (49). A mixture of nitro compound **46** (250 mg, 1.04 mmol), $SnCl_2\cdot 2H_2O$ (1.17 g, 5.18 mmol), and ethanol (8 mL) was heated at 70 °C for 1 h. After the reaction was cooled to room temperature, 10% aq NaOH was added until the mixture became strongly alkaline. Extraction of the mixture with ethyl acetate (15 mL) followed by usual work-up yielded, after column chromatographic separation, amino phenol **49** as a colorless liquid in 19% yield along with amine **48** in 45% yield. ν_{max} (KBr, cm^{-1}): 3457, 3376, 1723, 1655, 1598, 1451, 1291, 1261, 1189, 1026, 799, 758; ^1H NMR (200 MHz, $CDCl_3$): δ 11.61 (br s, 1H), 6.78 (d, 1H, J= 8.1 Hz), 6.56 (d, 1H, J=8.1 Hz), 4.43 (q, 2H, J=7.2 Hz), 3.80 (s, 3H), 2.83 (br s, 2H), 1.42 (t, 3H, J=7.2 Hz).

5.5.36. Ethyl 3-ethoxyamino-2-methoxy-6-methylbenzoate (50). This was obtained as a co-product during the reduction of nitro compound **46** by hydrogenation over 10% Pd–C in ethanol. Reddish liquid. Yield: 18%; ν_{max} (KBr, cm^{-1}): 3401 (br s), 1728, 1608, 1504, 1456, 1329, 1265, 1118, 1062, 802; ^1H NMR (200 MHz, $CDCl_3$): δ 6.83 (d, 1H, J=8.2 Hz), 6.31 (d, 1H, J=8.2 Hz), 4.40 (q, 2H, J=7.1 Hz), 3.80 (s, 3H), 3.14 (q, 2H, J=7.1 Hz), 2.20 (s, 3H), 1.38 (t, 3H, J=7.1 Hz), 1.25 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$,): 168.3, 149.4, 143.6, 139.5, 127.9, 126.1, 122.7, 112.2, 60.9, 60.7, 38.2, 18.2, 14.7, 14.1.

5.5.37. Ethyl 3-fluoro-2-methoxy-6-methylbenzoate (52). Amine **48** (210 mg, 1.0 mmol) was dissolved in a mixture of concd HCl (2 mL) and water (5 mL). The solution was cooled and held at the range of 0 to −10 °C. Diazotization was done by dropwise addition of an aq solution of $NaNO_2$ (80 mg, 1.16 mmol) dissolved in water. While this solution was still cold, 65% aq HPF_6 (0.2 mL) was added rapidly in one portion with the help of plastic disposal syringe. The mixture was cooled again to 0–5 °C before filtration. The phosphorous hexafluoride salt **51** was collected by filtration, washed with cold water followed by a 4:1 mixture of diethyl ether, and MeOH to facilitate drying. The solid was powdered and dried in vacuum overnight. Decomposition of phosphorous hexafluoride salt **51** was carried out by portionwise addition through the condenser fitted with a flask held at decomposition temperature at 120–125 °C. After the decomposition was complete, the residue was extracted with ethyl acetate (20 mL) and worked up in the

usual manner to furnish the crude product. The crude product was purified by column chromatography (ethyl acetate–petroleum ether, 1:15) to give **52** as a colorless liquid. Yield: 19%; ν_{max} (KBr, cm^{-1}): 1731, 1608, 1490, 1417, 1276, 1133, 1066, 1020, 958, 813; ^1H NMR (200 MHz, $CDCl_3$): δ 7.00 (dd, 1H, J=8.5 and 11.2 Hz), 6.83 (dd, 1H, J=5.1 and 8.5 Hz), 4.39 (q, 2H, J=7.1 Hz), 3.93 (d, 3H, J=1.8 Hz), 2.25 (s, 3H), 1.38 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 167.0 (d, J=3.5 Hz), 153.3 (d, J=244 Hz), 144.5 (d, J=12.3 Hz), 131.4 (d, J=3.6 Hz), 129.6, 125.2 (d, J=6.7 Hz), 117.5 (d, J=18.9 Hz), 61.8 (d, J=5.6 Hz), 61.3, 18.6, 14.2.

5.5.38. Ethyl 6-dibromomethyl-3-fluoro-2-methoxybenzoate (53). This compound was prepared from **52** using 2 equiv of NBS following the procedure described for the preparation of compound **40** from **39**. Colorless liquid. Yield: 57%; ν_{max} (KBr, cm^{-1}): 1723, 1458, 1266, 935, 703; ^1H NMR (200 MHz, $CDCl_3$): δ 7.71 (dd, 1H, J=4.5 and 9.0 Hz), 7.31 (dd, 1H, J=9.0 and 15.3 Hz), 6.79 (s, 1H), 4.45 (q, 2H, J=6.9 Hz), 3.96 (d, 3H, J=1.9 Hz), 1.42 (t, 3H, J=6.9 Hz).

5.5.39. 6-Fluoro-3-hydroxy-7-methoxy-3*H*-isobenzofuran-1-one (54). This compound was prepared from the dibromo compound **53** following the procedure described for the synthesis of compound **41** from **40**. White crystalline solid. Yield: 75%; mp: 131 °C; ν_{max} (KBr, cm^{-1}): 3352, 1731, 1503, 1426, 1294, 1261, 1139, 1108, 1057, 1031, 908, 839, 772, 732; ^1H NMR (200 MHz, $CDCl_3$): δ 7.42 (dd, 1H, J=8.2 and 11.6 Hz), 7.20 (dd, 1H, J=3.5 and 8.2 Hz), 6.50 (s, 1H), 4.20 (d, 3H, J=2.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 165.4, 154.7 (d, J=247 Hz), 145.8 (d, J=11.5 Hz), 142.4, 123.3 (d, J=21.6 Hz), 119.2, 117.3 (d, J=8.1 Hz), 96.4, 62.0 (d, J=4.9 Hz); HRMS m/z (ESI) calcd for $C_9H_7FO_4$ (M^++H): 199.0407; found: 199.0406.

5.5.40. 3-Cyano-6-fluoro-7-methoxy-3*H*-isobenzofuran-1-one (55). This compound was prepared from the phthalaldehydic acid **54** according to the procedure adopted for the preparation of chlorocyanophthalide **3a** from **41**. White crystalline solid. Yield: 83%; mp: 104–105 °C; ν_{max} (KBr, cm^{-1}): 1789, 1603, 1501, 1291, 1255, 1087, 1022, 971, 925; ^1H NMR (200 MHz, $CDCl_3$): δ 7.53 (dd, 1H, J=8.3 and 11.7 Hz), 7.24 (dd, 1H, J=8.3 and 8.5 Hz), 5.98 (d, 1H, J=0.7 Hz), 4.24 (d, 3H, J=3.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 159.1, 151.5 (d, J=250 Hz), 146.3 (d, J=11.8 Hz), 137.3, 124.1 (d, J=22.6 Hz), 111.5, 111.3 (d, J=8.1 Hz), 108.6, 59.5, 57.4 (d, J=6.0 Hz); HRMS m/z (ESI) calcd for $C_{10}H_6FNO_3$ (M^++H): 208.0410; found: 208.0405.

5.5.41. Methyl 9-fluoro-6-hydroxy-8-methoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione-2-carboxylate (56). This compound was prepared by annulation of 6-fluoro-7-methoxycyanophthalide (**55**) with Michael acceptor **4** following the general procedure in Section 5.2. Orange solid. Yield: 74%; mp: 153–54 °C; ν_{max} (KBr, cm^{-1}): 3432, 1731, 1631, 1572, 1449, 1411, 1327, 1262, 1102, 1017, 796; ^1H NMR (200 MHz, $CDCl_3$): δ 13.02 (s, 1H), 8.02 (dd, 1H, J=5.0 and 8.7 Hz), 7.45 (dd, 1H, J=8.8 and 10.1 Hz), 7.06 (s, 1H), 4.08 (d, 3H, J=1.3 Hz), 3.74 (s, 3H), 3.60 (dd, 1H, J=5.3 and 18.2 Hz), 3.30 (dd, 1H, J=9.5 and 18.2 Hz), 2.97–2.89 (m, 2H), 2.76–2.68 (m, 1H), 2.21–2.12 (m, 1H), 1.98–1.90 (m, 1H); HRMS m/z (ESI) calcd for $C_{21}H_{17}FO_6$ (M^++H): 385.1087; found: 385.1057.

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References and notes

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