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Total Synthesis of Chlorocyclinone A, a PPAR-γ Antagonist

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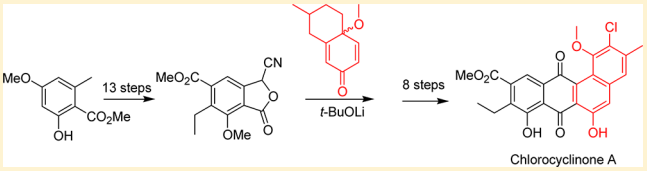
Supporting Information

ABSTRACT: The first total synthesis of chlorocyclinone A (**1**) is regioselectively completed in 28 steps. The key steps are Pd-catalyzed methoxycarbonylation, unprecedented Hauser annulation, Krohn photo-oxidation, and regioselective *gem*-dichlorination.



INTRODUCTION

The angucycline family of antibiotics, characterized as benz[*a*]anthraquinone derivatives, has been the subject of growing interest due to the wide range of their structures and biological activities.[1] In 2007, four new chlorinated members, namely chlorocyclinones A−D (**1**−**4**, Figure 1), were isolated from a broth culture of *Streptomyces sp.* (DSM 17045) by Potterat and co-workers and their structures were elucidated by spectroscopic methods.[2] Seven different substituents/functionalities including chlorine at C2, similar to that of the antitumor antibiotic BE-45985A$_1$ (**5**),[3] have featured this unique group of angucyclines. Each of the chlorocyclinones (**1**−**4**), the first PPAR-γ antagonists of natural origin, has been reported to antagonize rosiglitazone-induced PPAR-γ activity with IC$_{50}$ values between 0.60 and 7.0 μM, thus implying therapeutic potential in antidiabetic therapies, especially for the treatment of type II diabetes. The combination of the structural novelty and the unique PPAR-γ activity of the molecules prompted us to undertake their total synthesis. Although the synthesis of angucyclines, in general, is an active area of research,[4] that of chlorocyclinones has not so far been reported.[5]

The primary challenge of the synthesis of such molecules is regioselective assembly of the peripheral substituents/functionalities with concomitant fabrication of the skeletal features. In continuation of our work on the application of Hauser annulation[6] toward the total synthesis[7a,b] of angucycline natural products, we undertook the project of the total synthesis of chlorocyclinone A−D (**1**−**4**). The major impetus for choosing the annulation was its regiochemical integrity and high chemoselectivity. Since the structural attributes of A, B, and C rings are identical for all the members **1**−**4**, we proposed Hauser donor **6** (Scheme 1) as the common intermediate for the synthesis of chlorocyclinone A (**1**). It can be annulated with cyclohexenone carboxylate **7** to furnish tetracyclic angular quinol **8**, which, in turn, can be aromatized to the advanced intermediate **9** having all requisite functionalities.

RESULTS AND DISCUSSION

Although the Hauser chemistry of such angular phthalides (e.g., **6**) is unprecedented, the earlier studies with linear phthalides suggested the sure success of the outlined scheme (Scheme 1). Yet, an annulation study on the model angular phthalide **10** was initially conducted. Synthesis of the phthalide **10** was developed in nine steps (Scheme 2), starting from commercially available 6-hydroxytetralin (**11**) via carboxylation and *ortho*-lithiation followed by phenylsulfanylation. Following the literature procedure,[8] 6-hydroxytetralin-7-carboxylic acid (**12**)[8] was prepared in two steps from **11**. The ^{1}H and ^{13}C NMR data of **12** are in good agreement with the reported values. The resulting hydroxy acid **12** was then converted into corresponding amide **13**[9] in 72% yield (over three steps). The sequence consisted of (i) Me_2SO_4, K_2CO_3 mediated esterification to furnish **14**,[10] (ii) ester hydrolysis to give acid **15**,[8] and (iii) amidation of the resulting acid **15** by treatment with oxalyl chloride followed by diethylamine. Directed *ortho*-metalation[11] of the amide **13** with *t*-BuLi, TMEDA, and DMF provided aldehyde **16** (55%). This was then converted into angular phthalaldehydic acid **17** in 85% yield by acid catalyzed hydrolysis. Treatment of **17** with thiophenol and a catalytic amount of *p*-TSA in refluxing benzene gave angular phthalide **18**. Regioselective benzylic oxidation[12] of **18** with $K_2S_2O_8$−$CuSO_4{\cdot}5H_2O$ in CH_3CN−H_2O produced the desired 3-substituted angular phthalide **10** in 78% yield.

An attempted Hauser annulation of the phthalide **10** with 2-cyclohexenone in the presence of *t*-BuOLi, *t*-BuOK, or LDA at −78 °C resulted in recovery of the starting phthalide (Scheme 3). The desired Hauser product (*cf.* **8**) was not formed. However, angular phthalide **18** underwent reaction with 2-cyclohexenone under the above conditions to yield conjugate addition product **19a** in good yield (67%). Unfortunately its transformation to the desired annulation product **20a** under treatment with *t*-BuOLi−THF, NaOEt−EtOH, or *t*-BuOK/$Na_2S_2O_4$−THF at −78 °C (Scheme 3) could not be effected. Similarly, annulation of methyl acrylate with phthalide **18** in the presence of *t*-BuOLi−THF at −78 °C, as a test case, also produced corresponding 1,4-addition product **21** (82%, Figure 2), while that of phthalide **18** with **22** (Figure 2) yielded an intractable mixture of products.

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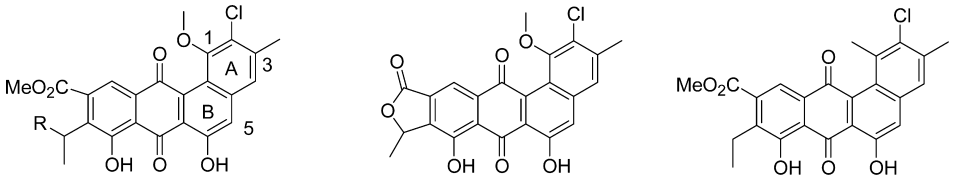
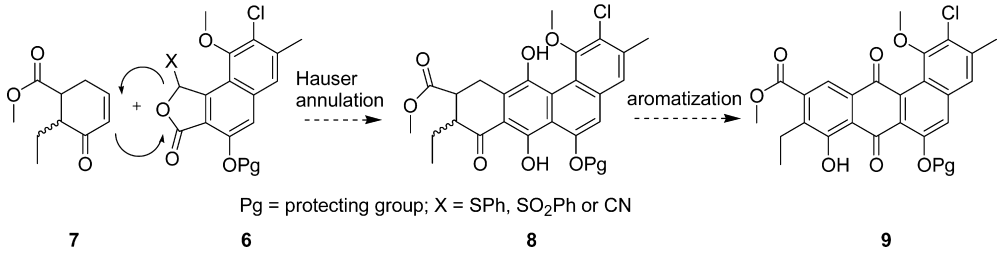
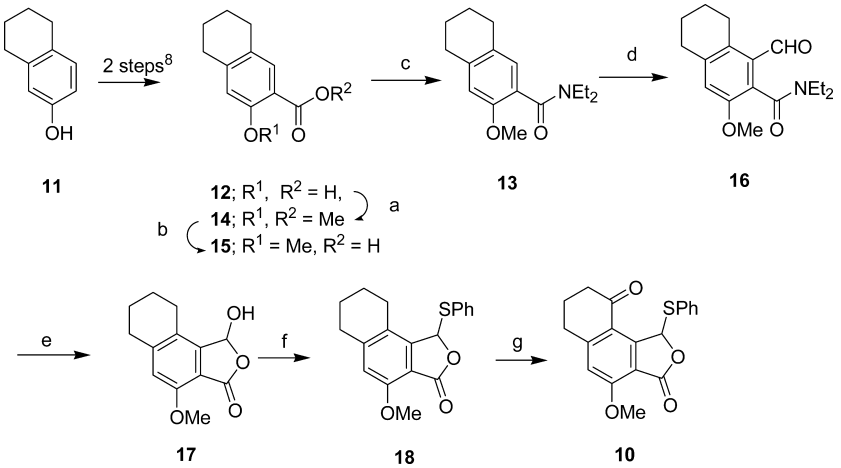


Figure 1. Structures of A-ring chlorinated angucyclinones.

Scheme 1. First Approach: Hauser Reactivity of Angular Phthalides

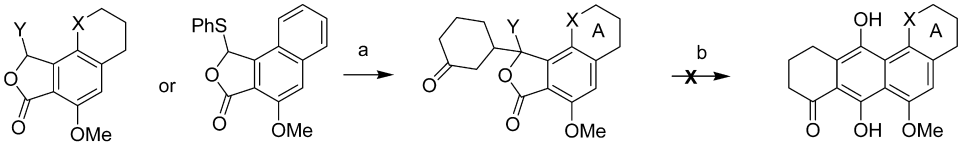


Scheme 2. Synthesis of Angular Phthalides 10 and 18[a]



[a]Reagents and conditions: (a) Me_2SO_4, K_2CO_3, acetone, reflux, 3 h, 90%; (b) 5% aq KOH solution, reflux, 0.5 h, 82%; (c) (i) oxalyl chloride, DMF (cat.), dry C_6H_6, 65 °C, 2 h and (ii) Et_2NH, dry THF, 0 °C–rt, 15 min, 98%; (d) *t*-BuLi, TMEDA, DMF, dry THF, N_2 atm, −78 °C–rt, overnight, 59%; (e) glacial AcOH, aq HCl, reflux, 10 h, 85%; (f) PhSH, *p*-TSA (cat.), dry C_6H_6, reflux, 10 h, 70%; (g) $K_2S_2O_8$, $CuSO_4{\cdot}5H_2O$, $CH_3CN–H_2O$ (1:1), reflux, 20 min, 78%.

Scheme 3. Results on the Hauser Chemistry of Angular Phthalides[a]



[a]Reagents and conditions: (a) *t*-BuOLi, *t*-BuOK or LDA or LiHMDS, 2-cyclohexenone, THF, −78–60 °C. (b) *t*-BuOLi, THF or NaOEt, EtOH, etc.

The unanticipated failed annulations prompted us to examine the reactivity of a few modified angular phthalides, e.g. **23**–**25** (Scheme 4), toward Hauser annulation. Oxidation of **18** with *m*-CPBA in CH_2Cl_2 furnished corresponding sulfone phthalide **23** in 91% yield. DDQ mediated dehydrogenation of **18** produced aromatized phthalide **24** in moderate yield (55%). For the synthesis of cyanophthalide **25**, compound **17** was treated with KCN and conc. HCl followed by Vilsmeier's salt or

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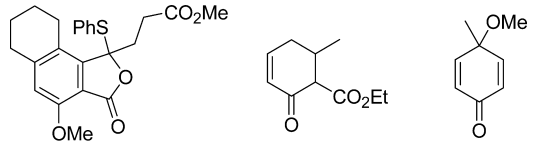


Figure 2. Michael acceptors and 1,4-addition product.

NaCN−AcOH, but to no avail. After several experimentations, the desired 3-cyanophthalide **25** was obtained in 95% yield by treatment of formamide **16** with trimethylsilyl cyanide in the presence of a catalytic amount of potassium cyanide and 18-crown-6.[13]

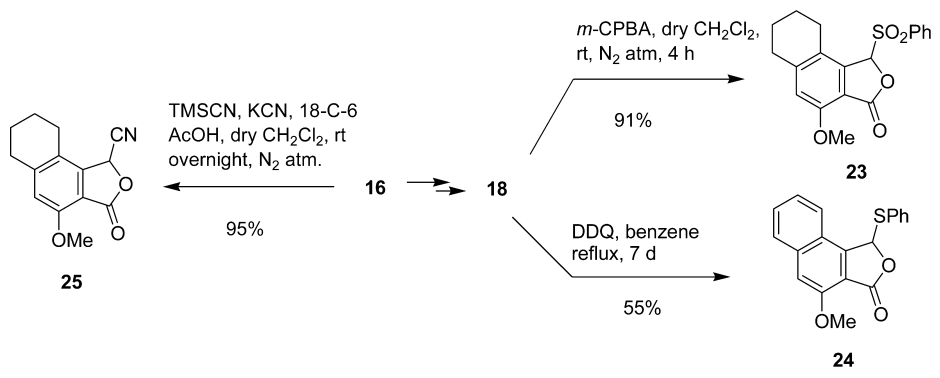
Once again, to our dismay, angular phthalides **23** and **24** failed to produce annulation products, when subjected to a reaction with 2-cyclohexenone under varied reaction conditions (*t*-BuOLi, LDA or LiHMDS in THF at −78−60 °C). In both cases, the corresponding 1,4-addition products, i.e. **19b** (5%) and **19d** (80%), were respectively obtained (Scheme 3). When 3-cyanophthalide **25** was treated with 2-cyclohexenone in the presence of *t*-BuOLi, K^{t}OBu or LDA in dry THF at −78 °C or *t*-BuOK-DMSO at rt, a complex mixture of products was obtained. The presence of the corresponding 1,4-addition product **19c** was indicated from analysis of the ^{1}H NMR spectrum of the crude reaction mixture.

Anticipating that 2-cyclohexenone might undergo base-catalyzed polymerization, we investigated a base-stable Michael acceptor, i.e., **26** (Figure 2). Its reaction with cyanophthalide **25** in the presence of *t*-BuOLi in dry THF at −78 °C again furnished an intractable mixture of products.

The exceptional failures of the Hauser annulation of angular phthalides **10**, **23**, **24**, and **25** compelled us to formulate the sequence (Scheme 5) involving annulation of phthalide **27** with napthalenone **28**[7b] and the directed *ortho*-metalation[14] or Yu lactonization[15] of the tetracyclic carboxylic acid **29**. The structure **29** was envisaged as the common intermediate on account of the fact that the structural diversity of the target chlorocyclinones (**1**−**4**) emanates from C9.

The intermediate **29** was synthesized in 22 steps from commercially available chemicals (Scheme 6). Base catalyzed condensation of methyl acetoacetate with methyl crotonate produced compound **30**.[16] $Hg(OAc)_2$[17] mediated aromatization and Tf_2O-lutidine[18] promoted selective triflation afforded known compounds **31**[19] (73%) and **32**[20] (87%) respectively. *O*-Methylation of **32** with MeI−K_2CO_3 furnished toluate **33** in excellent yield. Methoxycarbonylation[20] of the triflate **33** with CO, dry MeOH, dppf, Et_3N, and $Pd(OAc)_2$ catalyst in DMF at 90−120 °C afforded compound **34** in 48% yield (Scheme 6). Before undertaking the synthesis of required phthalide **27** from diester **34**, its bromination at C3 was attempted using Br_2−AcOH, with the idea that a late stage coupling reaction through Stille, Suzuki, and Negishi cross-coupling would introduce vinyl or ethyl side chains at C9 of the targets. But, unfortunately, the undesired bromoterephthalate **35** was obtained. The site of the bromine atom at C2 was established by NOESY experiment.[21] The terephthalate **34** was converted into cyanoisobenzofuranone **27** in four steps: benzylic bromination followed by thermal cyclization,[22] selective lateral bromination, hydrolysis, and hydrocyanation via lactone **36** and 3-bromoisobenzofuranone **37**, with an overall yield of 34%. During hydrolysis of **37**, the temperature of H_2O was maintained at 80−85 °C to obtain **38** solely or to obviate C5 ester hydrolyzed product **39**, as indicated in the ^{1}H NMR spectrum. The AB ring synthon **28**[7b] was obtained in five known steps. Annulation of phthalide **27** with acceptor **28** in the presence of LDA gave a very low yield of **40** along with the starting materials. But, in the presence of *t*-BuOLi at −78 °C, the benzanthraquinone **40** was obtained in 71% yield. Krohn photo-oxidation[23] of **40** under sunlight provided keto derivative **41** in quantitative yield. After several experimentations, monochlorination[24] of **41** at C2 could be achieved using *N*-chlorosuccinimide and a catalytic amount of thiourea in MeOH−$CHCl_3$, yielding **42** as a mixture of diastereomers in 65% yield. Aromatization of the 2-chlorotetracyclic compound **42** by the Saegusa method[25] and DDQ[25] mediated oxidation posed serious problems. Consequently, the *ortho*-chloro phenolic A-ring motif was thought to be fabricated by *gem*-α-dichlorination of **43**, followed by aromatization via dehydrochlorination. The inverse sequence, i.e., aromatization of **43** followed by chlorination at C2, was avoided due to the anticipated problems in selectivities.[26] After brief experimentations, *O*-methyl ether **43** was *gem*-α-dichlorinated by the application of the Prugh method[27] using SO_2Cl_2 and dry HCl gas to form **44** in 85% yield. Dehydrohalogenation[28] of **44** with NaOMe in refluxing methanol gave A-ring aromatized product **45** in 94% yield, the C1-OH and C10-CO_2H protection of which yielded compound **46** in 81% yield. Hydrolysis of the ester group of **46** with LiOH (19 equiv) furnished 2-chlorotetracyclic intermediate **29** in 89% yield with A−C ring substituents in desired positions. Although the proposed Hauser annulation, i.e. **27**→**40**, was successful this time (Scheme 6), the projected directed *ortho*-metalation and Yu cyclization of **29** at the C9 position failed.[29] In analogy with Mortier's work,[14] several attempts were made to install an ethyl

Scheme 4. Synthesis of Angular Phthalide Derivatives



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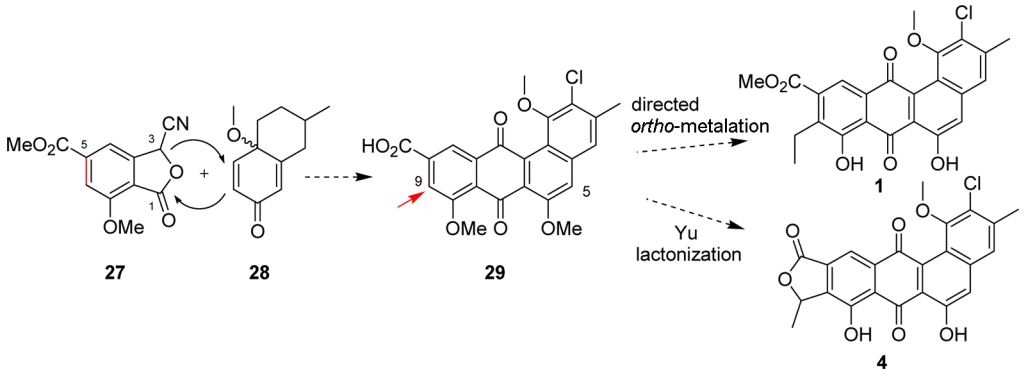
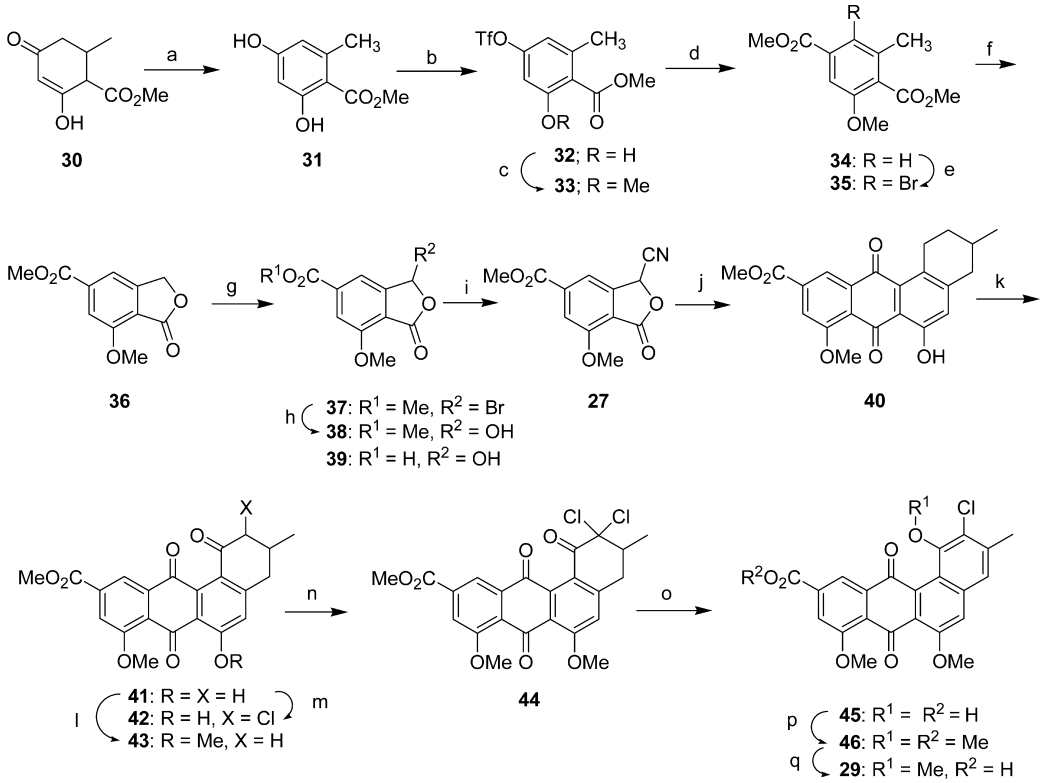
Scheme 5. Second Approach: Annulation of Linear Phthalide Combined with Directed *ortho*-Metalation or Yu Lactonization



Scheme 6. Synthesis of Tetracyclic Chlorocyclinone 29[a]



[a]Reagents and conditions: (a) $Hg(OAc)_2$, NaOAc, AcOH, reflux, 2 h, 82%; (b) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C−rt, N_2 atm, 18 h, 70%; (c) MeI, K_2CO_3, acetone, 0 °C−rt, 96%; (d) CO, MeOH, Et_3N, dppf, $Pd(OAc)_2$, DMF, 90−120 °C, 48%; (e) Br_2−AcOH, rt, 70%; (f) (i) NBS, AIBN, CCl_4, hν, reflux and (ii) 150−160 °C, 30 min, 69% (2 steps); (g) NBS, AIBN, CCl_4−C_6H_6, hν, reflux, 70%; (h) H_2O, 80 °C, 90%; (i) KCN, conc. HCl, 0 °C−rt, 71%; (j) **28**, *t*-BuOLi, THF, N_2 atm, −78 °C−rt; 71%; (k) $CHCl_3$, sunlight, 5−6 h, quantitative yield; (l) MeI, K_2CO_3, acetone, 0 °C−rt, 87%; (m) NCS, thiourea (cat.), MeOH−$CHCl_3$, rt, 65%; (n) SO_2Cl_2, dry HCl, $CHCl_3$, rt, 85%; (o) NaOMe, MeOH, reflux, 94%; (p) MeI, K_2CO_3, acetone, 0 °C−rt, 81%; (q) LiOH, THF−H_2O (5:1), rt, 4 h, 89%. dppf: 1,1-diphenylphosphinoferrocene; LTMP: Lithium tetramethylpiperidide; TMP: 2,2,6,6-tetramethylpiperidine; TMEDA: tetramethylethylenediamine; NCS: *N*-chlorosuccinimide.

group at C9 of tetracyclic acid **29**. Lithiation with LTMP (*n*-BuLi + TMP) followed by treatment with EtI in THF at −30 to 60 °C failed to give the desired product. The model reaction of 4-methoxy-9,10-anthraquinone-2-carboxylic acid amide with *t*-BuLi, TMEDA, and EtI at −78 °C in THF returned only the starting material. Nevertheless, Scheme 6 paved the way for the standardization of A-ring chemistry, especially the introduction of C1 methoxy and C2 chlorine.

In the revised approach, annulation of isobenzofuranone **47** was investigated, which differs from **27** with respect to an ethyl substituent at C6. Its synthesis began with Friedel−Crafts acylation[30] of **48**[31] in the presence of $TiCl_4$ to provide heavily substituted benzene derivative **49** in 75% yield (Scheme 7). To achieve selectivity in bromination, compound **49** was converted into its acetate **50**. NBS bromination of **50** followed by thermolysis[22] followed by deacetylation of **51** provided compound **52** (52% over two steps). The sequence involving (i) reduction[32] of the acyl carbonyl in **52** with trifluoroacetic acid and triethylsilane, (ii) BBr_3-mediated demethylation of **53**,[33] and (iii) selective protection[20] leading to activation of phenolic OH group of **54** using *N*-phenyltriflimide and Cs_2CO_3 at 10−15 °C, followed by *O*-methylation of ensuing triflate **55**,

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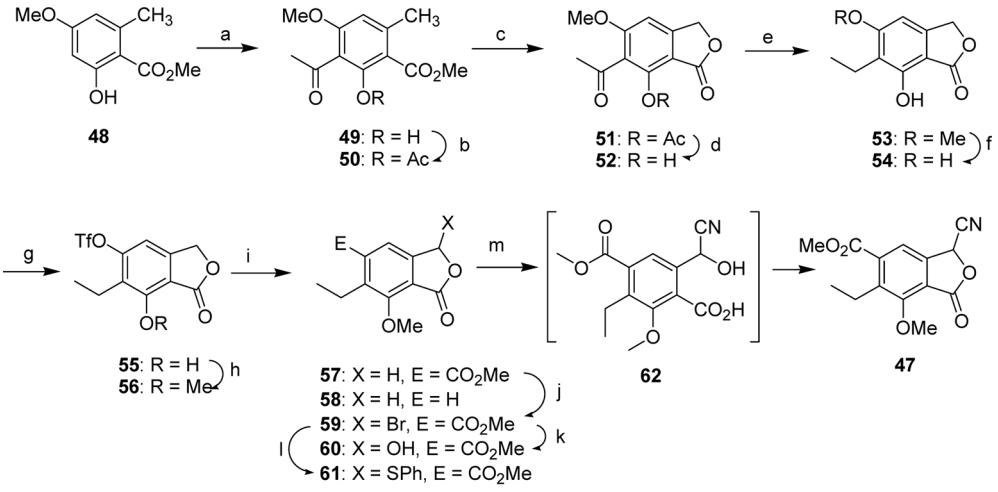
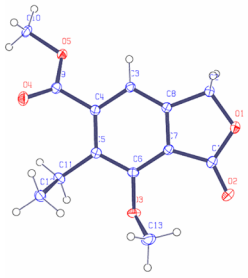
Scheme 7. Synthesis of Isobenzofuranone 47[a]

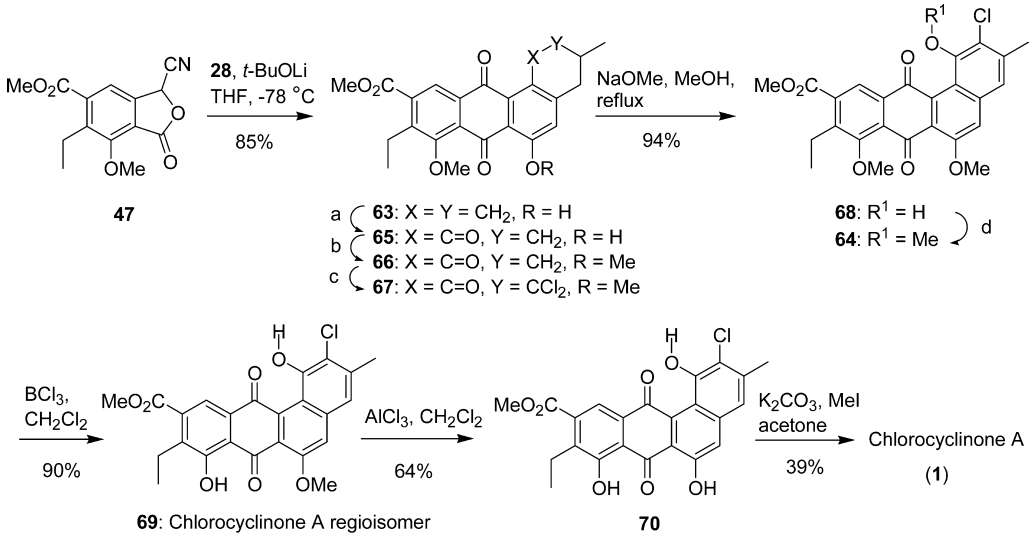




ORTEP view of **57**

[a]Reagents and conditions: (a) $TiCl_4$, CH_3COCl, CH_2Cl_2, 0 °C–rt, 75%; (b) CH_3COCl, Et_3N, CH_2Cl_2, 0 °C–rt, 96%; (c) (i) NBS, $(PhCO)_2O_2$, CCl_4, hν, reflux and (ii) 150–160 °C, 63% (2 steps); (d) MeOH, K_2CO_3, 0 °C–rt, 83%; (e) TFA, Et_3SiH, rt, 87%; (f) BBr_3, CH_2Cl_2, 0 °C–rt, 86%; (g) $PhNTf_2$, Cs_2CO_3, acetone, 0–15 °C, 66%; (h) MeI, K_2CO_3, acetone, 0 °C–rt, 100%; (i) CO, $Pd(OAc)_2$, dppf, MeOH, Et_3N, DMF, 90–120 °C, 50%; (j) NBS, AIBN, CCl_4, hν, reflux, 58%; (k) H_2O, 80 °C, 95%; (l) PhSH, Et_3N, CH_2Cl_2, rt, 6 h, 74%; (m) (i) KCN, conc. HCl, 0 °C–rt and (ii) *p*-TSA (cat.), $CHCl_3$, rt, 71%. TFA: trifluoroacetic acid; AIBN: azobisisobutylonitrile.

Scheme 8. Successful Synthesis of Chlorocyclinone A (1)[a]



[a]Reagents and conditions: (a) $CHCl_3$, sunlight, quantitative; (b) MeI, K_2CO_3, acetone, 0 °C–rt, 88%; (c) SO_2Cl_2, dry HCl gas, $CHCl_3$, rt, 94%; (d) MeI, K_2CO_3, acetone, 0 °C–rt, 65%.

produced compound **56** (49% over four steps). During selective *O*-triflation, the low temperature was crucial to avoiding ditriflation[34] of **54** and thus low overall yield. Pd-catalyzed methoxycarbonylation[20] of the triflate **56** with carbon monoxide afforded ester **57** (50%) along with 6-ethyl-7-methoxy-3*H*-isobenzofuran-1-one (**58**) as a side product (10%). The structure of **57** was confirmed by an X-ray crystallographic analysis.[21] NBS mediated bromination of

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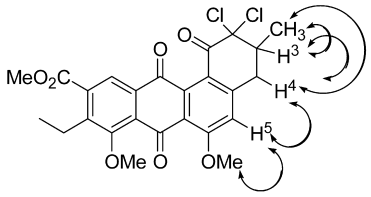
Table 1. Key NOESY Interaction of 67 and HMBC Correlations of 69[a]

NOESY interaction of **67**



HMBC correlations of **69**

H-4	C2 (s, 123.3), C5 (s, 117.5), C13 (s, 21.0)
H-5	C4 (s, 120.6), C6a (s, 127.2), C12b (s, 117.3)
H-11	C7a (s, 115.8), C9 (s, 143.4), C12 (s, 188.7), C16 (s, 166.8)
H3-13	C2 (2, 123.3), C3 (s, 141.1), C4(s, 120.6)
H2-14	C8 (s, 160.4), C9 (s, 143.4), C10 (s, 135.2), C15 (s, 14.1)
H3-15	C9 (s, 143.4), C14 (s, 21.4)
OH-1	C1(s, 150.5), C2 (s, 123.3)
OCH3-16	C16 (s, 166.8)
OCH3-6	C6 (s, 156.0)
OH-8	C7a (s, 115.8), C8 (s, 160.4), C9 (s, 143.4)

[a]s: strong $^{1}H-^{13}C$ HMBC interaction.

phthalide **57** in refluxing CCl_4 under light (100 W) selectively produced **59** in 58% yield as the sole product. The resulting 3-bromophthalide **59** was carefully heated in water at 80 °C (to avoid C5 ester hydrolysis) to obtain acid **60** in 95% yield. Compound **59**, when treated with thiophenol and Et_3N, furnished corresponding 3-SPh phthalide **61** in 74% yield. Treatment of the compound **60** with KCN in an acidic medium at 0 °C resulted in the corresponding cyanohydrin **62**, which underwent lactonization to the desired cyanophthalide **47** in 71% yield, upon standing overnight at rt in chloroform solvent containing a catalytic amount of *p*-TSA.

Next, we explored the competition between the Hauser annulation and Staunton–Weinreb annulation[35] of isobenzofuranone **47** under the influence of a base weaker than LDA, which is known to effect both of the annulations. When cyanophthalide **47** and napthalenone **28** were submitted to annulation (Scheme 8) in the presence of *t*-BuOLi at −78 °C, tetracycle **63** was formed as the sole product (85%). There was no sign of a Staunton–Weinreb product, i.e., a Michael–Claisen product arising from lithiation of the ethyl chain of **47**. It should be noted that sulfanylphthalide **61** failed to provide annulation product **63**, when treated with napthalenone **28** under similar conditons. Then intermediate **64** was regioselectively prepared in five steps from **63** (Scheme 8). As earlier, compound **63** was selectively oxidized to keto compound **65** in quantitative yield under Krohn conditions.[23] In a similar manner as described for **41**→**46**, compound **65** was converted to **64** via **66**–**68**, the chlorocyclinone A methyl diether, having all the groups in desired positions, with an overall yield of 51% (four steps).

The site of the chlorine atoms in **67** was ascertained by NOE studies.[21] The cross peaks due to NOE interaction between H^4 and H^5 confirm the location of two chlorine atoms at the C2 position and not at C4 (Table 1). The $^{1}H-^{13}C$ HMBC[21] studies of **68** again support its structural arrangement. Finally, we attempted the selective demethylation of the C6 and C8 OMe group of **64** to complete the total synthesis. $AlCl_3$, a well-known reagent for selective demethylations,[36] was employed to meet this purpose. But, to our dismay, the reaction resulted in a complex mixture of products. BBr_3-mediated demethylation at −78 °C was unsuccessful. Treatment of **64** or **68** with BCl_3 in CH_2Cl_2 at −78 °C produced a compound with two H-bonded phenolic OH groups (δ 12.72 and 10.80 respectively) in excellent yield (90%), which is confirmed as **69** by analysis of HMBC[21] and HSQC spectral data (Table 1). With selective demethylation being abortive at the final step, selective methylation was perceived to be applied. For the preparation of the required trihydroxy compound **70**, compound **69** was treated with a large excess of $AlCl_3$ (40 equiv) in CH_2Cl_2 to furnish the trihydroxy compound **70** in 64% yield, which was strikingly unstable, apparently due to its susceptibility toward oxidation. The resulting crude compound **70** was immediately subjected to methylation using MeI–K_2CO_3 in acetone and the chlorocyclinone A (**1**) was obtained in 39% yield. The spectral data of the synthetic **1** are in good agreement with the reported values.[2]

CONCLUSIONS

In conclusion, the first total synthesis of chlorocyclinone A (**1**) has been achieved in 28 steps from commercially available starting materials. This study also has resulted in two methyl ethers, namely, **64** and **69**. Although selective demethylation of **64** remains a factual challenge, selective methylation of the phenolic OH group is found to be more convenient than selective *O*-demethylation.

EXPERIMENTAL SECTION

General. All reactions utilizing moisture-sensitive reagents were performed under an inert atmosphere. Solvents DMF, CH_2Cl_2, THF, MeOH, etc. were dried prior to use, according to the standard protocols. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60-F254). All solvents for chromatography were distilled prior to use. The products were purified by column chromatography on silica gel. Columns were prepared with silica gel (60–120 or 230–400 mesh). NMR spectra were recorded with a 400 MHz (^{1}H: 400 MHz, ^{13}C: 100 MHz) and 200 MHz (^{1}H: 200 MHz, ^{13}C: 50 MHz) spectrometer and referenced to the signal of $CHCl_3$ at 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C) for $CDCl_3$. Another solvent used for recording NMR data was d_6-DMSO. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet. Infrared spectra were recorded with FT-IR spectrophotometers and reported as wavenumbers (cm^{-1}). Melting points are uncorrected. High-resolution mass spectra were recorded with a mass spectrometer in positive ion mode. The phrase "usual workup" refers to washing of the organic phase with water (2 × 1/4 the volume of organic phase) and brine (1 × 1/4 the volume of organic phase) and drying (Na_2SO_4), filtration, and concentration under reduced pressure. Solvents used for the column chromatography are ethyl acetate and petroleum ether. Due to partial decomposition under thermal conditions, HRMS data of compounds **37**, **59**, **62**, and **70** could not satisfactorily be recorded. All the known compounds were characterized by matching with the ^{1}H NMR data reported in the literature.

***N,N*-Diethyl-3-methoxy-5,6,7,8-tetrahydronaphthalene-2-carboxamide (13).**[9] To a stirred solution of **15** (2.4 g, 0.011 mol) in dry benzene (80 mL) were added oxalyl chloride (5.08 mL, 0.058 mol) and a catalytic amount of DMF (0.24 mL), and the reaction mixture was heated at 65 °C under a N_2 atmosphere for 2 h. Benzene was removed under reduced pressure and dried, and then the crude residue was dissolved in dry THF (80 mL). To the resultant mixture Et_2NH (3.65 mL, 0.035 mol) was added dropwise at 0 °C in a N_2 atmosphere and stirred for 15 min at the same temperature. Solvent

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was evaporated under reduced pressure, and the residue was diluted with water (30 mL) and dichlomethane (100 mL). The layers were separated, and the aqueous part was extracted with CH_2Cl_2 (3 × 100 mL). The combined layers were worked up in the usual manner. The crude residue was purified by column chromatography (50% ethyl acetate−petroleum ether) on silica gel to afford compound **13** (2.97 g, 98%) as a yellowish solid. R_f = 0.3 (30% ethyl acetate−petroleum ether); mp 58−60 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.84 (s, 1H), 6.54 (s, 1H), 3.73 (s, 3H), 3.52 (q, 2H, J = 7.2 Hz), 3.15 (q, 2H, J = 7.2 Hz), 2.73−2.63 (m, 4H), 1.76−1.70 (m, 4H), 1.20 (t, 3H, J = 7.1 Hz), 1.01 (t, 3H, J = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.3, 152.9, 138.8, 129.3, 127.9 (*C*H), 124.4, 111.3 (CH), 55.6 (OCH_3), 42.9 (CH_2), 38.8 (CH_2), 29.8 (CH_2), 28.4 (CH_2), 23.3 (CH_2), 23.0 (CH_2), 13.9, 12.9.

***N*,*N*-Diethyl-1-formyl-3-methoxy-5,6,7,8-tetrahydronaphthalene-2-carboxamide (16).** To a stirred solution of **13** (2 g, 0.007 mol) in dry THF (80 mL) was added TMEDA (6.9 mL, 0.046 mol) at rt, and then the reaction mixture was cooled to −78 °C. To the reaction mixture, *t*-BuLi (1.7 M) (27 mL, 0.046 mol) was added dropwise in an inert atmosphere with the same temperature maintained for 45 min. To the cooled solution DMF (4.7 mL, 0.061 mol) was added dropwise and allowed to stir at rt for 12 h. The reaction mixture was quenched with a few drops of water, THF was evaporated, and the crude residue was diluted with water (60 mL) and diethyl ether (150 mL). The layers were separated, and the aqueous part was extracted with diethyl ether (3 × 150 mL). The combined extracts were subjected to the usual workup. The crude residue was purified by column chromatography (30% ethyl acetate−petroleum ether) on silica gel to afford compound **16** (1.3 g, 59%) as a yellowish solid. R_f = 0.2 (50% ethyl acetate−petroleum ether); mp 105−107 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.23 (s, 1H), 6.83 (s, 1H), 3.80 (s, 3H), 3.71−3.45 (m, 2H), 3.18−3.05 (m, 4H), 2.89−2.71 (m, 2H), 1.83−1.75 (m, 4H), 1.27 (t, 3H, J = 7.1 Hz), 1.02 (t, 3H, J = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 192.3, 167.5, 153.1, 140.3, 131.9, 131.3, 128.1, 117.2, 56.1, 43.0, 39.1, 30.7, 26.4, 23.1, 22.3, 13.7, 12.6; HRMS (ES+) m/z calcd for $C_{17}H_{23}NO_3$ $[M + H]^+$: 290.1756, found 290.1741.

1-Hydroxy-4-methoxy-6,7,8,9-tetrahydro-1*H*-naphtho[1,2-*c*]furan-3-one (17). To a stirred suspension of compound **16** (1.32 g, 0.004 mol) in glacial AcOH (20 mL) was added 10% aq HCl (22 mL), and the resulting mixture was allowed to reflux for 10 h. Afterward, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 80 mL). The combined extracts were then subjected to the usual workup. On evaporation of organic solvent followed by a hexane wash, **17** was obtained as a white solid (860 mg, 85%). R_f = 0.2 (80% ethyl acetate−petroleum ether); mp 192−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ δ 6.70 (s, 1H), 6.45 (s, 1H), 3.93 (s, 3H), 2.96−2.85 (m, 3H), 2.70−2.63 (m, 1H), 1.90−1.76 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.5, 155.5, 147.6, 146.8, 125.5, 113.4 (Ar−CH), 111.6, 96.0 (CH−OH), 55.9 (OCH_3), 30.5 (CH_2), 24.1 (CH_2), 22.5 (CH_2), 22.4 (CH_2); IR (KBr, cm^{-1}) ν_{max} 1768, 1749, 1698, 1621, 1498, 1302, 1072, 1053, 949, 775. HRMS (ES+) m/z calcd for $C_{13}H_{14}O_4$ $[M + H]^+$: 235.0970, found 235.0956.

4-Methoxy-1-phenylsulfanyl-6,7,8,9-tetrahydro-1*H*-naphtho[1,2-*c*]furan-3-one (18). To a stirred solution of **17** (600 mg, 2.56 mmol) in dry benzene (50 mL), taken in a round-bottom flask fitted with a Dean−Stark apparatus, was added *p*-TSA (cat.) followed by PhSH (0.21 mL, 2.1 mmol), and the mixture was allowed to reflux for 10 h. Benzene was removed under reduced pressure. The crude residue was then diluted with water (30 mL) and extracted with ethyl acetate (3 × 70 mL). The combined extract was then subjected to the usual workup. Purification by column chromatography (30% ethyl acetate−petroleum ether) yielded a white solid **18** (560 mg, 70%). R_f = 0.3 (50% ethyl acetate−petroleum ether); mp 161−163 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.54−7.48 (m, 2H), 7.31−7.26 (m, 3H), 6.62 (s, 1H), 6.47 (s, 1H), 3.88 (s, 3H), 3.29−3.15 (m, 1H), 2.90−2.79 (m, 2H), 2.67−2.55 (m, 1H), 1.99−1.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 155.8, 147.2, 146.5, 133.6 (Ar−CH), 130.9, 129.0 (CH), 128.8 (CH), 124.4, 112.7 (CH), 111.5, 85.0 (CH−SPh), 55.9 (OCH_3), 30.6 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 22.4 (CH_2); HRMS (EI+) m/z calcd for $C_{19}H_{18}O_3S$ $[M^+]$: 326.0977, found 326.0973.

4-Methoxy-1-phenylsulfanyl-7,8-dihydro-1*H*,6*H*-naphtho-[1,2-*c*]furan-3,9-dione (10). To a stirred solution of **18** (100 mg, 0.307 mmol) in 1:1 CH_3CN−H_2O (15 mL) was added $K_2S_2O_8$ (248 mg, 0.92 mmol) and $CuSO_4{\cdot}5H_2O$ (77 mg, 0.307 mmol) at rt, and the mixture was allowed to reflux for 20 min. Solvents were then evaporated under reduced pressure, and the crude residue was diluted with water (10 mL) and extracted with ethyl acetate (3 × 40 mL). The combined ethyl acetate part was then subjected to the usual workup. The crude solid on chromatographic purification (80% ethyl acetate−petroleum ether) yielded **10** as a white solid (78%). R_f = 0.2 (50% ethyl acetate−petroleum ether); mp 129−130 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.46 (dd, 2H, J = 1.8 Hz, 7.6 Hz), 7.27 − 7.22 (m, 3H), 7.04 (s, 1H), 6.72 (s, 1H), 3.95 (s, 3H), 3.07−2.98 (m, 2H), 2.84−2.52 (m, 2H), 2.24−2.10 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.4, 166.1, 160.5, 154.9, 151.7, 135.0 (CH), 133.6, 130.3, 129.1 (CH), 128.9 (CH), 120.8, 111.6 (CH), 86.9 (CH), 56.5 (OCH_3), 39.3 (CH_2), 31.0 (CH_2), 22.7 (CH_2); HRMS (EI+) m/z calcd for $C_{19}H_{16}O_4S$ $[M^+]$: 340.0769, found 340.0772.

4-Methoxy-1-(3-oxo-cyclohexyl)-1-phenylsulfanyl-6,7,8,9-tetrahydro-1*H*-naphtho[1,2-*c*]furan-3-one (19a). To a stirred suspension of *t*-BuOLi (52 mg, 0.644 mmol) in dry THF (5 mL) was added a solution of phthalide **18** (70 mg, 0.214 mmol) in THF (3 mL) at −78 °C under an inert atmosphere. The resulting light yellow colored solution was stirred at −78 °C for 30 min. Then a solution of acceptor 2-cycloxhexenone (0.03 mL, 0.322 mmol) in THF (2 mL) was added dropwise into it. The same temperature was maintained for another 1 h. The cooling bath was removed, and the reaction mixture was allowed to stir at rt overnight. It was then quenched with a saturated aq. NH_4Cl solution (2 mL). The resulting solution was concentrated under reduced pressure, and the residue was diluted with water (4 mL) and extracted with ethyl acetate (3 × 15 mL). The combined extracts were then subjected to the usual workup. Column chromatography of the crude product using 50% ethyl acetate−petroleum ether as the eluant gave **19a** as a yellowish solid (60 mg, 67%). mp 124−126 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ (7:3 mixture of diastereomers) 7.23−7.00 (m), 6.44 (s), 6.42 (s), 3.74 (s), 3.72 (s), 3.65−3.43 (m), 3.13−3.01 (m), 2.95−2.72 (m), 2.65−2.17 (m), 2.16−1.90 (m), 1.89−1.67 (m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.2, 210.0, 166.7, 166.5, 155.4, 148.6, 148.0, 147.4, 147.3, 136.7 (Ar−CH), 136.6 (Ar−CH), 129.7 (Ar−CH), 128.5 (Ar−CH), 128.4 (Ar−CH), 128.0, 127.8, 123.7, 123.6, 112.4 (Ar−CH), 112.3 (Ar−CH), 112.0, 111.8, 98.0, 97.9, 55.8 (OCH_3), 44.1, 44.0, 43.2 (CH_2), 42.6 (CH_2), 41.1 (CH_2), 41.0 (CH_2), 30.9 (CH_2), 30.8 (CH_2), 26.5 (CH_2), 25.9 (CH_2), 24.8 (CH_2), 24.7 (CH_2), 24.5 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 22.3 (CH_2); IR (KBr, cm^{-1}) ν_{max} 1773, 1705, 1654, 1617, 1492, 1300, 1042, 752, 693; HRMS (EI+) m/z calcd for $C_{25}H_{26}O_4S$ $[M^+]$: 422.1552, found 422.1554.

Methyl-3-(4-methoxy-3-oxo-1-phenylsulfanyl-1,3,6,7,8,9-hexahydronaphtho[1,2-*c*]furan-1-yl)-propionate (21). Compound **21** was synthesized from **18** (40 mg, 0.123 mmol) and methacrylate (0.014 mL, 0.147 mmol), following the protocol described for the transformation **18**→**19a**. Purification was done by PLC using 50% ethyl acetate−petroleum ether to afford **21** as a semisolid. R_f = 0.3 (50% ethyl acetate−petroleum ether); Yield = 41 mg (82%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26−7.05 (m, 5H), 6.48 (s, 1H), 3.75 (s, 3H), 3.56 (s, 3H), 3.56−3.36 (m, 1H), 2.85−2.75 (m, 2H), 2.70−2.52 (m, 2H), 2.44−2.28 (m, 1H), 2.17−1.15 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.6, 166.3, 155.4, 148.2, 147.4, 136.5 (CH), 129.7 (CH), 128.6 (CH), 128.2, 124.1, 112.7 (CH), 112.2, 94.7, 55.8 (OCH_3), 51.8 (OCH_3), 31.8 (CH_2), 30.9 (CH_2), 28.9 (CH_2), 24.6 (CH_2), 22.7 (CH_2), 22.4 (CH_2); HRMS (EI+) m/z calcd for $C_{23}H_{24}O_5S$ $[M + H]^+$: 413.1431, found 413.1420.

1-Benzenesulfonyl-4-methoxy-6,7,8,9-tetrahydro-1*H*-naphtho[1,2-*c*]furan-3-one (23). To a stirred solution of **18** (420 mg, 1.29 mmol) in dry CH_2Cl_2 (30 mL) was added *m*-CPBA (1.00 g, 5.79 mmol) at rt, and the reaction mixture was allowed to stir at the same temperature for 4 h. CH_2Cl_2 was evaporated, and the crude residue was diluted with water (30 mL) and extracted with ethyl

acetate (3 × 60 mL). The combined ethyl acetate part was then washed with an aqueous saturated $NaHCO_3$ solution (2 × 10 mL), followed by the usual workup which gave a solid compound, which upon chromatographic purification (50% ethyl acetate−petroleum ether) yielded compound **23** (420 mg, 91%) as a white solid. R_f = 0.2 (30% ethyl acetate−petroleum ether); mp 199−202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 2H, J = 7.2 Hz), 7.68 (t, 1H, J = 7.6 Hz), 7.60−7.52 (m, 2H), 6.76 (s, 1H), 6.08 (s, 1H), 3.91 (s, 3H), 3.38−3.28 (m, 1H), 3.00−2.80 (m, 2H), 2.80−2.72 (m, 1H), 2.05−1.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 156.1, 148.4, 139.8, 134.7 (Ar-*C*H), 133.7, 129.7 (Ar−*C*H), 129.1 (Ar−*C*H), 128.2, 114.3 (Ar−*C*H), 111.5, 90.2 (CH_2−SO_2Ph), 56.0 (OCH_3), 30.6 (CH_2), 26.2 (CH_2), 22.4 (CH_2), 22.2 (CH_2); IR (KBr, cm^{-1}) ν_{max} 1763, 1617, 1493, 1322, 1304, 1232, 1153, 1008, 726, 592, 541; HRMS (ES+) m/z calcd for $C_{19}H_{18}O_5S$ [M+H]$^+$: 359.0953, found 359.0931.

4-Methoxy-1-phenylsulfanyl-1*H*-naphtho[1,2-*c*]furan-3-one (24). To a stirred solution of **18** (200 mg, 0.613 mmol) in dry benzene (10 mL) was added DDQ (840 mg, 3.68 mmol) and refluxed for 7 d (168 h). Benzene was removed under reduced pressure. The resulting residue was charged into a silica gel column. Compound **24** (100 mg, 55%) was eluted with 30% ethyl acetate−petroleum ether as a white solid. R_f = 0.4 (30% ethyl acetate−petroleum ether); mp 146−148 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.35 (d, 1H, J = 8 Hz), 7.85 (d, 1H, J = 8.2 Hz), 7.71−7.52 (m, 2H), 7.43 (dd, 2H, J = 1.6 Hz, J = 8 Hz), 7.32−7.15 (m, 3H), 7.14 (s, 1H), 6.91 (s, 1H), 4.01 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.2, 153.8, 147.8, 138.3, 134.1 (*C*H), 129.8 (*C*H), 129.7, 129.2 (*C*H), 129.0 (*C*H), 127.8 (*C*H), 125.1 (*C*H), 124.9 (*C*H), 122.1, 115.5, 108.1 (*C*H), 84.5 (*C*H), 56.0 (OCH_3); IR (KBr, cm^{-1}) ν_{max} 1751, 1634, 1470, 1310, 1051, 961, 750; HRMS (EI +) m/z calcd for $C_{19}H_{14}O_3S$ [M$^+$]: 322.0664, found 322.0666.

4-Methoxy-3-oxo-1,3,6,7,8,9-hexahydronaphtho[1,2-*c*]-furan-1-carbonitrile (25). To a stirred solution of **16** (600 mg, 2.07 mmol) in dry CH_2Cl_2 (mL) was added TMSCN (0.28 mL, 2.28 mmol) at 0 °C, followed by KCN (27 mg, 0.415 mmol) and 18-crown-6 (110 mg, 0.415 mmol) at the same temperature in a N_2 atmosphere. The resulting reaction mixture was allowed to stir at 0 °C for 1.5 h and at rt for 3 h. Thereafter, the reaction mixture was concentrated under reduced pressure, and the residue was dissolved in AcOH (20 mL) and stirred at rt for 15 h. Then an aqueous NaOH solution (40 mL, 1 M) was added dropwise until turbidity appeared and then extracted with ethyl acetate (3 × 120 mL). The combined ethyl acetate part was then subjected to the usual workup to give a solid compound, which on chromatographic purification (50% ethyl acetate−petroleum ether) yielded compound **25** (480 mg, 95%) as a white solid. R_f = 0.3 (60% ethyl acetate−petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.77 (s, 1H), 5.83 (s, 1H), 3.95 (s, 3H), 2.95−2.78 (m, 3H), 2.62−2.47 (m, 1H), 1.95−1.75 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.9, 156.5, 148.7, 142.1, 124.0, 113.8 (Ar−*C*H), 113.1, 109.4, 64.1 (*C*H−CN), 56.1 (OCH_3), 30.5 (CH_2), 24.2 (CH_2), 22.2 (CH_2), 22.1 (CH_2); HRMS (ES+) m/z calcd for $C_{14}H_{13}NO_3$ [M+H]$^+$: 244.0974, found 244.0970.

4-Methoxy-1-(3-oxo-cyclohexyl)-1-phenylsulfanyl-1*H*-naphtho[1,2-*c*]furan-3-one (19d). Compound **19d** was synthesized from **24** (40 mg, 0.124 mmol) and 2-cyclohexenone, following the protocol described for the transformation **18**→**19a**. Purification was done by PLC using 30% ethyl acetate−petroleum ether. R_f = 0.2 (30% ethyl acetate−petroleum ether); Yield = 42 mg (80%, white solid); mp 168−170 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ (6:4 mixture of diastereomers) 8.43−8.32 (m), 7.80−7.69 (m), 7.67−7.47 (m), 7.09−6.98 (m), 6.96 (s), 6.93 (s), 6.90−6.82 (m), 3.85 (s), 3.83 (s), 3.25−2.65 (m), 2.40−2.10 (m), 1.93−1.29 (m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.9, 209.4, 166.3, 153.3, 150.0, 149.4, 138.4, 136.3, 136.2, 129.8, 128.5, 128.2, 127.4, 127.2, 125.3, 124.8, 124.7, 121.5, 115.7, 108.0, 107.8, 97.5, 55.9, 45.9, 43.3, 42.2, 41.0, 26.6, 25.7, 24.6, 24.2; IR (KBr, cm^{-1}) ν_{max} 1774, 1705, 1630, 1465, 1401, 1302, 1262, 1170, 1102, 1037, 752, 693; HRMS (ES+) m/z calcd for $C_{25}H_{22}O_4S$ [M + H]$^+$: 419.1317, found 419.1298.

Methyl 2-Methoxy-6-methyl-4-trifluoromethanesulfonyloxybenzoate (33). It was obtained from **32** as a low melting solid. Experimental procedure is similar to that described for the transformation **55**→**56**. R_f = 0.5 (15% ethyl acetate−petroleum ether); mp 49−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (s, 1H), 6.66 (d, 1H, J = 1.6 Hz), 3.92 (s, 3H), 3.84 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 157.7, 150.3, 138.8, 123.8, 118.67 (q, J = 319 Hz), 114.7(CH), 102.4(CH), 56.2, 52.4, 19.3; HRMS (EI +) m/z calcd for $C_{11}H_{11}F_3O_6S$ [M]$^+$: 328.0228, found 328.0225.

Dimethyl 2-Methoxy-6-methyl-terephthalate (34). It was obtained from **33** as a yellowish solid. The experimental procedure is similar to that described for the transformation **56**→**57**. R_f = 0.2 (15% ethyl acetate−petroleum ether); mp 84−86 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50 (d, 1H, J = 0.6 Hz), 7.41 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 168.1, 166.5, 156.3, 136.6, 131.7, 127.8, 123.7 (Ar−*C*H), 109.2 (Ar−*C*H), 56.0, 52.3, 52.4, 19.1; HRMS (EI+) m/z calcd for $C_{12}H_{14}O_5$ [M]$^+$: 238.0841, found 238.0840.

Dimethyl 2-Bromo-5-methoxy-3-methyl-terephthalate (35). To a stirred solution of **34** (200 mg, 0.84 mmol) in AcOH (4 mL) was added Br_2 (0.04 mL, 0.84 mmol) dropwise at 0 °C, and the mixture was allowed to stir at rt overnight. Then it was diluted with water (15 mL) and extracted with ethyl acetate (3 × 30 mL). The combined extract was then submitted to the usual workup. Column purification of the crude material resulted in compound **35** as a yellowish solid (185 mg, 70%). mp 71−74 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.02 (s, 1H), 3.91 (s, 6H), 3.81 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.4, 167.3, 155.0, 137.5, 135.6, 127.7, 114.6, 110.6, 56.4, 52.8, 52.7, 21.0; HRMS (ES+) m/z calcd for $C_{12}H_{13}O_5Br$ [M + H]$^+$: 317.0025, found 317.0039.

Methyl 7-Methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate (36). It was obtained from **34** as a fluffy white solid. The experimental procedure is similar to that described for the transformation **50**→**51**. R_f = 0.1 (30% ethyl acetate−petroleum ether); mp 186−188 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.73 (d, 1H, J = 0.8 Hz), 7.64 (s, 1H), 5.32 (s, 2H), 4.10 (s, 3H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 165.7, 158.4, 149.3, 137.4, 123.4, 116.7, 114.8 (Ar−*C*H), 111.7 (Ar−*C*H), 68.7 (CH_2), 56.3, 52.8; IR (KBr, cm^{-1}) ν_{max} 1758, 1718, 1612, 1440, 1336, 1244, 1106, 1051, 769; HRMS (EI+) m/z calcd for $C_{11}H_{10}O_5$ [M]$^+$: 222.0528, found 222.0529.

Methyl 3-Bromo-7-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate (37). It was obtained from **36** as a white solid. The experimental procedure is similar to that described for the transformation **57**→**59**. R_f = 0.5 (30% ethyl acetate−petroleum ether); mp 185−190 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.66 (s, 1H), 7.34 (s, 1H), 4.07 (s, 3H), 3.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.1, 164.3, 158.4, 151.4, 138.7, 116.2 (Ar−*C*H), 114.7 (*tert*-C), 113.7 (Ar−CH), 73.6 (CH−Br), 56.7, 53.0

Methyl 3-Hydroxy-7-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate (38). It was obtained from **37** as a white solid. The experimental procedure is similar to that described for the transformation **59**→**60**. R_f = 0.2 (80% ethyl acetate−petroleum ether); mp 199−200 °C; ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.17 (s, 1H, broad), 7.63 (s, 1H), 7.61 (s, 1H), 6.58 (s, 1H, broad), 3.97 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 171.0, 165.6, 157.7, 150.8, 137.5, 117.5, 116.0 (Ar−CH), 113.5 (Ar−CH), 97.0 (CH−OH), 56.6, 53.3; HRMS (TOF-ES+) m/z calcd for $C_{11}H_{10}O_6$ [M + Na]$^+$: 261.0375, found 261.0381.

Methyl 3-Cyano-7-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate (27). It was obtained from **38** as a white solid. The experimental procedure is similar to that described for the transformation **60**→**47**. But, addition of $CHCl_3$ and *p*-TSA (cat.) was not required here. Compound **27** was obtained directly from **38** without isolation of the cyanohydrin intermediate, when treated with KCN in an acidic medium; R_f = 0.3 (30% ethyl acetate−petroleum ether); mp 194−196 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.75 (s, 1H), 6.04 (s, 1H), 4.09 (s, 3H), 4.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.8, 164.4, 158.8, 144.2, 139.0, 115.1 (Ar−CH), 114.9, 114.3 (Ar−CH), 113.4, 64.8 (CH−CN), 56.7, 53.1; IR (KBr, cm^{-1}) ν_{max} 1758, 1718, 1612, 1440, 1336, 1244, 1106, 1051, 7691803, 1718,

1610, 1488, 1344, 1259, 1020, 765; HRMS (ES+) m/z calcd for $C_{12}H_9NO_5$ $[M + H]^+$: 248.0559, found 248.0564.

Methyl 6-Hydroxy-8-methoxy-3-methyl-7,12-dioxo-1,2,3,4,7,12-hexahydrobenz[*a*]anthracene-10-carboxylate (40). This was obtained from **27** as a red solid. The experimental procedure is similar to that described for the transformation **47→63**. mp 216–218 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.1 (s, 1H, OH), 8.48 (d, 1H, J = 1.2 Hz), 7.92 (d, 1H, J = 0.8 Hz), 7.03 (s, 1H), 4.12 (s, 3H), 4.00 (s, 3H), 3.45–3.37 (m, 1H), 3.17–3.06 (m, 1H), 2.90 (dd, 1H, J = 3.2 Hz, 17.2 Hz), 2.48 (dd, 1H, J = 10.8, 17.2 Hz), 2.02–1.95 (m, 1H), 1.89–1.84 (m, 1H), 1.39–1.24 (m, 1H), 1.07 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.4, 184.1, 165.4, 160.6, 160.1, 149.1, 137.5, 135.9, 134.0, 129.5, 124.7, 122.9, 120.7, 117.2, 116.4, 56.9, 52.8, 39.8, 31.4, 28.8, 27.8, 21.5; HRMS (TOF-ES+) m/z calcd for $C_{22}H_{20}O_6$ $[M^+]$: 380.1260, found 380.1267.

Methyl 6-Hydroxy-8-methoxy-3-methyl-1,7,12-trioxo-1,2,3,4,7,12-hexahydrobenz[*a*]anthracene-10-carboxylate (41). This was obtained from **40** as a red solid. The experimental procedure is similar to that described for the transformation **63→65**. R_f = 0.2 (40% ethyl acetate–petroleum ether); mp 218–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.86 (s, 1H, OH), 8.37 (s, 1H), 7.95 (s, 1H), 6.99 (s, 1H), 4.11 (s, 3H), 3.99 (s, 3H), 2.95–2.85 (m, 2H), 2.65–2.57 (m, 1H), 2.51–2.30 (m, 2H), 1.17 (d, 3H, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.6, 187.9, 183.9, 165.1, 163.6, 160.3, 152.7, 138.0, 137.2, 136.8, 128.3, 122.4, 121.2 (Ar–*C*H), 120.6 (Ar–*C*H), 117.8 (Ar–*C*H), 117.7, 57.0, 53.0, 47.5(CH_2), 38.7(CH_2), 30.3, 21.3; HRMS (TOF-ES+) m/z calcd for $C_{22}H_{18}O_7$ $[M + H]^+$: 395.1131, found 395.1128.

Methyl 2-Chloro-6-hydroxy-8-methoxy-3-methyl-1,7,12-trioxo-1,2,3,4,7,12-hexahydrobenz[*a*]anthracene-10-carboxylate (42, 1:1 Mixture of Diastereomers). To a stirred solution of *N*-chlorosuccinimide (122 mg, 0.913 mmol) in a mixture of dry methanol and chloroform (3:2, 10 mL) was added a catalytic amount of thiourea at rt. After 5 min, compound **41** (100 mg, 0.254 mmol) was added to the resulting solution and the mixture was allowed to stir at rt overnight under a nitrogen atmosphere. After completion of the reaction the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to provide the chlorotetracycle **42** as a yellow solid (70 mg, 65%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.89 (s, 1H), 12.87 (s, 1H), 8.39 (s, 2H), 7.96 (s, 2H), 6.99 (s, 2H), 4.54 (d, 1H, J = 2.4 Hz), 4.48 (d, 1H, J = 8.4 Hz), 4.12 (s, 6H), 3.99 (s, 6H), 3.29 (dd, 2H, J = 17.1 Hz, 4.5 Hz), 3.04–2.55 (m, 4H), 1.26 (t, 6H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.6, 187.8, 183.0, 165.1, 164.0, 163.9, 160.4, 151.0, 150.5, 138.1, 137.6, 137.0, 125.8, 122.3, 121.2 (Ar–*C*H), 120.7 (Ar–*C*H), 118.0, 117.9 (Ar–*C*H), 66.3 (*C*H–Cl), 66.2 (*C*H–Cl), 57.0 (OCH_3), 53.0 (OCH_3), 38.6, 35.8, 35.7 (CH_2), 33.7 (CH_2), 19.3, 17.3; HRMS (TOF-ES+) m/z calcd for $C_{22}H_{17}ClO_7$ $[M + H]^+$: 429.0742, found 429.0734.

Methyl 6,8-Dimethoxy-3-methyl-1,7,12-trioxo-1,2,3,4,7,12-hexahydrobenz[*a*]anthracene-10-carboxylate (43). It was obtained from **41** as an orange solid. The experimental procedure is similar to that described for the transformation **65→66**. R_f = 0.2 (50% ethyl acetate–petroleum ether); mp 234–236 °C (charring); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, 1H, J = 1.2 Hz), 7.88 (s, 1H), 6.93 (s, 1H), 4.04 (s, 3H), 4.02 (s, 3H), 3.98 (s, 3H), 2.93 (m, 2H), 2.66 (m, 1H), 2.48 (m, 2H), 1.18 (d, 3H, J = 6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.3, 185.6, 181.2, 165.5, 160.9, 158.7, 151.0, 139.3, 137.1, 135.1, 127.2, 126.2, 123.9, 119.3, 117.3, 114.6, 56.7, 52.7, 47.4, 38.9, 30.5, 21.3 (one C missing). HRMS (TOF-ES+) m/z calcd for $C_{23}H_{20}O_7$ $[M + Na]^+$: 431.1107, found 431.1106.

Methyl 2,2-Dichloro-6,8-dimethoxy-3-methyl-1,7,12-trioxo-1,2,3,4,7,12-hexahydrobenz[*a*]anthracene-10-carboxylate (44). It was obtained from **43** as a deep red solid. The experimental procedure is similar to that described for the transformation **66→67**; R_f = 0.2 (50% ethyl acetate–petroleum ether); mp 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, 1H, J = 0.8 Hz), 7.90 (s, 1H), 6.89 (s, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.98 (s, 3H), 3.09 (dd, 2H, J = 5.6 Hz, J = 8.4 Hz), 2.86–2.75 (m, 1H), 1.46 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 184.3, 183.9, 180.6, 165.4, 161.6, 158.8, 148.0, 140.9, 136.7, 135.3, 125.9, 124.7, 122.9, 119.4 (Ar–*C*H), 117.5 (Ar–*C*H), 114.0 (Ar–*C*H), 92.1, 56.8, 56.7, 52.8, 45.2, 36.3 (CH_2), 16.1; HRMS (TOF-ES+) m/z calcd for $C_{23}H_{18}Cl_2O_7$ $[M + H]^+$: 477.0508, found 477.0515 or, $[M + Na]^+$: 499.0328, found 499.0326.

2-Chloro-1-hydroxy-6,8-dimethoxy-3-methyl-7,12-dioxo-7,12-dihydrobenz[*a*]anthracene-10-carboxylic acid (45). It was obtained from **44** as a black solid. The experimental procedure is similar to that described for the transformation **67→68**; R_f = 0.2 (90% ethyl acetate–petroleum ether); mp >242 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.69 (s, 1H), 8.45 (s, 1H), 7.97 (s, 1H), 7.49 (s, 1H), 7.22 (s, 1H), 4.10 (s, 3H), 4.05 (s, 3H), 2.54 (s, 3H); HRMS (ES+) m/z calcd for $C_{22}H_{15}O_7Cl$ $[M + H]^+$: 427.0585, found 427.0578. ^{13}C NMR could not be recorded due to decomposition under ambient conditions.

Methyl 2-Chloro-1,6,8-trimethoxy-3-methyl-7,12-dioxo-7,12-dihydrobenz[*a*]anthracene-10-carboxylate (46). R_f = 0.3 (60% ethyl acetate–petroleum ether); state: red solid; mp 245–248 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.88 (s, 1H), 7.41 (s, 1H), 7.31 (s, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 4.00 (s, 3H), 3.86 (s, 3H), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 186.4, 181.2, 165.5, 158.5, 155.5, 153.5, 140.0, 137.9, 137.0, 136.5, 135.2, 126.5, 126.3, 126.0, 123.2, 118.0, 117.9, 117.0, 111.7, 61.4, 56.7, 56.5, 52.8, 21.2; HRMS (ES+) m/z calcd for $C_{24}H_{19}ClO_7$ $[M + H]^+$: 455.0897, found 455.0899.

2-Chloro-1,6,8-trimethoxy-3-methyl-7,12-dioxo-7,12-dihydrobenz[*a*]anthracene-10-carboxylic Acid (29). To a stirred solution of **46** (40 mg, 0.088 mmol) in THF (4 mL) was added a solution of LiOH (40 mg, 1.67 mmol, 19 equiv) in a 5:1 mixture of THF–H_2O (2.4 mL) dropwise, and the mixture was allowed to stir at rt for 4 h. Solvent was evaporated under reduced pressure, and the residue was acidified with 6 N HCl and diluted with ethyl acetate (15 mL). The usual workup of the mixture using ethyl acetate and H_2O, followed by evaporation of organic solvent, gave compound **29** (34 mg, 89%) as a red solid. R_f = 0.2 (ethyl acetate); mp 239 °C (charring); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.92 (s, 1H), 7.42 (s, 1H), 7.32 (s, 1H), 4.08 (s, 3H), 4.06 (s, 3H), 3.88 (s, 3H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 186.3, 181.1, 168.5, 158.5, 155.4, 153.3, 140.0, 137.9, 136.8, 136.6, 134.1, 126.8, 126.5, 126.0, 123.2, 118.6, 117.9, 117.2, 111.7, 61.3, 56.7, 56.5, 21.2; HRMS (TOF-ES+) m/z calcd for $C_{23}H_{17}ClO_7$ $[M + Na]^+$: 463.0561, found 463.0558.

Methyl 3-Acetyl-2-hydroxy-4-methoxy-6-methylbenzoate (49). To a stirred solution of **48** (28 g, 0.142 mol) in dry CH_2Cl_2 (1 lit) was added $TiCl_4$ (62.6 mL, 0.57 mol) dropwise at 0 °C in a N_2 atmosphere. Afterward, CH_3COCl (24.5 mL, 0.36 mol) was added dropwise at the same temperature. The solution was stirred for 12 h at rt. After addition of water (300 mL) and 10% aq HCl (200 mL) the mixture was extracted with CH_2Cl_2 (3 × 800 mL) and worked up in the usual manner. The crude product was purified by column chromatography to obtain acetyl compound **49** (31 g, 91%) as a yellow solid. mp 47–49 °C; R_f = 0.4 (15% ethyl acetate–petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 13.66 (s, 1H, OH), 6.24 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.62 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 204.2, 168.4, 162.5, 161.8, 145.9, 115.0, 110.1, 103.7, 55.9, 52.3, 33.4, 21.5; IR (KBr, cm^{-1}) ν_{max} 3450, 1727, 1610, 1452, 1292, 1189. HRMS (ES+): calcd for $C_{12}H_{14}O_5$ $[M + Na]^+$ 261.0739, found 261.0741.

Methyl 2-Acetoxy-3-acetyl-4-methoxy-6-methylbenzoate (50). To an oven-dried round-bottomed flask fitted with a magnetic stirring bar were added compound **49** (54 g, 0.227 mol) and CH_2Cl_2 (300 mL) followed by Et_3N (62 mL, 0.45 mol) dropwise at 0 °C. The resulting reaction mixture was then allowed to stir for 10 min at the same temperature. Afterward, CH_3COCl (24.3 mL, 0.34 mol) was added dropwise at 0 °C and allowed to stir for 5 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (400 mL), and water (100 mL) was added. The layers were separated, and the aqueous part was extracted with CH_2Cl_2 (3 × 200 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel to afford compound **50** (61 g, 96%) as a white crystalline solid. mp 116–120 °C; ^{1}H NMR ($CDCl_3$, 200

MHz): δ 6.67 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.47 (s, 3H), 2.43 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 199.6, 168.9, 166.1, 158.2, 146.3, 141.9, 122.4, 119.3, 111.0, 56.0, 52.1, 31.6, 21.1, 20.6; IR (KBr, cm^{-1}) ν_{max} 1781, 1724, 1700, 1655, 1610, 1563, 1527, 1461, 1438, 1408, 1371, 1319, 1275, 1238, 1206, 1106, 1041, 1017, 968, 857; HRMS (ES+) *m/z* calcd for $C_{14}H_{16}O_6$ [M—(CH_2═C═O + OMe)]$^+$: 207.0657, found 207.0649.

Acetic Acid 5-Acetyl-6-methoxy-3-oxo-1,3-dihydroisobenzofuran-4-yl ester (51). To a stirred solution of **50** (5 g, 0.017 mol) in dry CCl_4 (70 mL) in an oven-dried round-bottomed flask fitted with a reflux condenser was added *N*-bromosuccinimide (3.87 g, 0.023 mol) and benzoyl peroxide (30 mg). Under the exposure of a 100 W lamp, the reaction mixture was then allowed to reflux at 80 °C for 2.5 h, cooled to rt, and filtered. The residue was washed with CCl_4, and the resulting filtrate was evaporated under reduced pressure. The resulting gummy material, without further purification, was heated at 150−160 °C in a round-bottomed flask for 40 min. The resulting black solid was purified by column chromatography on silica gel to afford compound **51** (2.5 g, 63%, brsm) as a white crystalline solid along with deacetylated compound **52** (800 mg, 24%, brsm). R_f = 0.4 (50% ethyl acetate−petroleum ether); mp 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 1H), 5.23 (s, 2H), 3.95 (s, 3H), 2.45 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 198.8, 168.7, 167.6, 162.8, 151.2, 146.1, 126.3, 111.3, 102.1, 69.0, 56.9, 32.0, 20.6; IR (KBr, cm^{-1}) ν_{max} 1779, 1754, 1705, 1620, 1468, 1444, 1362, 1338, 1304, 1255, 1186, 1165, 1091, 1008, 876, 747; HRMS (ES+) *m/z* calcd for $C_{13}H_{12}O_6$ [M + H]$^+$: 265.0712, found 265.0706.

6-Acetyl-7-hydroxy-5-methoxy-3*H*-isobenzofuran-1-one (52). To a stirred solution of **51** (13 g, 0.049 mol) in dry methanol (200 mL) was added oven-dried K_2CO_3 (14.2 g, 0.098 mol), and the resulting suspension was allowed to stir at rt for 1 h. Then the mixture was decanted off and evaporated under reduced pressure. The resulting residue was diluted with CH_2Cl_2 (200 mL), and water (70 mL) was added, acidified with 2 N HCl. The layers were separated, and the aqueous part extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were then subjected to the usual workup. The crude residue was purified by column chromatography on silica gel to afford compound **52** (9 g, 83%) as white solid. R_f = 0.3 (50% ethyl acetate−petroleum ether); mp 187−191 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 14.43 (s, 1H, OH), 6.47 (s, 1H), 5.16 (s, 2H), 4.01 (s, 3H), 2.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 205.2, 168.0, 166.8, 164.1, 156.6, 110.9, 106.1, 95.0, 68.6, 56.6, 33.6; IR (KBr, cm^{-1}) ν_{max} 1760, 1633, 1601, 1463, 1423, 1387, 1358, 1266, 1196, 1162, 1101, 1057, 1015, 906, 793, 702, 602; HRMS (EI+) *m/z* calcd for $C_{11}H_{10}O_5$ [M + H]$^+$: 223.0615, found 223.0620.

6-Ethyl-7-hydroxy-5-methoxy-3*H*-isobenzofuran-1-one (53).[33] To a stirred solution of **52** (27.9 g, 0.125 mol) in trifluoroacetic acid (100 mL) was added triethylsilane (62 mL, 0.388 mol) at rt and under a N_2 atmosphere. The resulting reaction mixture was stirred at rt for 12 h. After completion (TLC monitoring) of the reaction, trifluoroacetic acid was removed by bubbling nitrogen gas into the round-bottomed flask. The residue was diluted with ethyl acetate (300 mL) and water (100 mL). The layers were separated, and the aqueous part extracted with ethyl acetate (3 × 150 mL). The combined extracts were then worked up in the usual manner. The crude residue was purified by column chromatography on silica gel to afford compound **53** (22.6 g, 87%) as a white crystalline solid. R_f = 0.6 (25% ethyl acetate−petroleum ether); mp 168−169 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.70 (s, 1H), 6.48 (s, 1H), 5.24 (s, 2H), 3.89 (s, 3H), 2.67 (q, 2H, *J* = 7.4 Hz), 1.10 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.9, 164.9, 154.3, 146.0, 119.1, 104.0, 96.2, 70.5, 56.5, 56.2, 15.8, 13.3; IR (KBr, cm^{-1}) ν_{max} 1729, 1609, 1625, 1495, 1463, 1348, 1290, 1256, 1143, 1095, 1054, 999, 983, 835, 744, 659.

6-Ethyl-5,7-dihydroxy-3*H*-isobenzofuran-1-one (54). To a stirred solution of **53** (10.5 g, 0.05 mol) in dry CH_2Cl_2 (120 mL) was added neat BBr_3 (34 mL, 0.353 mol) at 0 °C under a N_2 atmosphere. The resulting red color suspension was then allowed to come to rt and stirred overnight. After completion of the reaction, CH_2Cl_2 was removed under reduced pressure and the residue was diluted with ethyl acetate (200 mL) and water (50 mL). The resultant mixture was then subjected to the usual workup. The crude residue was purified by column chromatography on silica gel to afford compound **54** (8.4 g, 86%) as a white solid. R_f = 0.2 (40% ethyl acetate−petroleum ether); Mp 197−198 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.82 (s, 1H, OH), 6.43 (s, 1H), 5.21 (s, 2H), 2.69 (q, 2H, *J* = 7.5 Hz), 1.16 (t, 3H, *J* = 7.5); ^{13}C NMR (d_6-DMSO, 100 MHz): δ 170.3, 162.5, 154.5, 147.0, 117.2, 102.8, 100.4, 68.8, 15.6, 13.5; IR (KBr, cm^{-1}) ν_{max} 1691, 1630, 1449, 1347, 1320, 1260, 1143, 1100, 1052, 1018, 993, 829, 750; HRMS (ES+): calcd for $C_{10}H_{10}O_4$ [M + Na]$^+$ 217.0477, found 217.0480.

6-Ethyl-7-hydroxy-1-oxo-1,3-dihydroisobenzofuran-5-yl Trifluoromethanesulfonate (55). To a stirred solution of **54** (2.5 g, 0.013 mol) in dry acetone (140 mL) was added Cs_2CO_3 (4.2 g, 0.013 mol) and $PhNTf_2$ (4.12 g, 0.011 mol) at 0 °C under a N_2 atmosphere and allowed to stir for 3.5 h at temperatures not higher than 15 °C. After completion of reaction (evaluated by TLC), acetone was removed under reduced pressure and diluted with ethyl acetate (80 mL) and a 5% aq solution of NH_4Cl (50 mL) was also added. The layers were separated, and the aqueous part was extracted with ethyl acetate (3 × 80 mL). The combined extracts were worked up in the usual manner. The crude residue was purified by column chromatography on silica gel to afford compound **55** (2.7 g, 66%) as a white crystalline solid along with a small amount of a ditriflate compound. R_f = 0.7 (10% ethyl acetate−petroleum ether); mp 75−76 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.15 (s, 1H), 6.69 (s, 1H), 5.34 (s, 2H), 2.79 (q, 2H, *J* = 7.5 Hz), 1.21 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 173.1, 157.2, 154.2, 146.0, 126.5, 119.7 (q, *J* = 300 Hz), 111.6, 108.2, 71.8, 18.45, 14.2; IR (KBr, cm^{-1}) ν_{max} 1737, 1629, 1610, 1424, 1407, 1244, 1220, 1137, 1088, 1008, 959, 868, 729; HRMS (ES+) *m/z* calcd for $C_{11}H_9O_6SF_3$ [M+H]$^+$: 327.0150, found 327.0143. Bistriflate of **54**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.52 (s, 1H), 5.36 (s, 2H), 2.91 (q, 2H, *J* = 7.6 Hz), 1.27 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 152.3, 147.4, 144.4, 132.8, 118.9, 118.5 (OTf, q, *J* = 319 Hz), 118.3 (OTf, q, *J* = 318 Hz), 115.8 (Ar-CH), 68.6, 18.5 (CH_2), 13.2 (CH_3).

6-Ethyl-7-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-yl Trifluoromethanesulfonate (56). To a stirred solution of **55** (4 g, 0.012 mol) in dry acetone (140 mL) was added K_2CO_3 (6.8 g, 0.049 mol). The mixture was stirred for 5 min, and then MeI (4 mL, 0.06 mol) was added dropwise at 0 °C. The reaction flask was stoppered. The resulting reaction mixture was allowed to come to rt, with stirring continued for 12 h. After completion of the reaction, the suspended acetone solution was filtered and the filtrate evaporated under reduced pressure. The residue was treated with ethyl acetate (90 mL) and water (30 mL). The layers were separated, and the aqueous part was extracted with ethyl acetate (3 × 90 mL). The combined extracts were worked up in the usual manner. The crude residue was purified by column chromatography on silica gel to afford compound **56** (4.17 g, 100%) as a colorless liquid. R_f = 0.3 (10% ethyl acetate−petroleum ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.13 (s, 1H), 5.27 (s, 2H), 4.20 (s, 3H), 2.78 (q, 2H, *J* = 7.5 Hz), 1.18 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.3, 159.0, 152.1, 147.4, 131.1, 118.4 (q, CF_3, *J* = 318 Hz), 116.3, 109.7, 68.6, 63.4, 17.8, 13.8; IR (KBr, cm^{-1}) ν_{max} 1765, 1613, 1545, 1527, 1460, 1419, 1362, 1318, 1292, 1215, 1138, 1109, 1082, 1011, 967, 943, 867, 810, 764, 732, 697; HRMS (ES+) *m/z* calcd for $C_{12}H_{11}F_3O_6S$ [M + H]$^+$: 341.0306, found 341.0298.

Methyl 6-Ethyl-7-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate (57). To compound **56** (1.02 g, 0.003 mol) taken in an oven-dried pressure tube were added dppf (24×10^{-3} mol, 0.083 g), $Pd(OAc)_2$ (15×10^{-3} mol, 0.033 g), MeOH (12 mL), Et_3N (93×10^{-2} mol, 1.29 mL), and finally DMF (15 mL) sequentially in a N_2 atmosphere. Freshly generated CO gas was then allowed to purge through the reaction mixture for 10 min. The pressure tube was then sealed with a teflon cap and heated at 90−120 °C for 17 h. After completion of the reaction (checked by TLC), the reaction mixture was cooled to rt, and water (90 mL) and diethyl ether (100 mL) were added. The layers were separated. The aqueous part was then extracted with diethyl ether (3 × 50 mL). The combined organic layer was subjected to the usual workup. Column chromatography of the

resulting crude gummy material gave compound **57** (340 mg, 50%) as a colorless crystal. This reaction also provides a white solid compound in 10% yield, which was characterized as **58**. R_f = 0.3 (10% ethyl acetate−petroleum ether); mp 57−59 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.49 (s, 1H), 5.25 (s, 2H), 4.13 (s, 3H), 3.94 (s, 3H), 2.94 (q, 2H, J = 7.4 Hz), 1.19 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 168.3, 167.7, 158.3, 145.9, 139.0, 138.1, 119.1, 117.9, 69.0, 63.0, 63.4, 52.8, 20.6, 15.5; IR (KBr, cm^{-1}) ν_{max} 1752, 1723, 1686, 1654, 1615, 1585, 1561, 1544, 1525, 1509, 1457, 1413, 1365, 1299, 1254, 1223, 1113, 1083, 1019, 996, 908, 782; HRMS (ES+) m/z calcd for $C_{13}H_{15}O_5$ [M + H]$^+$: 251.0919, found 251.0901; X-ray structure provided.

6-Ethyl-7-methoxy-3*H*-isobenzofuran-1-one (58). R_f = 0.8 (20% ethyl acetate−petroleum ether); white needle-shaped solid; mp 144−145 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.49 (d, 1H, J = 7.6 Hz), 7.08 (d, 1H, J = 7.6 Hz), 5.22 (s, 2H), 4.10 (s, 3H), 2.72 (q, 2H, J = 7.5 Hz), 1.21 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.0, 157.4, 146.9, 137.8, 136.3, 117.0, 116.9, 68.9, 62.8, 22.9, 15.3; HRMS (EI+) m/z calcd for $C_{11}H_{12}O_3$ [M]$^+$: 192.0786, found 192.0776.

Methyl 3-Bromo-6-ethyl-7-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate (59). To a stirred solution of **57** (1.2 g, 0.0048 mol) in dry CCl_4, in a round bottomed flask, fitted with a condenser and a $CaCl_2$ guard tube were added *N*-bromosuccinimide (0.85 g, 0.0048 mol) and catalytic amount of AIBN. The reaction mixture was then heated at reflux for 1.5 h under the exposure of a 100 W lamp. After 1.5 h, when the reaction was completed, the reaction mixture was filtered and washed with CCl_4. The filtrate was evaporated under reduced pressure. The resulting gummy brown residue was chromatographed to afford pure compound **59** (600 mg, 58%, brsm) as a light yellow gum. R_f = 0.5 (10% ethyl acetate−petroleum ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.62 (s, 1H), 7.33 (s, 1H), 4.18 (s, 3H), 3.96 (s, 3H), 2.95 (q, 2H, J = 7.4 Hz), 1.20 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.9, 164.5, 158.3, 147.7, 141.1, 138.9, 119.0, 116.3, 74.0, 63.4, 52.8, 20.8, 15.1; IR (KBr, cm^{-1}) ν_{max} 1752, 1718, 1636,1543, 1458, 1298, 1220, 1104, 1035, 939, 772.

Methyl 6-Ethyl-3-hydroxy-7-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate (60). A water (5 mL) suspension of bromo compound **59** (200 mg, 0.61 mmol) was heated at 80 °C for 0.5 h and then diluted with ethyl acetate (30 mL). The layers were separated. The aqueous part was then washed with ethyl acetate (3 × 20 mL), and the combined organic part was subjected to the usual workup. Column chromatography of the crude product yielded pure compound **60** in 95% yield (150 mg) as a white solid. R_f = 0.2 (ethyl acetate); mp 55−57 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.64 (s, 1H), 6.52 (d, 1H, J = 4.8 Hz), 4.14 (s, 3H), 3.94 (s, 3H), 2.93 (q, 2H, J = 7.3 Hz), 1.17 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.7, 166.7, 157.5, 146.0, 140.9, 138.2, 119.6, 119.3, 97.0, 63.4, 52.8, 20.6, 15.3; IR (KBr, cm^{-1}) ν_{max} 1732, 1618, 1591, 1459, 1443, 1407, 1292, 1220, 1116, 1082, 1038, 928, 769. HRMS (ES+) m/z calcd for $C_{13}H_{14}O_6$ [M + Na]$^+$: 289.0688, found 289.0687.

Methyl 6-Ethyl-7-methoxy-1-oxo-3-phenylsulfanyl-1,3-dihydroisobenzofuran-5-carboxylate (61). To a stirred solution of **59** (200 mg, 0.608 mmol) in dry CH_2Cl_2 (10 mL) was added Et_3N (0.1 mL, 0.668 mmol) and thiophenol (0.07 mL, 0.668 mmol) at rt. The reaction mixture was then allowed to stir at rt for 6 h. After completion of the reaction, monitored by TLC, the reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with 10 mL of a 5% aq NaOH solution followed by 10 mL of water. Then the resulting CH_2Cl_2 part was worked up in the usual manner. The crude residue was purified by column chromatography on silica gel to afford compound **61** (160 mg, 74%) as a semisolid. R_f = 0.2 (10% ethyl acetate−petroleum ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.66 (s, 1H), 7.51−7.45 (m, 2H), 7.30−7.25 (m, 3H), 6.64 (s, 1H), 3.97 (s, 3H), 2.89 (q, 2H, J = 7.3 Hz), 1.50 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.3, 166.2, 157.8, 145.5, 140.0, 138.0, 134.4 (Ar−CH), 129.9, 129.2 (Ar−CH), 119.1 (Ar−CH), 119.0, 85.6 (CH−SPh), 63.2, 52.8, 20.6 (CH_2), 15.4 (one C missing); HRMS (ES+) m/z calcd for $C_{19}H_{18}O_5S$ [M + H]$^+$: 359.0953, found 359.0959.

5-(Cyano-hydroxymethyl)-2-ethyl-3-methoxyterephthalic Acid 1-Methyl Ester (62). Semisolid; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.88 (s, 1H), 5.73 (s, 1H), 3.95 (s, 1H), 3.93 (s, 1H), 3.02 (q, 2H, J = 7.6 Hz), 1.21 (t, 3H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 169.5, 167.2, 157.2, 141.7, 133.8, 132.6, 128.9, 125.0, 118.5, 63.5, 61.2, 52.7, 21.0, 15.2.

Methyl 3-Cyano-6-ethyl-7-methoxy-1-oxo-1,3-dihydroisobenzofuran-5-carboxylate (47). To a stirred suspension of **60** (200 mg, 0.75 mmol) in water (10 mL) was added KCN (727 mg, 11.3 mmol) in portions, and the mixture was allowed to stir at rt for 10 min. The reaction mixture was then cooled to 0 °C and treated with conc. HCl (1.2 mL, 52 equiv) and again stirred at rt for another 5 h. The reaction mixture was then extracted with ethyl acetate (3 × 40 mL), and the combined extracts were subjected to the usual workup to obtain a semisolid compound (cyanohydrin **62**), which without further purification was dissolved in $CHCl_3$ (10 mL) containing *p*-TSA (cat.) followed by 1 h of heating. The resulting solution was allowed to stand at rt overnight. $CHCl_3$ was evaporated, and the residue was charged to column chromatography to obtain compound **47** as a pure yellow semisolid (146 mg, 71%). R_f = 0.9 (90% ethyl acetate−petroleum ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.69 (s, 1H), 6.00 (s, 1H), 4.18 (s, 1H), 3.97 (s, 1H), 2.97 (q, 2H, J = 7.4 Hz), 1.20 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.7, 164.9, 158.9, 141.8, 140.7, 139.3, 118.3, 116.9, 113.9, 65.2, 63.7, 53.0, 20.8, 15.2; IR (KBr, cm^{-1}) ν_{max} 1790, 1729, 1611, 1589, 1451, 1410, 1296, 1254, 1220, 1086, 1017, 910, 767; HRMS (EI+) m/z calcd for $C_{14}H_{13}NO_5$ [M$^+$]: 275.0794, found 275.0798.

Methyl 9-Ethyl-6-hydroxy-8-methoxy-3-methyl-7,12-dioxo-1,2,3,4,7,12-hexahydrobenz[*a*]anthracene-10-carboxylate (63). To a stirred solution of *t*-BuOLi (117 mg, 1.46 mmol) in THF (7 mL) was added a solution of phthalide **47** (125 mg, 0.454 mmol) in THF (3.5 mL) at −78 °C under an inert atmosphere. The resulting red color solution was stirred at −78 °C for 30 min, after which a solution of acceptor **28** (87 mg, 0.453 mmol) in THF (3.5 mL) was added dropwise. After 1 h at −78 °C, the cooling bath was removed and reaction mixture was allowed to stir at rt overnight. The resulting deep red colored reaction mixture turned yellow when quenched with a saturated aq. NH_4Cl solution (5 mL). The resulting solution was concentrated, and the residue was diluted with ethyl acetate (15 mL). The ethyl acetate layer was separated from an aqueous layer. The aq part was extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The crude product was washed with 15% ethyl acetate−petroleum ether to get **63** (158 mg, 85%) as a pure red solid. mp 162−164 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.16 (s, 1H), 8.40 (s, 1H), 7.05 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.43 (m, 1H), 3.17−3.10 (m, 1H), 3.05 (q, 2H, J = 7.50 Hz), 2.91 (dd, 1H, J = 3 Hz, J = 17 Hz), 2.53−2.46 (m, 1H), 2.02−1.98 (m, 1H), 1.89−1.85 (m, 1H), 1.39−1.32 (m, 1H), 1.24 (t, 3H, J = 7.4 Hz), 1.05 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 188.4, 184.0, 167.0, 160.9, 159.5, 149.6, 146.8, 137.0, 134.7, 134.2, 129.7, 126.2, 125.0, 124.8, 116.7, 62.9, 52.8, 40.0, 31.7, 28.9, 28.0, 21.7, 20.9, 15.4; IR (KBr, cm^{-1}) ν_{max} 1724, 1636, 1582, 1450, 1337, 1293, 1267, 1228, 1082, 1042, 800; HRMS (EI+) m/z calcd for $C_{24}H_{24}O_6$ [M$^+$]: 408.1573, found 408.1575.

Methyl 9-Ethyl-6-hydroxy-8-methoxy-3-methyl-1,7,12-trioxo-1,2,3,4,7,12-hexahydrobenz[*a*]anthracene-10-carboxylate (65). A $CHCl_3$ (distilled) solution (8 mL) of compound **63** (20 mg, 0.049 mmol) was taken in a dry test tube and allowed to stand for 6 h in open air, in sunlight. Removal of $CHCl_3$ solvent under reduced pressure gave **65** (20 mg, 100%) as a red solid which did not require any purification. R_f = 0.2 (30% ethyl acetate−petroleum ether); mp 86−90 °C ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.87 (s, 1H), 8.32(s, 1H), 7.00 (s, 1H), 3.96 (s, 1H), 3.94 (s, 1H), 3.06 (q, 2H, J = 7.3 Hz), 2.95−2.91 (m, 2H), 2.65−2.58 (m, 1H), 2.51−2.41 (m, 2H), 1.24 (t, 3H, J = 7.4 Hz), 1.18 (d, 3H, J = 6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 197.7, 187.9, 183.2, 166.5, 163.5, 163.6, 159.7, 152.8, 147.4, 137.5, 137.3, 134.6, 128.5, 125.7, 124.8, 121.1, 117.7, 62.9, 52.7, 47.5, 38.7, 30.3, 21.3, 20.8, 15.2; IR (KBr, cm^{-1}) ν_{max} 1731, 1700, 1674, 1638, 1587, 1446, 1405, 1367, 1342, 1294, 1229, 1167, 1082, 1040, 798;

HRMS (TOF-ES+) m/z calcd for $C_{24}H_{22}O_7$ $[M + Na]^+$: 445.1263, found 445.1275.

Methyl 9-Ethyl-6,8-dimethoxy-3-methyl-1,7,12-trioxo-1,2,3,4,7,12-hexahydrobenz[*a*]anthracene-10-carboxylate (66). To a stirred solution of **65** (42 mg, 0.099 mmol) in dry acetone (5 mL) was added K_2CO_3 (90 mg, 0.652 mmol). After 5 min, MeI (0.15 mL, 2.39 mmol) was added dropwise into it at 0 °C. The reaction vessel was stoppered. The resulting reaction mixture was then allowed to come to rt and stirred for 12 h. After completion of the reaction, the suspended acetone solution was filtered and the filtrate was evaporated under reduced pressure. The resulting residue was diluted with water (5 mL) and ethyl acetate (15 mL). The layers were separated, and the aqueous part was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was then washed with an aq. saturated $Na_2S_2O_3$ solution (5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by PLC (40% ethyl acetate−petroleum ether) gave **66** (38 mg, 88%) as a pure yellowish solid. R_f = 0.2 (40% ethyl acetate−petroleum ether); mp 228−230 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.22 (s, 1H), 6.93 (s, 1H), 4.03 (s, 1H), 3.95 (s, 1H), 3.94 (s, 1H), 3.05 (q, 2H, J = 7.3 H_3), 3.04−2.90 (m, 2H), 2.73−2.43 (m, 3H), 1.25−1.17 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 197.5, 185.1, 181.9, 166.8, 160.9, 158.3, 151.3, 146.6, 139.6, 135.7, 133.9, 129.1, 127.5, 124.0, 123.4, 114.7, 63.4, 56.9, 52.6, 47.6, 39.1, 30.7, 21.4, 20.9, 15.3; IR (KBr, cm^{-1}) ν_{max} 1728, 1679, 1586, 1451, 1294, 1232, 1089, 1043; HRMS (ES+) m/z calcd for $C_{25}H_{24}O_7$ $[M + H]^+$: 437.1600, found 437.1605.

Methyl 2,2-Dichloro-9-ethyl-6,8-dimethoxy-3-methyl-1,7,12-trioxo-1,2,3,4,7,12-hexahydrobenz[*a*]anthracene-10-carboxylate (67). Freshly prepared dry HCl gas was purged through a solution of **66** (32 mg, 0.073 mmol) in dry CH_2Cl_2 (6 mL) for 10 min. Afterward, SO_2Cl_2 (0.06 mL, 0.74 mmol) was added dropwise. The flask was stoppered, and the mixture was stirred at rt for 2.5 h. Thereafter, solvent was evaporated under reduced pressure, and $CHCl_3$ (6 mL) was added to the resulting yellow solid. Again, dry HCl gas was purged through the solution for 10 min, SO_2Cl_2 (0.06 mL, 0.74 mmol) was added, and the mixture was allowed to stir at rt for 60 h. Removal of $CHCl_3$ under reduced pressure followed by column chromatography gave **67** (30 mg, 94%) as a pure yellow solid. R_f = 0.2 (40% ethyl acetate−petroleum ether); mp 182−186 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (s, 1H), 6.90 (s, 1H), 4.04 (s, 1H), 3.96 (s, 1H), 3.94 (s, 1H), 3.16−3.02 (m, 4H), 2.86−2.82 (m, 1H), 1.46 (d, 3H, J = 8 Hz), 1.22 (t, 3H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 184.1, 183.7, 181.3, 166.7, 161.7, 158.5, 148.3, 147.0, 141.2, 135.9, 133.5, 128.9, 124.9, 123.6, 123.2, 114.2, 92.3, 63.4, 57.1, 52.7, 45.4, 36.5, 20.9, 16.3, 15.3; IR (KBr, cm^{-1}) ν_{max} 1727, 1684, 1636, 1588, 1458, 1296, 1233, 1100, 1065, 866, 802. HRMS (EI+) m/z calcd for $C_{25}H_{22}Cl_2O_7$ $[M^+]$: 504.0743, found 504.0739.

Methyl 2-Chloro-9-ethyl-1-hydroxy-6,8-dimethoxy-3-methyl-7,12-dioxo-7,12-dihydrobenz[*a*]anthracene-10-carboxylate (68). To a methanolic solution (5 mL) of **67** (45 mg, 0.089 mmol) in an oven-dried round bottomed flask, fitted with a condenser, was added NaOMe (15 mg, 0.277 mmol). The red colored solution immediately turned black. It was then heated at reflux for 1 h. After completion of the reaction, methanol was evaporated under reduced pressure, diluted with ethyl acetate (15 mL), and 2 N HCl was also added. After the usual workup, followed by evaporation of ethyl acetate, a black solid was obtained. This, on purification by silica gel column chromatography, gave **68** as a black solid (39 mg, 94%). R_f = 0.7 (40% ethyl acetate−petroleum ether); mp 188−190 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 12.09 (s, 1H), 8.30 (s, 1H), 7.44 (s, 1H), 7.16 (s, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 3.97 (s, 3H), 3.05 (q, 2H, J = 6.7 Hz), 2.51 (s, 3H), 1.23 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 189.8, 184.1, 166.8, 157.7, 154.1, 150.7, 147.6, 140.0, 136.7, 135.9, 133.4, 132.0, 131.9, 127.9, 125.1, 122.1, 120.2, 117.1, 116.0, 63.7, 56.8, 52.9, 21.3, 15.2; IR (KBr, cm^{-1}) ν_{max} 1732, 1682, 1653, 1582, 1455, 1400, 1364, 1287, 1260, 1221, 1109, 1056, 866. HRMS (EI+) m/z calcd for $C_{25}H_{21}ClO_7$ $[M^+]$: 468.0976, found 468.0972. $[M^{+2}]$ peak also found.

Methyl 2-Chloro-9-ethyl-1,6,8-trimethoxy-3-methyl-7,12-dioxo-7,12-dihydrobenz[*a*]anthracene-10-carboxylate (64). To a stirred solution of **68** (36 mg, 0.077 mmol) in dry acetone (5 mL) was added K_2CO_3 (104 mg, 0.753 mmol). After 5 min, MeI (0.072 mL, 1.15 mmol) was added dropwise at 0 °C and the flask was stoppered. The resulting reaction mixture was then allowed to come to rt. After 12 h of stirring, on completion of reaction, the suspended acetone solution was filtered and the filtrate was evaporated under reduced pressure. The resulting residue was diluted with water (5 mL) and ethyl acetate (15 mL). The layers were separated, and the aqueous part was extracted with ethyl acetate (3 × 15 mL). The combined organic part was then washed with an aq. saturated $Na_2S_2O_3$ solution (5 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by PLC (25% ethyl acetate−petroleum ether) gave **64** (24 mg, 65%) as a red solid. R_f = 0.3 (20% ethyl acetate−petroleum ether); mp 206−208 °C; ^{1}H ($CDCl_3$, 200 MHz): δ 8.15 (s, 1H), 7.41 (s, 1H), 7.31 (s, 1H), 4.05 (s, 3H), 3.40 (s, 3H), 3.97 (s, 3H), 3.86 (s, 3H), 3.06 (q, 2H, J = 7 Hz), 2.55 (s, 3H), 1.23 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 185.5, 182.0, 167.1, 158.3, 155.5, 153.8, 145.8, 140.3, 137.4, 136.9, 135.8, 134.8, 129.0, 126.8, 126.5, 123.4, 122.0, 118.2, 111.8, 63.5 61.7, 56.8, 52.8, 21.4, 21.0, 15.4; IR (KBr, cm^{-1}) ν_{max} 1732, 1680, 1608, 1588, 1543, 1446, 1408, 1363, 1275, 1226, 1119, 1081, 1053, 869; HRMS (EI+) m/z calcd for $C_{26}H_{23}ClO_7$ $[M^+]$: 482.1132, found 482.1130.

Methyl 2-Chloro-9-ethyl-1,8-dihydroxy-6-methoxy-3-methyl-7,12-dioxo-7,12-dihydrobenz[*a*]anthracene-10-carboxylate (69). To a stirred solution of **64** (16 mg, 0.033 mmol) in dry CH_2Cl_2 (10 mL) was added BCl_3 (1 M CH_2Cl_2, 0.208 mL, 0.208 mmol) dropwise under a N_2 atmosphere at −78 °C. The resulting solution immediately turned black after addition of BCl_3, and it was then allowed to stir at the same temperature for 1 h. The reaction was quenched with water (1 mL) at −78 °C. The usual workup of the resulting mixture using CH_2Cl_2 and H_2O, followed by evaporation of the organic solvent, gave compound **69** (13 mg, 90%) as a black solid. R_f = 0.4 (30% ethyl acetate−petroleum ether); mp >255 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.72 (s, 1H, OH), 10.80 (s, 1H, OH), 8.12 (s, 1H), 7.54 (s, 1H), 7.25 (s, 1H), 4.10 (s, 3H), 4.00 (s, 3H), 3.06 (q, 2H, J = 7.3 Hz), 2.55 (s, 3H), 1.27 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.3, 188.7, 166.8, 160.4, 156.0, 150.5, 143.4, 141.1, 137.5, 137.2, 135.2, 131.0, 127.2, 123.3, 121.3 (Ar−CH), 120.6 (Ar−CH), 117.5 (Ar−CH), 117.3, 115.8, 56.9 (OCH_3), 52.9 (OCH_3), 21.4, 21.0 (CH_2), 14.1; HRMS (EI+) m/z calcd for $C_{24}H_{19}ClO_7$ $[M^+]$: 454.0819, found 454.0816.

Methyl 2-Chloro-9-ethyl-1,6,8-trihydroxy-3-methyl-7,12-dioxo-7,12-dihydrobenz[*a*]anthracene-10-carboxylate (70). To a stirred solution of **69** (8 mg, 0.017 mmol) in dry CH_2Cl_2 (5 mL) was added anhydrous $AlCl_3$ (95 mg, 0.704 mmol, 40 equiv) portionwise under a N_2 atmosphere at 0 °C. The resulting solution gradually turned deep blue, and it was then allowed to stir at rt for 18 h. The reaction was quenched with water (2 mL), and 2 N HCl (1 mL) was added. An usual workup of the mixture using CH_2Cl_2 and H_2O, followed by evaporation of organic solvent, gave compound **70** (5 mg, 64%) as a yellowish solid. R_f = 0.4 (15% ethyl acetate−petroleum ether); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 12.20 (s, 1H, OH), 12.06 (s, 1H, OH), 11.30 (s, 1H), 8.14 (s, 1H), 7.59 (s, 1H), 7.13 (s, 3H), 4.00 (s, 3H), 3.05 (q, 2H, J = 7.3 Hz), 2.51 (s, 3H), 1.28 (t, 3H, J = 7.4 Hz).

Chlorocyclinone A (1).[2] To a stirred solution of **70** (5 mg, 0.011 mmol) in dry acetone (3 mL) was added K_2CO_3 (6 mg, 0.04 mmol) followed by MeI (1 μL, 0.018 mmol) which was added dropwise at 0 °C, and the flask was stoppered. The resulting reaction mixture was then allowed to come to rt, while stirring was continued for 12 h. The newly formed spot found on the TLC plate showed blue coloration when exposed to NH_3 vapor. After completion of the reaction, the suspension was filtered and the filtrate was evaporated under reduced pressure. The resulting residue was diluted with water (2 mL) and ethyl acetate (6 mL), and the layers were separated. The aqueous part was extracted with ethyl acetate (3 × 6 mL). The combined organic part was then washed with aq saturated $Na_2S_2O_3$ solution (2 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by PLC (10% ethyl acetate−petroleum ether) gave **1** (2 mg, 39%) as a red solid. R_f = 0.5 (10% ethyl acetate−petroleum ether);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.10 (s, 1H, OH), 11.50 (s, 1H, OH), 7.98 (s, 1H), 7.43 (s, 1H), 7.36 (s, 1H), 3.99 (s, 3H), 3.83 (s, 3H), 3.04 (q, 2H, J = 7.2 Hz), 2.54 (s, 3H), 1.27 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.3, 183.6, 166.8, 160.7, 156.6, 154.0, 141.6, 140.8, 139.0, 138.1, 137.3, 133.3, 127.1, 123.0, 119.7, 119.6, 119.2, 117.8, 115.7, 61.4, 52.5, 21.3, 20.7, 14.1; HRMS (EI+) m/z calcd for $C_{24}H_{19}ClO_7$ [M + H$^+$]: 455.0897, found 455.0891.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, 2D spectra for all new compounds and X-ray structure of **57**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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