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A consecutive Diels–Alder approach toward a Tet repressor directed combinatorial library

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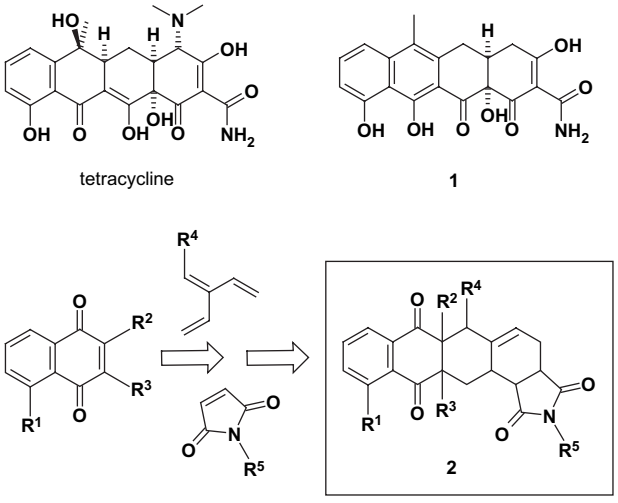
Abstract—A combinatorial library of 180 tetracycline analogs was generated by solution phase parallel synthesis applying a consecutive Diels–Alder strategy. Chemical methodology suitable for three-dimensional solution phase parallel synthesis was developed that enabled us to generate a collection of potential TetR inducers. The synthesis was built on cross-conjugated trienes as central building blocks facilitating two consecutive cycloaddition processes with different dienophiles. Upon sequential exposure to naphthoquinone and maleimide derivatives, the generation of a carbocyclic skeleton of type **2** incorporating the diversity elements R^1–R^5 was envisaged.

1. Introduction

Linking chemical synthesis of natural product derivatives with genetic evolution of biologically active proteins creates an effective bridge between a basic understanding of functional proteins and the discovery of highly potent and selective modulators for gene regulation in prokaryotes and eukaryotes.[1,2] Following this approach, we constructed a mutant of the tetracycline-inducible repressor protein TetR[3,4] displaying specificity for the tetracycline analog **1** (Scheme 1) preventing both antibiotic activity and induction of the wild-type Tet repressor.[5] As a complement to our recent efforts on solid-phase supported combinatorial synthesis,[6,7] we herein present a solution phase parallel synthesis[8] of a tetracycline related compound library of type **2**. According to preliminary studies, the tetracycline mimetic core structure of **2** could be docked into the binding pocket of TetR crystal structure.[9] To provide an efficient approach to the identical four-ring carbocyclic structure as a basic skeleton, our forward directed plan of synthesis was built on a homo-Diels–Alder (HDA) approach allowing an efficient and stereospecific construction of multiple carbon–carbon bonds. Our strategy involved cross-conjugated trienes as central building blocks facilitating two consecutive cycloaddition processes with different dienophiles.[10,11] Upon sequential exposure to naphthoquinone and maleimide derivatives, the generation of a carbocyclic skeleton of type **2** incorporating the diversity elements R^1–R^5 was envisaged.



Scheme 1. Lead compounds and plan of synthesis.

2. Results and discussion

2.1. Elaboration of the key reactions

The usage of Diels–Alder reactions represents a particularly efficient strategy for the parallel synthesis of complex molecular structures.[12] Since we aimed to generate a

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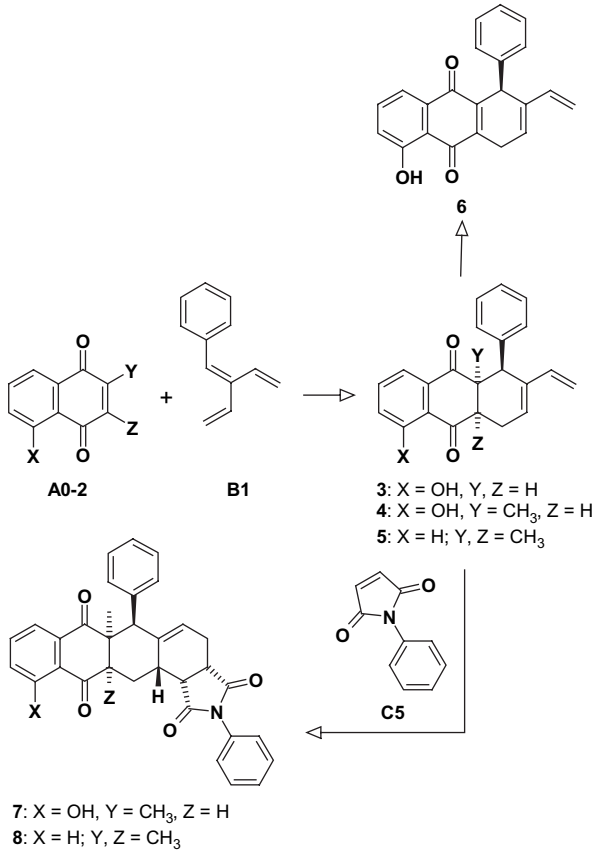
combinatorial compound collection of suitable purity and yield, appropriate reaction conditions for the consecutive Diels–Alder processes have to be elaborated by investigating a model reaction sequence. As a representative central building block, we chose the cross-conjugated triene **B1** that was expected to provide sufficient chemical stability and efficient accessibility. The preparation of **B1**[10,11] was done by γ-pentadienylation of benzaldehyde using 5-bromo-1,3-pentadiene[13] in the presence of indium dust followed by sulfonylation of the formed secondary alcohol and β-elimination. Our initial synthetic investigations were directed to the HDA reaction of the triene **B1** with 5-hydroxynaphthoquinone (**A0**) when heating both components in toluene at 40–60 °C gave a hardly separable mixture of regioisomers together with the respective dehydro-derivatives, which were obviously produced by intermolecular electron transfer. Performing the transformation under Lewis acid-catalyzed conditions at −60 °C produced the cycloaddition product **3** as a pure regioisomer. However, the formation of a substantial amount of the oxidation product **6** was observed after chromatography. To exclude this side reaction, we subjected the 2-methyl substituted hydroxynaphthoquinone **A1** (plumbagin) as well as the 2,3-dimethyl derivative **A2**[14,15] being devoid of an activating 5-hydroxy group to the above mentioned reaction conditions resulting in the formation of the tricyclic products **4** and **5**, respectively. Besides the thermally induced HDA processes, we investigated Lewis acid-mediated conditions at low temperature (−60 °C) using scandium trifluoromethanesulfonate[16] and, alternatively, boron trifluoride diethyl etherate[17] when pure cycloaddition products could be isolated in 70–85% yield. Due to economic reasons, we chose the BF_3 promoted variant as the method of choice. To accommodate conditions in a parallel reactor, the reaction temperature was raised to −30 °C which proved to be possible without significant loss of yield and purity. For the transformation of the hydroxynaphthoquinone derivative **A1**, complete regioselectivity was observed, which is obviously due to secondary orbital interactions. The regiochemical outcome of the reaction could be unambiguously determined by NMR spectroscopy when HMBC experiments clearly indicated that the carbonyl carbon located in β-position to the hydroxy substituent showed cross-peaks to both methylene hydrogens whereas the C═O with the remote hydroxyl group displaying coupling via three bonds with an aromatic hydrogen interacted with the proton adjacent to the phenyl substituent. Since the sterically demanding phenyl group of **B1** was expected to predominantly adopt a trans-orientation with respect to the reactive diene substructure and substantial *endo*-selectivity was assumed for the Diels–Alder process, we anticipated a trans-disposition between the phenyl and the vicinally positioned methyl group, which was confirmed at the final product stage.

An efficient approach of the pentacyclic model compounds **7** and **8** by cycloaddition of the synthetic intermediates **4** and **5**, respectively, with *N*-phenylmaleimide (**C5**) was investigated employing both microwave technology (80 °C for 20 min without use of a solvent) and conventional heating (toluene at 68 °C for 3 days). In fact, application of both techniques resulted in the formation of the final products **7** and **8** in >80% yield (Scheme 2). According to diagnostic NOEs, complete diastereospecifity was observed indicating a cis-selective *endo*-approach of the dienophile opposite to the phenyl substituent to avoid steric interactions. The molecular structure of the racemic pentacyclic target compound **8** could be elucidated by X-ray crystallography (Fig. 1). Interestingly, the pentacyclic scaffold shows a concave shape when the phenyl moiety is located in a sandwich-like manner over the aromatic system of the former naphthoquinone.



Scheme 2. Representative model reactions.

Based on our model studies, reaction conditions could be found that seemed to be robust and reproducible and, thus, suitable for an efficient production of a liquid organic phase supported 3D-library. Since the parallelization of the conventional heating requires substantially less technical sophistication than parallel microwave assisted synthesis, we decided to perform the library production without microwave technology.

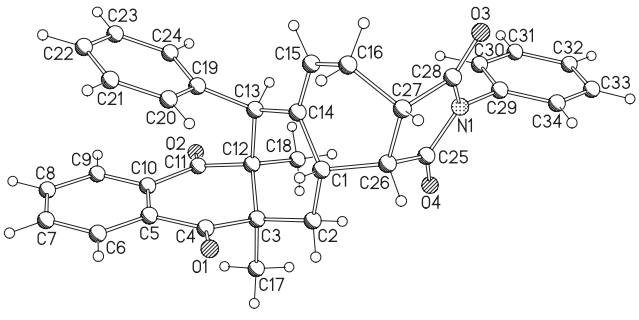
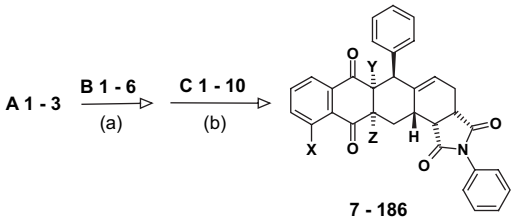


Figure 1. Crystal structure of (3a*S*,6*R*,6a*S*,12a*R*,13a*S*,13b*R*)-**8**.

2.2. Library production

Following the procedure described above, 180 tetracycline analogs should be prepared starting from the naphthoquinones **A1–3**, the cross-conjugated trienes **B1–6** and the maleimides **C1–10** (Scheme 3, Fig. 2).



Scheme 3. Solution phase parallel synthesis. (a) **B1–6**, $BF_3 \cdot Et_2O$, CH_2Cl_2, −30 °C, 16 h. (b) **C1–10**, toluene, 68 °C, 3 days.

Thus, each of the quinones **A1–3** was reacted with the set of cross-conjugated trienes **B1–6** in the presence of boron trifluoride diethyl etherate at −30 °C. After extraction with water, the organic layer had to be separated. This could be done in a very practical manner by adding *n*-hexane to convey the organic layer to the top followed by freezing the aqueous layer at −60 °C and sucking off the liquid organic part. After removal of nonpolar impurities on a short pad of silica gel, each of the 18 tricyclic compounds {**A1–3B1–6**} was distributed to 10 reaction vessels and stirred with the maleimides {**C1–10**} in toluene to afford the 180 tetracycline analogs **7–186** {**A1–3B1–6C1–10**}. After preparative HPLC, the members of the compound collection were obtained in 26.7–86.4% yield. Ninety-five percent of the final products showed purities higher than 90% (Table 1).

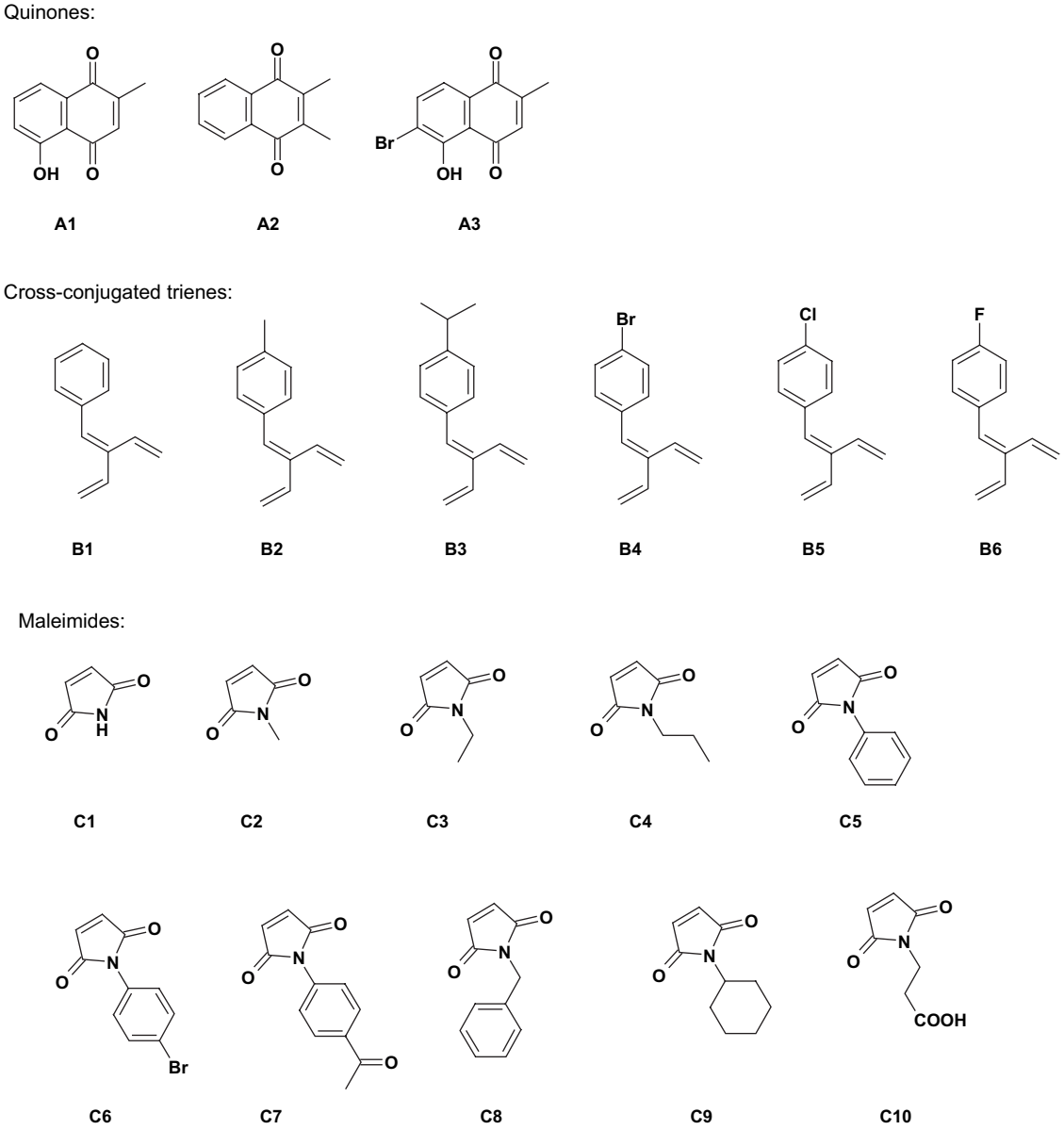


Figure 2. Building blocks.

Table 1. Purities and yields of library products

No.	Building blocks	Purity (LC–MS) (%)	Yield (over two steps) (%)	No.	Building blocks	Purity (LC–MS) (%)	Yield (over two steps) (%)
9	A1B1C1	>99.0	62.4	**97**	A2B4C1	89.9	55.9
10	A1B1C2	>99.0	84.0	**98**	A2B4C2	>99.0	29.8
11	A1B1C3	>99.0	86.4	**99**	A2B4C3	>99.0	54.1
12	A1B1C4	>99.0	83.5	**100**	A2B4C4	>99.0	55.1
7	A1B1C5	>99.0	73.5	**101**	A2B4C5	>99.0	56.9
13	A1B1C6	89.1	82.6	**102**	A2B4C6	98.6	59.2
14	A1B1C7	>99.0	76.6	**103**	A2B4C7	81.7	69.9
15	A1B1C8	>99.0	73.8	**104**	A2B4C8	>99.0	59.2
16	A1B1C9	>99.0	70.4	**105**	A2B4C9	>99.0	42.8
17	A1B1C10	94.0	77.2	**106**	A2B4C10	93.8	65.2
18	A1B2C1	98.0	61.7	**107**	A2B5C1	88.0	54.6
19	A1B2C2	>99.0	70.1	**108**	A2B5C2	>99.0	65.9
20	A1B2C3	>99.0	72.2	**109**	A2B5C3	>99.0	59.9
21	A1B2C4	>99.0	71.8	**110**	A2B5C4	98.9	49.4
22	A1B2C5	>99.0	67.9	**111**	A2B5C5	>99.0	38.0
23	A1B2C6	>99.0	43.4	**112**	A2B5C6	>99.0	67.1
24	A1B2C7	>99.0	61.1	**113**	A2B5C7	88.7	55.7
25	A1B2C8	>99.0	57.4	**114**	A2B5C8	>99.0	57.0
26	A1B2C9	>99.0	71.0	**115**	A2B5C9	>99.0	48.8
27	A1B2C10	>99.0	57.8	**116**	A2B5C10	91.0	58.9
28	A1B3C1	97.7	69.5	**117**	A2B6C1	98.9	64.2
29	A1B3C2	>99.0	85.2	**118**	A2B6C2	94.7	52.0
30	A1B3C3	>99.0	76.1	**119**	A2B6C3	>99.0	61.7
31	A1B3C4	>99.0	61.2	**120**	A2B6C4	>99.0	57.6
32	A1B3C5	97.1	81.7	**121**	A2B6C5	>99.0	47.7
33	A1B3C6	91.1	76.8	**122**	A2B6C6	98.4	54.7
34	A1B3C7	>99.0	75.9	**123**	A2B6C7	95.4	53.5
35	A1B3C8	96.0	58.8	**124**	A2B6C8	>99.0	56.9
36	A1B3C9	94.6	72.3	**125**	A2B6C9	>99.0	68.4
37	A1B3C10	>99.0	56.6	**126**	A2B6C10	95.6	62.9
38	A1B4C1	>99.0	68.6	**127**	A3B1C1	95.5	33.0
39	A1B4C2	>99.0	60.6	**128**	A3B1C2	96.1	47.9
40	A1B4C3	97.4	74.1	**129**	A1B1C3	97.3	58.6
41	A1B4C4	>99.0	60.5	**130**	A3B1C4	96.7	45.7
42	A1B4C5	>99.0	69.6	**131**	A3B1C5	97.4	53.9
43	A1B4C6	96.6	40.3	**132**	A3B1C6	95.7	41.1
44	A1B4C7	>99.0	58.3	**133**	A3B1C7	93.6	31.7
45	A1B4C8	>99.0	84.3	**134**	A3B1C8	92.3	26.7
46	A1B4C9	>99.0	73.7	**135**	A3B1C9	95.1	43.5
47	A1B4C10	87.3	71.4	**136**	A3B1C10	98.2	48.2
48	A1B5C1	>99.0	80.2	**137**	A3B2C1	93.3	45.8
49	A1B5C2	98.4	75.7	**138**	A3B2C2	96.5	33.5
50	A1B5C3	>99.0	53.8	**139**	A3B2C3	>99.0	31.1
51	A1B5C4	>99.0	66.6	**140**	A3B2C4	94.6	27.3
52	A1B5C5	>99.0	55.8	**141**	A3B2C5	93.4	35.8
53	A1B5C6	96.7	43.1	**142**	A3B2C6	96.5	28.2
54	A1B5C7	>99.0	41.0	**143**	A3B2C7	96.0	25.4
55	A1B5C8	>99.0	83.2	**144**	A3B2C8	97.7	30.8
56	A1B5C9	>99.0	61.8	**145**	A3B2C9	95.9	38.3
57	A1B5C10	82.0	60.9	**146**	A3B2C10	98.7	43.3
58	A1B6C1	>99.0	58.7	**147**	A3B3C1	92.1	31.4
59	A1B6C2	97.1	49.5	**148**	A3B3C2	97.6	32.3
60	A1B6C3	>99.0	63.4	**149**	A3B3C3	95.4	28.4
61	A1B6C4	>99.0	76.5	**150**	A3B3C4	98.0	38.5
62	A1B6C5	>99.0	72.3	**151**	A3B3C5	96.3	27.7
63	A1B6C6	95.7	59.6	**152**	A3B3C6	97.4	30.1
64	A1B6C7	>99.0	76.3	**153**	A3B3C7	>99.0	40.2
65	A1B6C8	>99.0	68.1	**154**	A3B3C8	96.6	37.1
66	A1B6C9	>99.0	79.4	**155**	A3B3C9	90.6	31.8
67	A1B6C10	88.6	73.5	**156**	A3B3C10	92.7	20.5
68	A2B1C1	>99.0	61.3	**157**	A3B4C1	>99.0	42.2
69	A2B1C2	>99.0	65.4	**158**	A3B4C2	>99.0	35.8
70	A2B1C3	>99.0	68.0	**159**	A3B4C3	>99.0	38.2
71	A2B1C4	>99.0	63.4	**160**	A3B4C4	>99.0	32.2
8	A2B1C5	98.9	52.4	**161**	A3B4C5	>99.0	38.1
72	A2B1C6	94.9	63.7	**162**	A3B4C6	>99.0	37.6
73	A2B1C7	>99.0	62.2	**163**	A3B4C7	>99.0	48.1
74	A2B1C8	>99.0	59.3	**164**	A3B4C8	>99.0	39.2
75	A2B1C9	>99.0	73.3	**165**	A3B4C9	95.6	32.2
76	A2B1C10	>99.0	71.1	**166**	A3B4C10	93.9	46.5
77	A2B2C1	86.0	58.9	**167**	A3B5C1	95.2	38.7

(*continued*)

Table 1. (*continued*)

No.	Building blocks	Purity (LC–MS) (%)	Yield (over two steps) (%)	No.	Building blocks	Purity (LC–MS) (%)	Yield (over two steps) (%)
78	A2B2C2	>99.0	35.2	**168**	A3B5C2	>99.0	36.0
79	A2B2C3	98.5	80.0	**169**	A3B5C3	>99.0	44.5
80	A2B2C4	94.4	56.8	**170**	A3B5C4	>99.0	34.4
81	A2B2C5	98.2	57.2	**171**	A3B5C5	96.9	43.2
82	A2B2C6	>99.0	54.7	**172**	A3B5C6	>99.0	37.1
83	A2B2C7	>99.0	58.4	**173**	A3B5C7	>99.0	43.8
84	A2B2C8	>99.0	61.4	**174**	A3B5C8	>99.0	36.3
85	A2B2C9	98.7	47.3	**175**	A3B5C9	>99.0	38.7
86	A2B2C10	94.1	55.1	**176**	A3B5C10	94.2	33.7
87	A2B3C1	>99.0	64.7	**177**	A3B6C1	>99.0	40.3
88	A2B3C2	>99.0	64.5	**178**	A3B6C2	>99.0	36.2
89	A2B3C3	>99.0	44.4	**179**	A3B6C3	>99.0	33.4
90	A2B3C4	>99.0	57.0	**180**	A3B6C4	>99.0	37.9
91	A2B3C5	>99.0	59.7	**181**	A3B6C5	>99.0	37.6
92	A2B3C6	95.1	54.3	**182**	A3B6C6	>99.0	29.6
93	A2B3C7	96.1	41.0	**183**	A3B6C7	>99.0	32.1
94	A2B3C8	>99.0	58.2	**184**	A3B6C8	>99.0	38.3
95	A2B3C9	97.1	55.2	**185**	A3B6C9	>99.0	42.2
96	A2B3C10	>99.0	53.9	**186**	A3B6C10	98.5	39.6

3. Summary

In summary, a consecutive Diels–Alder approach was exploited for a highly regio- and stereoselective two-step synthesis of a TetR directed library of carbocyclic scaffolds in racemic form. Chemical methodology suitable for three-dimensional solution phase parallel synthesis was developed that enabled us to generate a collection of 180 potential TetR inducers.

4. Experimental

4.1. General

Absolute solvents (over molecular sieves) and starting materials obtained from commercial source were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were determined on a BRUKER AVANCE 360 or a BRUKER AVANCE 600 spectrometer in solution. COSY, HSQC, HMBC and NOE spectra (600 MHz) spectra were determined in solution using instrument BRUKER AVANCE 600. LC–MS analyses were conducted using an Agilent Binary Gradient System in combination with ChemStation Software (MeOH/0.1 N aq HCOOH 10/90–90/10) applying a Zorbax SB-C8 (4.6 mm×150 mm, 5 μm) column, UV detection at 254 nm and a flow rate of 0.5 mL/min. Mass detection was pointed out with a Bruker Esquire 2000 ion-trap-mass spectrometer using an APC ionization source. EIMS spectra were recorded on FINNIGAN MAT TSQ 700 spectrometer. HRMS were determined on a JOEL GCmateII at a resolution of $M/\Delta M>5000$. CHN elementary analyses were done at the laboratory of Ilse Beetz, Kronach. Silica gel (40–63 μm) was used for a purification step. Preparative HPLC was conducted using an Agilent 1100 Series system applying a Eurospher-C18 (4.6 mm×250 mm, 7 μm) with H_2O and acetonitrile both containing 0.1% of trifluoroacetic acid (gradient 0–80% acetonitrile) with a flow rate of 20 mL/min.

4.2. Preparation of the quinones A1–3

A2 was readily prepared by a chromium-(VI)-oxide catalyzed oxidation of 2,3-dimethylnaphthalene with periodic acid.[14] **A3** was obtained by the bromination of commercially available **A1**.[18]

4.3. Preparation of the cross-conjugated trienes B1–6[10,11,19]

Indium powder (100 mesh, 282 mg, 2.46 mmol) was added in portions to a solution of 5-bromo-1,3-pentadiene (657 mg, 4.47 mmol) and aromatic aldehyde (2.23 mmol) in DMF (2.23 mL) at 0 °C. After stirring for 5 h at 0 °C, temperature was allowed to rise to 10 °C. The mixture was diluted with CH_2Cl_2 (15 mL) and poured into diethyl ether (190 mL). The resulting turbid mixture was filtered through a pad of silica gel and washed with an additional amount of ether. Evaporation of the solvent and purification of the crude intermediate by flash chromatography on silica gel using *n*-hexane/ethyl acetate (10:1) resulted in the desired secondary alcohol. Mesyl chloride (1.35 mL, 17.5 mmol) was added dropwise to a solution of this intermediate (13.1 mmol) and triethylamine (2.74 mL, 19.7 mmol) in CH_2Cl_2 (100 mL) at −50 °C. The resulting mixture was allowed to warm to −30 °C over 45 min and poured into a half saturated aqueous solution of $NaHCO_3$ (100 mL). Subsequent extraction with diethyl ether (3×100 mL), treatment with Na_2SO_4, filtration and evaporation of the solvent resulted in the crude methane sulfonate, which was dissolved in dry benzene (100 mL), treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (2.4 mL, 15.7 mmol) and gently heated at 44 °C for 3 h. Flash column chromatography of the concentrated crude mixture employing *n*-hexane furnished the trienes **B1–6** in 54–66% overall yield.

4.3.1. 1-Isopropyl-4-(2-vinylbuta-1,3-dienyl)benzol B3. MS *m/z* 198 (M^+). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.29 (d, J=7.0 Hz, 6H), 2.94 (sept, J=7.0 Hz, 1H), 5.22 (d,

J=10.7 Hz, 1H), 5.37 (d, J=11.1 Hz, 1H), 5.47 (d, J=17.7 Hz, 1H), 5.55 (d, J=17.3 Hz, 1H), 6.58 (dd, J=17.3 Hz, 10.7 Hz, 1H), 6.65 (br s, 1H), 6.76 (dd, J=17.7 Hz, 11.1 Hz, 1H), 7.20–7.25 (m, 2H), 7.32–7.36 (m, 2H).

4.3.2. 1-Brom-4-(2-vinylbuta-1,3-dienyl)benzol B4. MS m/z 234 (M^+ ^{79}Br). ^1H NMR (360 MHz, $CDCl_3$): δ 5.26 (dd, J=10.8 Hz, 1.0 Hz, 1H), 5.41 (dt, J=11.0 Hz, 1.4 Hz, 1H), 5.49 (d, J=17.7 Hz, 1.5 Hz, 1H), 5.57 (dd, J=17.3 Hz, 1.4 Hz, 1H), 6.56 (ddd, J=17.3 Hz, 10.8 Hz, 1.0 Hz, 1H), 6.57 (br s, 1H), 6.66 (dd, J=17.7 Hz, 11.1 Hz, 1H), 7.24–7.29 (m, 2H), 7.41–7.46 (m, 2H).

4.3.3. 1-Chlor-4-(2-vinylbuta-1,3-dienyl)benzol B5. MS m/z 190 (M^+). ^1H NMR (360 MHz, $CDCl_3$): δ 5.26 (dd, J=10.7 Hz, 1.0 Hz, 1H), 5.41 (dt, J=11.0 Hz, 0.9 Hz, 1H), 5.49 (dd, J=17.6 Hz, 1.6 Hz, 1H), 5.57 (dd, J=17.4 Hz, 1.5 Hz, 1H), 6.57 (ddd, J=17.4 Hz, 10.7 Hz, 1.0 Hz, 1H), 6.60 (br s, 1H), 6.66 (ddd, J=17.6 Hz, 11.1 Hz, 0.9 Hz, 1H), 7.31–7.35 (m, 4H).

4.3.4. 1-Fluor-4-(2-vinylbuta-1,3-dienyl)benzol B6. MS m/z 174 (M^+). ^1H NMR ($CDCl_3$): δ 5.23 (br d, J=10.6 Hz, 1H), 5.38 (br d, J=11.1 Hz, 1H), 5.47 (dd, J=17.8 Hz, 1.3 Hz, 1H), 5.54 (dd, J=17.2 Hz, 1.3 Hz, 1H), 6.55 (br dd, J=17.2 Hz, 10.6 Hz, 1H), 6.60 (br s, 1H), 6.65 (br dd, J=17.8 Hz, 11.1 Hz, 1H), 7.01–7.06 (m, 2H), 7.33–7.37 (m, 2H).

4.4. General procedure for synthesis of tricyclic compounds {A1–3/B1–6}

A solution of quinone **A1–3** (1.5 mmol) and cross-conjugated triene **B1–6** (1.5 mmol) in dichloromethane (6 mL) was cooled to −30 °C under inert atmosphere. Boron trifluoride diethyl etherate (0.5 mL) was added dropwise within 5 min. After stirring for 1 h, the reaction mixture was treated with an additional amount of **B1–6** (0.75 mmol). The solution was allowed to stir overnight. After addition of H_2O (6 mL) the reaction mixture was allowed to warm to 0 °C under vigorous stirring. Treatment with *n*-hexane (6 mL) followed by cooling to −60 °C resulted in freezing of the aqueous layer. The supernatant organic phase was removed by pipetting and evaporated under reduced pressure. Crude purification of the resulting residue was performed by adsorption to silica gel, whereas the un-reacted triene and non-polar side-products were removed by washing with *n*-hexane (500 mL). Elution using dichloromethane (500 mL) and subsequent evaporation of the solvent afforded the tricyclic compounds {**A1–3/B1–6**}, which were used for the next step without further purification.

4.4.1. (1*RS*,4a*RS*,9a*SR*)-5-Hydroxy-9a-methyl-1-phenyl-2-vinyl-1,4,4a,9a-tetrahydroanthracene-9,10-dione 4. MS m/z 344 (M^+). ^1H NMR (360 MHz, acetone-d_6): δ 1.65 (s, 3H), 2.53 (m, 1H), 3.42 (br d, J=8.2 Hz, 1H), 3.62 (br dd, J=20.3 Hz, 4.5 Hz, 1H), 3.79 (s, 1H), 4.77 (d, J=10.7 Hz, 1H), 4.78 (d, J=17.7 Hz, 1H), 6.21 (m, 1H), 6.34 (dd, J=17.7 Hz, 10.7 Hz, 1H), 6.76–6.87 (m, 5H), 6.91 (dd, J=8.1 Hz, 1.2 Hz, 1H), 7.34 (dd, J=7.7 Hz, 1.2 Hz, 1H), 7.42 (dd, J=8.1 Hz, 7.7 Hz, 1H), 11.72 (s, 1H). ^{13}C NMR (90 MHz, acetone-d_6): δ 20.1, 23.4, 47.6, 49.8, 52.0, 112.1, 117.6, 117.9, 122.0, 127.0, 127.6 (2C), 128.1, 129.2 (2C), 135.0, 135.2, 135.6, 138.2, 138.5, 159.7, 199.2, 203.2.

4.4.2. (1*RS*,4a*RS*,9a*SR*)-4a,9a-Dimethyl-1-phenyl-2-vinyl-1,4,4a,9a-tetrahydroanthracene-9,10-dione 5. MS m/z 342 (M^+). ^1H NMR (360 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.65 (s, 3H), 2.10 (m, 1H), 3.62 (br dd, J=19.8 Hz, 4.8 Hz, 1H), 3.84 (s, 1H), 4.65 (d, J=17.6 Hz, 1H), 4.78 (d, J=11.0 Hz, 1H), 6.15 (m, 1H), 6.26 (dd, J=17.6 Hz, 11.0 Hz, 1H), 6.68–6.83 (m, 5H), 7.39 (m, 2H), 7.55–7.61 (m, 1H), 7.77–7.81 (m, 1H).

4.5. General procedure for synthesis of pentacyclic compounds {A1–3/B1–6/C1–10}

Each of the compounds {**A1–3/B1–6**} was divided into 10 parts. Every part was placed in a sealed glass tube with the maleimides **C1–10** (5 equiv) under nitrogen. Toluene (1 mL) was added to each reaction vessel. The solution was stirred for 3 days at 68 °C. Removal of the solvent under reduced pressure and further purification by HPLC afforded the pentacyclic compounds {**A1–3/B1–6/C1–10**}.

4.5.1. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-11-Hydroxy-6a-methyl-6-phenyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 9 {A1,B1,C1}. MS m/z 441 (M^+). ^1H NMR (600 MHz, $CDCl_3$): δ 1.45 (s, 3H), 2.16 (m, 1H), 2.57–2.62 (2H), 2.85 (m, 1H), 2.99 (ddd, J=14.4 Hz, 10.0 Hz, 6.0 Hz, 1H), 3.18 (ddd, J=10.1 Hz, 8.3 Hz, 1.4 Hz, 1H), 3.24–3.27 (2H), 3.53 (br s, 1H), 5.46 (m, 1H), 6.99–7.03 (m, 2H), 7.04–7.07 (m, 1H), 7.07–7.11 (m, 2H), 7.10 (br d, J=8.2 Hz, 1H), 7.33 (br d, J=7.5 Hz, 1H), 7.49 (dd, J=8.2 Hz, 7.5 Hz, 1H), 7.97 (br s, 1H), 11.92 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.9, 24.9, 25.2, 32.6, 41.2, 45.2, 52.8, 53.2, 56.1, 117.2, 118.6, 122.9, 124.1, 127.1, 127.9 (2C), 130.6 (2C), 135.8, 136.6, 139.3, 140.3, 160.7, 178.2, 179.1, 199.4, 204.4. Exact mass (EI^+) m/z calcd for $C_{27}H_{23}NO_5$: 441.1576. Found: 441.1577.

4.5.2. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-2-Ethyl-11-hydroxy-6a-methyl-6-phenyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 11 {A1,B1,C3}. MS m/z 469 (M^+). ^1H NMR (600 MHz, $CDCl_3$): δ 1.11 (t, J=7.2 Hz, 3H), 1.45 (s, 3H), 2.13 (m, 1H), 2.63 (br dd, J=15.8 Hz, 7.4 Hz, 1H), 2.66 (ddd, J=14.0 Hz, 8.0 Hz, 5.7 Hz, 1H), 2.84 (m, 1H), 3.01–3.14 (2H), 3.17 (dd, J=8.5 Hz, 5.4 Hz, 1H), 3.29 (dd, J=5.7 Hz, 5.7 Hz, 1H), 3.45 (br s, 1H), 3.52 (q, J=7.2 Hz, 2H), 5.39 (m, 1H), 6.98–7.13 (m, 5H), 7.13 (dd, J=8.4 Hz, 8.0 Hz, 1H), 7.33 (dd, J=7.6 Hz, 1.0 Hz, 1H), 7.53 (dd, J=8.4 Hz, 7.6 Hz, 1H), 11.97 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.1, 23.2, 25.2 (2C), 33.0, 33.7, 40.0, 44.1, 52.9, 53.4, 56.2, 117.2, 118.7, 122.9, 123.9, 127.2, 127.9 (2C), 130.8 (2C), 136.0, 136.8, 139.0, 140.4, 160.8, 178.3, 179.3, 199.6, 204.6. Exact mass (EI^+) m/z calcd for $C_{29}H_{27}NO_5$: 469.1889. Found: 469.1890.

4.5.3. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-11-Hydroxy-6a-methyl-2,6-diphenyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 7 {A1,B1,C5}. MS m/z 517 (M^+). ^1H NMR (600 MHz, $CDCl_3$): δ 1.44 (s, 3H), 2.24 (m, 1H), 2.66–2.76 (2H), 2.93

(m, 1H), 3.04 (ddd, 15.0 Hz, 9.5 Hz, 6.0 Hz, 1H), 3.29–3.33 (2H), 3.39 (dd, *J*=8.6 Hz, 5.5 Hz, 1H), 3.50 (br s, 1H), 5.50 (m, 1H), 7.03–7.07 (m, 2H), 7.08–7.19 (6H), 7.35 (br d, *J*=7.5 Hz, 1H), 7.40–7.44 (m, 1H), 7.45–7.51 (m, 2H), 7.54 (dd, *J*=8.1 Hz, 7.5 Hz, 1H), 11.98 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 23.5, 25.2, 25.5, 33.1, 40.3, 44.4, 52.9, 53.5, 56.5, 117.1, 118.6, 122.9, 123.9, 126.5 (2C), 127.2, 128.0 (2C), 128.8 (2C), 129.3 (2C), 130.7, 131.8, 136.0, 136.8, 138.8, 140.6, 160.8, 177.6, 178.5, 199.4, 204.5. Exact mass (EI^+) *m*/*z* calcd for $C_{33}H_{27}NO_5$: 517.1889. Found: 517.1884. Anal. Calcd for $C_{33}H_{27}NO_5$: C, 76.58; H, 5.26; N, 2.71. Found: C, 76.58; H, 5.43; N, 2.40.

4.5.4. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-2-Ethyl-11-hydroxy-6a-methyl-6-(4-methylphenyl)-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 20 {A1,B2,C3}. MS *m*/*z* 483 (M^+). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.09 (t, *J*=7.2 Hz, 3H), 1.43 (s, 3H), 2.11 (m, 1H), 2.22 (s, 3H), 2.61 (br dd, *J*=15.5 Hz, 7.2 Hz, 1H), 2.65 (ddd, *J*=14.4 Hz, 7.9 Hz, 5.7 Hz, 1H), 2.80 (m, 1H), 3.04 (ddd, *J*=14.4 Hz, 9.8 Hz, 5.8 Hz, 1H), 3.09 (br dd, *J*=8.6 Hz, 7.7 Hz, 1H), 3.15 (dd, *J*=8.6 Hz, 5.7 Hz, 1H), 3.27 (dd, *J*=5.8 Hz, 5.7 Hz, 1H), 3.40 (br s, 1H), 3.50 (q, *J*=7.2 Hz, 2H), 5.38 (m, 1H), 6.85–6.89 (m, 2H), 6.89–6.94 (m, 2H), 7.14 (br d, *J*=8.2 Hz, 1H), 7.32 (br d, *J*=7.6 Hz, 1H), 7.53 (dd, *J*=8.2 Hz, 7.6 Hz, 1H), 12.00 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.1, 20.9, 23.3, 25.2, 25.3, 33.1, 33.7, 40.0, 44.0, 52.9, 53.4, 55.8, 117.2, 118.6, 122.7, 123.7, 126.5, 128.6 (2C), 130.5 (2C), 135.6, 136.1, 136.7, 136.8, 140.5, 160.8, 178.3, 179.2, 199.6, 204.6. Exact mass (EI^+) *m*/*z* calcd for $C_{30}H_{29}NO_5$: 483.2046. Found: 483.2045.

4.5.5. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-11-Hydroxy-6a-methyl-6-(4-methylphenyl)-2-phenyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 22 {A1,B2,C5}. MS *m*/*z* 531 (M^+). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.43 (s, 3H), 2.21 (m, 1H), 2.25 (s, 3H), 2.65–2.75 (2H), 2.90 (m, 1H), 3.02 (m, 1H), 3.25–3.32 (2H), 3.37 (dd, *J*=8.5 Hz, 5.7 Hz, 1H), 3.46 (br s, 1H), 5.49 (m, 1H), 6.69–6.94 (m, 2H), 6.94–6.99 (m, 2H), 7.12–7.20 (3H), 7.34 (br d, *J*=7.6 Hz, 1H), 7.39–7.45 (m, 1H), 7.45–7.51 (m, 2H), 7.54 (dd, *J*=8.3 Hz, 7.6 Hz, 1H), 12.01 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.9, 23.7, 25.3, 25.5, 33.2, 40.3, 44.4, 53.0, 53.4, 56.0, 117.2, 118.6, 122.8, 123.6, 126.5 (2C), 128.7 (2C), 128.8, 129.3 (2C), 130.6 (2C), 131.8, 135.4, 136.1, 136.8, 136.9, 140.8, 160.8, 177.6, 178.5, 199.6, 204.6. Exact mass (EI^+) *m*/*z* calcd for $C_{34}H_{29}NO_5$: 531.2046. Found: 531.2039.

4.5.6. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-2-(4-Bromophenyl)-11-hydroxy-6-(4-isopropylphenyl)-6a-methyl-3a,4,6,6a,12a,13,13a,13b-octa-hydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 34 {A1,B3,C7}. MS *m*/*z* 637 (M^+ ^{79}Br). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.12 (d, *J*=6.8 Hz, 3H), 1.13 (d, *J*=6.8 Hz, 3H), 1.46 (s, 3H), 2.27 (m, 1H), 2.67–2.77 (m, 3H), 2.94–3.05 (2H), 3.24 (dd, *J*=5.5 Hz, 4.8 Hz, 1H), 3.33 (ddd, *J*=10.4 Hz, 8.6 Hz, 2.0 Hz, 1H), 3.40 (br dd, *J*=8.6 Hz, 5.5 Hz, 1H), 3.52 (br s, 1H), 5.54 (m, 1H), 6.85–6.87 (m, 2H), 6.89–6.92 (m, 2H), 7.07 (br d, *J*=8.3 Hz, 1H), 7.08–7.11 (m, 2H), 7.32 (br d, *J*=7.6 Hz, 1H), 7.47 (dd, *J*=8.3 Hz, 7.6 Hz, 1H), 7.60–7.63 (m, 2H), 11.89 (s, 1H). Exact mass (EI^+) *m*/*z* calcd for $C_{36}H_{32}^{79}BrNO_5$ (M^+): 637.1464. Found: 637.1464.

4.5.7. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-6-(4-Bromophenyl)-2-cyclohexyl-11-hydroxy-6a-methyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 46 {A1,B4,C9}. MS *m*/*z* 601 (M^+ ^{79}Br). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.19–1.34 (m, 3H), 1.36 (s, 3H), 1.42–1.48 (m, 2H), 1.65–1.69 (m, 1H), 1.80–1.85 (m, 2H), 2.01–2.16 (m, 3H), 2.51–2.61 (m, 2H), 2.71 (m, 1H), 2.96 (ddd, *J*=14.5 Hz, 8.5 Hz, 6.1 Hz, 1H), 3.04–3.11 (m, 2H), 3.28–3.32 (m, 2H), 3.86–3.93 (m, 1H), 5.30 (m, 1H), 6.95–7.01 (m, 2H), 7.19 (dd, *J*=8.3 Hz, 0.9 Hz, 1H), 7.23–7.27 (m, 2H), 7.33 (dd, *J*=7.7 Hz, 0.9 Hz, 1H), 7.58 (dd, *J*=8.3 Hz, 7.7 Hz, 1H), 11.97 (s, 1H). Exact mass (EI^+) *m*/*z* calcd for $C_{33}H_{32}^{79}BrNO_5$ (M^+): 601.1464. Found: 601.1464.

4.5.8. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-6-(4-Chlorophenyl)-2-ethyl-11-hydroxy-6a-methyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 50 {A1,B5,C3}. MS *m*/*z* 503 (M^+). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.08 (t, *J*=7.1 Hz, 3H), 1.37 (s, 3H), 2.11 (m, 1H), 2.54–2.65 (m, 2H), 2.74 (m, 1H), 3.03 (ddd, *J*=14.6 Hz, 9.0 Hz, 6.2 Hz, 1H), 2.99–3.06 (m, 1H), 3.11–3.15 (m, 1H), 3.30 (dd, *J*=6.4 Hz, 6.2 Hz, 1H), 3.36 (br s, 1H), 3.49 (q, *J*=7.1 Hz, 2H), 5.32 (m, 1H), 6.99–7.03 (m, 2H), 7.09–7.13 (m, 2H), 7.18 (br d, *J*=8.4 Hz, 1H), 7.32 (br d, *J*=7.6 Hz, 1H), 7.56 (dd, *J*=8.4 Hz, 7.6 Hz, 1H), 11.96 (s, 1H). Exact mass (EI^+) *m*/*z* calcd for $C_{29}H_{26}ClNO_5$: 503.1499. Found: 503.1499.

4.5.9. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-2-Benzyl-6-(4-fluorophenyl)-11-hydroxy-6a-methyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 65 {A1,B6,C8}. MS *m*/*z* 549 (M^+). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.25 (s, 3H), 2.12 (m, 1H), 2.52 (ddd, *J*=14.6 Hz, 6.6 Hz, 6.4 Hz, 1H), 2.64 (br dd, *J*=15.3 Hz, 7.6 Hz, 1H), 2.74 (m, 1H), 2.94 (ddd, *J*=14.6 Hz, 9.0 Hz, 6.2 Hz, 1H), 3.11–3.18 (3H), 3.24 (dd, *J*=6.4 Hz, 6.2 Hz, 1H), 4.58 (d, *J*=14.2 Hz, 1H), 4.63 (d, *J*=14.2 Hz, 1H), 5.28 (m, 1H), 6.77–6.82 (m, 2H), 6.87–6.91 (m, 2H), 7.16 (br d, *J*=8.3 Hz, 1H), 7.24–7.32 (m, 5H), 7.29 (br d, *J*=7.6 Hz, 1H), 7.54 (dd, *J*=8.3 Hz, 7.6 Hz, 1H), 11.94 (s, 1H). Exact mass (EI^+) *m*/*z* calcd for $C_{34}H_{28}FNO_5$: 549.1952. Found: 549.1951.

4.5.10. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-6a,12a-Dimethyl-6-phenyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 68 {A2,B1,C1}. MS *m*/*z* 439 (M^+). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.22 (s, 3H), 1.59 (s, 3H), 2.17 (m, 1H), 2.54–2.60 (2H), 2.78 (dd, *J*=13.9 Hz, 12.3 Hz, 1H), 3.19 (m, 1H), 3.21 (ddd, *J*=8.6 Hz, 8.3 Hz, 2.1 Hz, 1H), 3.31 (dd, *J*=8.6 Hz, 6.1 Hz, 1H), 3.74 (br s, 1H), 5.46 (m, 1H), 6.60–6.65 (m, 2H), 6.82–6.87 (m, 3H), 7.47 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.1 Hz, 1H), 7.52 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.1 Hz, 1H), 7.60 (br d, *J*=7.5 Hz, 1H), 7.82 (br d, *J*=7.5 Hz, 1H), 8.25 (br s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.8, 25.1, 26.9, 29.4, 33.8, 41.3, 44.5, 51.7, 56.9, 57.3, 125.3, 125.9, 126.8, 126.8, 127.7 (2C), 130.1 (2C), 133.3, 133.6, 133.8, 135.7, 139.7, 141.1, 178.6, 179.5, 200.5, 201.2. Exact mass (EI^+) *m*/*z* calcd for $C_{28}H_{25}NO_4$: 439.1784. Found: 439.1784.

4.5.11. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-2-Ethyl-6a,12a-dimethyl-6-phenyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 70 {A2,B1,C3}. MS *m/z* 467 (M^+). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.10 (t, *J*=7.2 Hz, 3H), 1.23 (s, 3H), 1.57 (s, 3H), 2.13 (m, 1H), 2.55–2.61 (2H), 2.86 (dd, *J*=14.0 Hz, 12.2 Hz, 1H), 3.13 (ddd, *J*=8.5 Hz, 8.4 Hz, 1.6 Hz, 1H), 3.14 (m, 1H), 3.20 (dd, *J*=8.5 Hz, 5.9 Hz, 1H), 3.51 (q, *J*=7.2 Hz, 1H), 3.63 (br s, 1H), 5.37 (m, 1H), 6.57–6.61 (m, 2H), 6.85–6.91 (m, 3H), 7.50 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.54 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.61 (br d, *J*=7.5 Hz, 1H), 7.85 (br d, *J*=7.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.1, 20.9, 25.3, 26.7, 29.4, 33.6, 34.3, 40.1, 43.2, 51.8, 56.9, 57.2, 125.3, 126.0, 126.9, 126.9, 127.6 (2C), 130.1 (2C), 133.4, 133.6, 133.8, 135.9, 139.8, 140.6, 178.4, 179.3, 200.4, 201.1. Exact mass (EI^+) *m/z* calcd for $C_{30}H_{29}NO_4$: 467.2097. Found: 467.2098.

4.5.12. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-6a,12a-Dimethyl-2,6-diphenyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 8 {A2,B1,C5}. MS *m/z* 515 (M^+). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.58 (s, 3H), 2.26 (m, 1H), 2.64 (dd, *J*=13.9 Hz, 7.4 Hz, 1H), 2.67 (ddd, *J*=16.0 Hz, 6.8 Hz, 1.9 Hz, 1H), 2.86 (dd, *J*=13.9 Hz, 12.3 Hz, 1H), 3.25 (m, 1H), 3.33 (ddd, *J*=8.5 Hz, 8.3 Hz, 1.9 Hz, 1H), 3.43 (dd, *J*=8.5 Hz, 5.9 Hz, 1H), 3.70 (br s, 1H), 5.49 (m, 1H), 6.63–6.67 (m, 2H), 6.88–6.93 (m, 3H), 7.16–7.19 (m, 2H), 7.39–7.44 (m, 1H), 7.45–7.50 (m, 2H), 7.52 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.1 Hz, 1H), 7.56 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.1 Hz, 1H), 7.65 (br d, *J*=7.5 Hz, 1H), 7.87 (br d, *J*=7.5 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.9, 25.5, 26.8, 29.7, 34.3, 40.3, 43.5, 51.8, 57.0, 57.6, 125.2, 126.0, 126.5 (2C), 126.9, 127.0, 127.7 (2C), 128.7, 129.2 (2C), 130.1 (2C), 133.4, 133.7, 133.8, 135.8, 139.9, 140.5, 177.5, 178.6, 200.4, 201.1. Exact mass (EI^+) *m/z* calcd for $C_{34}H_{29}NO_4$: 515.2097. Found: 515.2097. Anal. Calcd for $C_{34}H_{29}NO_4$: C, 79.20; H, 5.67; N, 2.72. Found: C, 79.20; H, 5.64; N, 2.78.

4.5.13. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-6a,12a-Dimethyl-6-(4-methylphenyl)-2-propyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra-[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 80 {A2,B2,C4}. MS *m/z* 495 (M^+). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.82 (t, *J*=7.4 Hz, 3H), 1.22 (s, 3H), 1.46–1.56 (2H), 1.54 (s, 3H), 2.14 (m, 1H), 2.53–2.59 (2H), 2.86 (dd, *J*=14.1 Hz, 12.1 Hz, 1H), 3.08 (m, 1H), 3.12 (ddd, *J*=8.4 Hz, 8.2 Hz, 1.8 Hz, 1H), 3.18 (dd, *J*=8.6 Hz, 5.8 Hz, 1H), 3.42 (m, 2H), 3.58 (br s, 1H), 5.36 (m, 1H), 6.43–6.47 (m, 2H), 6.65–6.69 (m, 2H), 7.51 (ddd, *J*=8.6 Hz, 7.6 Hz, 1.1 Hz, 1H), 7.55 (ddd, *J*=8.6 Hz, 7.6 Hz, 1.1 Hz, 1H), 7.60 (br dd, *J*=7.6 Hz, 1.1 Hz, 1H), 7.85 (br dd, *J*=7.6 Hz, 1.1 Hz, 1H). Exact mass (EI^+) *m/z* calcd for $C_{32}H_{33}NO_4$: 495.2410. Found: 495.2410.

4.5.14. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-6a,12a-Dimethyl-6-(4-methylphenyl)-2-phenyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra-[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 81 {A2,B2,C5}. MS *m/z* 529 (M^+). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.22 (s, 3H), 1.54 (s, 3H), 2.11 (s, 3H), 2.23 (m, 1H), 2.61 (dd, *J*=14.1 Hz, 7.2 Hz, 1H), 2.67 (ddd, *J*=15.9 Hz, 6.8 Hz, 2.1 Hz, 1H), 2.84 (dd, *J*=14.1 Hz, 12.1 Hz, 1H), 3.19 (m, 1H), 3.31 (ddd, *J*=8.4 Hz, 8.2 Hz, 2.1 Hz, 1H), 3.41 (dd, *J*=8.4 Hz, 5.9 Hz, 1H), 3.63 (br s, 1H), 5.47 (m, 1H), 6.49–6.53 (m, 2H), 6.70–6.74 (m, 2H), 7.13–7.17 (m, 2H), 7.38–7.43 (m, 1H), 7.44–7.49 (m, 2H), 7.53 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.57 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.65 (br dd, *J*=7.5 Hz, 1.2 Hz, 1H), 7.87 (br dd, *J*=7.5 Hz, 1.2 Hz, 1H). Exact mass (EI^+) *m/z* calcd for $C_{35}H_{31}NO_4$: 529.2253. Found: 529.2253.

4.5.15. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-2-(4-Acetylphenyl)-6-(4-isopropylphenyl)-6a,12a-dimethyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 92 {A2,B3,C6}. MS *m/z* 599 (M^+). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.02 (d, *J*=6.8 Hz, 6H), 1.19 (s, 3H), 1.57 (s, 3H), 2.31 (m, 1H), 2.57–2.67 (2H), 2.65 (s, 3H), 2.68 (ddd, *J*=16.0 Hz, 6.8 Hz, 2.2 Hz, 1H), 2.76 (dd, *J*=14.1 Hz, 12.1 Hz, 1H), 3.33 (m, 1H), 3.36 (ddd, *J*=8.5 Hz, 8.3 Hz, 2.2 Hz, 1H), 3.47 (dd, *J*=8.5 Hz, 6.0 Hz, 1H), 3.73 (br s, 1H), 5.55 (m, 1H), 6.52–6.57 (m, 2H), 6.65–6.70 (m, 2H), 7.36–7.40 (m, 2H), 7.44 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.48 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.63 (br dd, *J*=7.5 Hz, 1.2 Hz, 1H), 7.78 (br dd, *J*=7.5 Hz, 1.2 Hz, 1H), 8.06–8.09 (m, 2H). Exact mass (EI^+) *m/z* calcd for $C_{39}H_{37}NO_5$: 599.2672. Found: 599.2672.

4.5.16. 3-[(3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-6-(4-Isopropylphenyl)-6a,12a-dimethyl-1,3,7,12-tetraoxo-1,3,3a,4,6,6a,7,12,12a,13,13a,13b-dodecahydro-2*H*-anthra[2,3-*e*]isoindol-2-yl]propanoic acid 96 {A2,B3,C10}. MS *m/z* 553 (M^+). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.01 (d, *J*=6.8 Hz, 6H), 1.19 (s, 3H), 1.56 (s, 3H), 2.18 (m, 1H), 2.54–2.63 (3H), 2.64 (t, *J*=7.2 Hz, 2H), 2.79 (dd, *J*=14.1 Hz, 12.0 Hz, 1H), 3.17 (ddd, *J*=8.4 Hz, 8.2 Hz, 2.1 Hz, 1H), 3.21 (m, 1H), 3.25 (dd, *J*=8.4 Hz, 5.9 Hz, 1H), 3.71 (br s, 1H), 3.80 (m, 2H), 5.43 (m, 1H), 6.49–6.53 (m, 2H), 6.62–6.66 (m, 2H), 7.42 (ddd, *J*=7.6 Hz, 7.6 Hz, 1.2 Hz, 1H), 7,45 (ddd, *J*=7.6 Hz, 7.6 Hz, 1.2 Hz, 1H), 7.59 (br dd, *J*=7.6 Hz, 1.2 Hz, 1H), 7.75 (br dd, *J*=7.6 Hz, 1.2 Hz, 1H). Exact mass (EI^+) *m/z* calcd for $C_{34}H_{35}NO_6$: 553.2464. Found: 553.2463.

4.5.17. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-6-(4-Bromophenyl)-2,6a,12a-trimethyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 98 {A2,B4,C2}. MS *m/z* 531 (M^+ ^{79}Br). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.56 (s, 3H), 2.15 (m, 1H), 2.54–2.61 (2H), 2.85 (dd, *J*=14.1 Hz, 12.0 Hz, 1H), 2.95 (s, 3H), 3.13 (m, 1H), 3.17 (ddd, *J*=8.4 Hz, 8.2 Hz, 2.1 Hz, 1H), 3.23 (dd, *J*=8.4 Hz, 5.9 Hz, 1H), 3.65 (br s, 1H), 5.36 (m, 1H), 6.44–6.50 (m, 2H), 6.93–6.99 (m, 2H), 7.53 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.57 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.60 (br dd, *J*=7.5 Hz, 1.2 Hz, 1H), 7.82 (br dd, *J*=7.5 Hz, 1.2 Hz, 1H). Exact mass (EI^+) *m/z* calcd for $C_{29}H_{26}^{79}BrNO_4$ (M^+): 531.1045. Found: 531.1041.

4.5.18. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-6-(4-Bromophenyl)-2-cyclohexyl-6a,12a-dimethyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 105 {A2,B4,C9}. MS *m/z* 599 (M^+ ^{79}Br). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.18–1.36 (m, 3H), 1.23 (s, 3H), 1.42–1.50 (m, 2H), 1.55 (s, 3H), 1.62–1.71 (m, 1H), 1.78–1.88 (m, 2H), 2.00–2.17 (3H), 2.52–2.58 (2H), 2.80 (dd, *J*=14.1 Hz, 12.1 Hz, 1H), 3.06 (m, 1H), 3.08

(ddd, *J*=15.9 Hz, 6.8 Hz, 2.1 Hz, 1H), 3.14 (dd, 8.4 Hz, 5.9 Hz, 1H), 3.56 (br s, 1H), 3.90 (m, 1H), 5.33 (m, 1H), 6.42–6.49 (m, 2H), 6.97–7.03 (m, 2H), 7.56 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.60 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.63 (br dd, *J*=7.5 Hz, 1.2 Hz, 1H), 7.87 (br dd, *J*=7.5 Hz, 1.2 Hz, 1H). Exact mass (EI^+) *m/z* calcd for $C_{34}H_{34}^{79}BrNO_4$ (M^+): 599.1671. Found: 599.1675.

4.5.19. 3-[(3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-6-(4-Bromophenyl)-6a,12a-dimethyl-1,3,7,12-tetra-oxo-1,3,3a,4,6,6a,7,12,12a,13,13a,13b-dodeca-hydro-2*H*-anthra-[2,3-*e*]isoindol-2-yl]propanoic acid 106 {A2,B4,C10}. MS *m/z* 589 (M^+ ^{79}Br). ^1H NMR (600 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.56 (s, 3H), 2.14 (m, 1H), 2.54–2.60 (2H), 2.61 (dd, *J*=7.2 Hz, *J*=7.2 Hz, 2H), 2.84 (dd, *J*=14.1 Hz, 12.1 Hz, 1H), 3.12 (m, 1H), 3.16 (ddd, *J*=8.5 Hz, 8.3 Hz, 1.6 Hz, 1H), 3.22 (dd, *J*=8.5 Hz, 5.7 Hz, 1H), 3.64 (br s, 1H), 3.78 (m, 2H), 5.35 (m, 1H), 6.45–6.50 (m, 2H), 6.95–6.99 (m, 2H), 7.54 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.56–7.62 (2H), 7.84 (dd, *J*=7.5 Hz, 1.2 Hz, 1H). Exact mass (EI^+) *m/z* calcd for $C_{31}H_{28}^{79}BrNO_6$ (M^+): 589.1100. Found: 589.1098.

4.5.20. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-6-(4-Chlorophenyl)-6a,12a-dimethyl-2-phenyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra-[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 111 {A2,B5,C5}. MS *m/z* 549 (M^+). ^1H NMR (600 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.56 (s, 3H), 2.25 (m, 1H), 2.62 (dd, *J*=14.1 Hz, 7.2 Hz, 1H), 2.69 (ddd, *J*=15.9 Hz, 6.8 Hz, 2.1 Hz, 1H), 2.85 (dd, *J*=14.1 Hz, 12.1 Hz, 1H), 3.22 (m, 1H), 3.33 (ddd, *J*=8.4 Hz, 8.2 Hz, 2.1 Hz, 1H), 3.42 (dd, *J*=8.4 Hz, 5.9 Hz, 1H), 3.68 (br s, 1H), 5.46 (m, 1H), 6.54–6.59 (m, 2H), 6.84–6.88 (m, 2H), 7.14–7.18 (m, 2H), 7.39–7.43 (m, 1H), 7.44–7.50 (m, 2H), 7.56 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.60 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.2 Hz, 1H), 7.65 (br dd, *J*=7.5 Hz, 1.2 Hz, 1H), 7.87 (br dd, *J*=7.5 Hz, 1.2 Hz, 1H). Exact mass (EI^+) *m/z* calcd for $C_{34}H_{28}ClNO_4$: 549.1707. Found: 549.1705.

4.5.21. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-2-Ethyl-6-(4-fluorophenyl)-6a,12a-dimethyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 119 {A2,B6,C3}. MS *m/z* 485 (M^+). ^1H NMR (600 MHz, $CDCl_3$): δ 1.09 (t, *J*=7.2 Hz, 3H), 1.22 (s, 3H), 2.55 (s, 3H), 2.12 (m, 1H), 2.57 (dd, *J*=14.2 Hz, 7.6 Hz, 1H), 2.59 (ddd, *J*=15.8 Hz, 6.8 Hz, 2.1 Hz, 1H), 2.85 (dd, *J*=14.2 Hz, 12.0 Hz, 1H), 3.10 (m, 1H), 3.13 (ddd, *J*=8.4 Hz, 8.2 Hz, 2.1 Hz, 1H), 3.19 (dd, *J*=8.4 Hz, 5.7 Hz, 1H), 3.51 (q, *J*=7.2 Hz, 2H), 3.63 (br s, 1H), 5.35 (m, 1H), 6.51–6.59 (m, 4H), 7.53 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.1 Hz, 1H), 7.57 (ddd, *J*=7.5 Hz, 7.5 Hz, 1.1 Hz, 1H), 7.62 (br dd, *J*=7.5 Hz, 1.1 Hz, 1H), 7.85 (br dd, *J*=7.5 Hz, 1.1 Hz, 1H). Exact mass (EI^+) *m/z* calcd for $C_{30}H_{28}FNO_4$: 485.2002. Found: 485.1999.

4.5.22. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-2-Benzyl-6-(4-fluorophenyl)-6a,12a-dimethyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 124 {A2,B6,C8}. MS *m/z* 547 (M^+). ^1H NMR (600 MHz, $CDCl_3$): δ 1.16 (s, 3H), 1.37 (s, 3H), 2.13 (m, 1H), 2.51 (dd, *J*=14.1 Hz, 7.6 Hz, 1H), 2.62 (ddd, *J*=15.8 Hz, 7.1 Hz, 2.1 Hz, 1H), 2.69 (dd, *J*=14.1 Hz, 12.0 Hz, 1H), 3.12 (m, 1H), 3.18 (ddd, *J*=8.4 Hz, 8.2 Hz, 2.1 Hz, 1H), 3.23 (dd, *J*=8.4 Hz, 5.9 Hz, 1H), 3.41 (br s, 1H), 4.58 (d, *J*=14.0 Hz, 1H), 4.65 (d, *J*=14.0 Hz, 1H), 5.32 (m, 1H), 6.41–6.47 (m, 2H), 6.47–6.53 (m, 2H), 7.25–7.32 (m, 5H), 7.50 (br dd, *J*=7.6 Hz, 7.6 Hz, 1H), 7.55 (br dd, *J*=7.6 Hz, 7.6 Hz, 1H), 7.55 (br d, *J*=7.6 Hz, 1H), 7.83 (br d, *J*=7.6 Hz, 1H). Exact mass (EI^+) *m/z* calcd for $C_{35}H_{30}FNO_4$: 547.2159. Found: 547.2159.

4.5.23. 3-[(3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-10-Bromo-11-hydroxy-6a,12a-dimethyl-1,3,7,12-tetraoxo-6-phenyl-1,3,3a,4,6,6a,7,12,12a,13,13a,13b-dodeca-hydro-2*H*-anthra[2,3-*e*]isoindol-2-yl]propanoic acid 136 {A3,B1,C10}. MS *m/z* 591 (M^+ ^{79}Br). ^1H NMR (600 MHz, $CDCl_3$): δ 1.46 (s, 3H), 2.16 (m, 1H), 2.61 (t, *J*=7.2 Hz, 2H), 2.61 (dd, 1H), 2.65 (ddd, *J*=14.5 Hz, 8.1 Hz, 5.4 Hz, 1H), 2.86 (m, 1H), 3.05 (ddd, *J*=14.5 Hz, 10.0 Hz, 6.0 Hz, 1H), 3.15 (ddd, *J*=8.5 Hz, 8.3 Hz, 1.3 Hz, 1H), 3.20 (dd, *J*=8.5 Hz, 5.4 Hz, 1H), 3.29 (dd, *J*=6.0 Hz, 5.4 Hz, 1H), 3.50 (br s, 1H), 3.78 (t, *J*=7.2 Hz, 2H), 5.42 (m, 1H), 6.94–7.00 (m, 2H), 7.04–7.12 (m, 3H), 7.21 (d, *J*=8.1 Hz, 1H), 7.76 (d, *J*=8.1 Hz, 1H), 12.61 (s, 1H). Exact mass (EI^+) *m/z* calcd for $C_{30}H_{26}^{79}BrNO_7$ (M^+): 591.0893. Found: 591.0896.

4.5.24. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-10-Bromo-2-ethyl-11-hydroxy-6a,12a-dimethyl-6-(4-methylphenyl)-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra-[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 139 {A3,B2,C3}. MS *m/z* 561 (M^+ ^{79}Br). ^1H NMR (600 MHz, $CDCl_3$): δ 1.10 (t, *J*=7.2 Hz, 3H), 1.45 (s, 3H), 2.13 (m, 1H), 2.19 (s, 3H), 2.62 (ddd, *J*=15.7 Hz, 7.2 Hz, 1.4 Hz, 1H), 2.67 (ddd, *J*=14.4 Hz, 8.1 Hz, 5.2 Hz, 1H), 2.86 (m, 1H), 3.05 (ddd, *J*=14.4 Hz, 10.1 Hz, 6.0 Hz, 1H), 3.12 (ddd, *J*=9.4 Hz, 8.1 Hz, 1.4 Hz, 1H), 3.17 (dd, *J*=8.5 Hz, 5.8 Hz, 1H), 3.27 (dd, *J*=6.0 Hz, 5.2 Hz, 1H), 3.44 (br s, 1H), 3.51 (q, *J*=7.2 Hz, 2H), 5.42 (m, 1H), 6.75–6.79 (m, 2H), 6.85–6.89 (m, 2H), 7.21 (d, *J*=8.1 Hz, 1H), 7.76 (d, *J*=8.1 Hz, 1H), 12.64 (s, 1H). Exact mass (EI^+) *m/z* calcd for $C_{30}H_{28}^{79}BrNO_5$ (M^+): 561.1151. Found: 561.1151.

4.5.25. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-10-Bromo-2-(4-bromophenyl)-11-hydroxy-6-(4-isopropylphenyl)-6a,12a-dimethyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 153 {A3,B3,C7}. MS *m/z* 717 (M^+ $^{79}Br/^{81}Br$). ^1H NMR (600 MHz, $CDCl_3$): δ 1.10 (d, *J*=6.8 Hz, 3H), 1.10 (d, *J*=6.8 Hz, 3H), 1.51 (s, 3H), 2.29 (m, 1H), 2.66–2.79 (3H), 3.01 (ddd, *J*=14.7 Hz, 10.5 Hz, 6.0 Hz, 1H), 3.11 (m, 1H), 3.25 (dd, *J*=5.5 Hz, 4.4 Hz, 1H), 3.35 (ddd, *J*=8.5 Hz, 8.5 Hz, 2.1 Hz, 1H), 3.43 (dd, *J*=8.7 Hz, 6.0 Hz, 1H), 3.60 (br s, 1H), 5.59 (m, 1H), 6.75–6.79 (m, 2H), 6.83–6.87 (m, 2H), 7.10–7.14 (m, 2H), 7.21 (d, *J*=8.2 Hz, 1H), 7.60–7.64 (m, 5H), 7.68 (d, *J*=8.2 Hz, 1H), 12.50 (s, 1H). Exact mass (EI^+) *m/z* calcd for $C_{36}H_{31}^{79}Br_2NO_5$ (M^+): 715.0569. Found: 715.0570.

4.5.26. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-2-Benzyl-10-bromo-11-hydroxy-6-(4-isopropylphenyl)-6a,12a-dimethyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra-[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 154 {A3,B3,C8}. MS *m/z* 651 (M^+ ^{79}Br). ^1H NMR (600 MHz, $CDCl_3$): δ 1.08 (d, *J*=6.8 Hz, 3H), 1.09 (d, *J*=6.8 Hz, 3H), 1.32

(s, 3H), 2.17 (m, 1H), 2.63–2.71 (3H), 2.94 (m, 1H), 2.99 (m, 1H), 3.17 (dd, *J*=5.9 Hz, 4.4 Hz, 1H), 3.20 (ddd, *J*=9.4 Hz, 8.1 Hz, 1.4 Hz, 1H), 3.24 (dd, *J*=8.7 Hz, 5.8 Hz, 1H), 3.42 (br s, 1H), 4.62 (d, *J*=14.0 Hz, 1H), 4.67 (d, *J*=14.0 Hz, 1H), 5.48 (m, 1H), 6.64–6.68 (m, 2H), 6.78–6.82 (m, 2H), 7.16 (d, *J*=8.2 Hz, 1H), 7.24–7.32 (m, 5H), 7.65 (d, *J*=8.2 Hz, 1H), 12.49 (s, 1H). Exact mass (EI^+) *m/z* calcd for $C_{37}H_{34}^{79}BrNO_5$ (M^+): 651.1620. Found: 651.1624.

4.5.27. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-10-Bromo-6-(4-bromophenyl)-11-hydroxy-6a,12a-dimethyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 157 {A3,B4,C1}. MS *m/z* 599 (M^+ $^{79}Br/^{81}Br$). ^1H NMR (600 MHz, $CDCl_3$): δ 1.41 (s, 3H), 2.16 (m, 1H), 2.56 (ddd, *J*=14,8 Hz, 8.3 Hz, 6.1 Hz, 1H), 2.62 (ddd, *J*=16.1 Hz, 7.2 Hz, 1.4 Hz, 1H), 2.78 (m, 1H), 3.00 (ddd, *J*=14.8 Hz, 9.3 Hz, 6.4 Hz, 1H), 3.19 (ddd, *J*=8.4 Hz, 8.3 Hz, 1.4 Hz, 1H), 3.24 (dd, *J*=8.7 Hz, 5.5 Hz, 1H), 3.31 (dd, *J*=6.4 Hz, 6.1 Hz, 1H), 3.45 (br s, 1H), 5.44 (m, 1H), 6.93–6.97 (m, 2H), 7.23 (d, *J*=8.1 Hz, 1H), 7.24–7.27 (m, 2H), 7.67 (br s, 1H), 7.83 (d, *J*=8.1 Hz, 1H), 12.60 (s, 1H). Exact mass (EI^+) *m/z* calcd for $C_{27}H_{21}^{79}Br_2NO_5$ (M^+): 596.9786. Found: 596.9783.

4.5.28. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-2-(4-Acetylphenyl)-10-bromo-6-(4-chlorophenyl)-11-hydroxy-6a,12a-dimethyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 172 {A3,B5,C6}. MS *m/z* 673 (M^+ ^{81}Br). ^1H NMR (600 MHz, $CDCl_3$): δ 1.38 (s, 3H), 2.27 (m, 1H), 2.62 (m, 1H), 2.64 (s, 3H), 2.74 (br dd, *J*=15.9 Hz, 7.1 Hz, 1H), 2.87 (m, 1H), 3.02 (ddd, *J*=14.9 Hz, 8.8 Hz, 6.2 Hz, 1H), 3.29 (ddd, *J*=9.0 Hz, 8.6 Hz, 1.9 Hz, 1H), 3.34 (dd, *J*=6.4 Hz, 6.2 Hz, 1H), 3.39 (dd, *J*=8.6 Hz, 5.3 Hz, 1H), 3.42 (br s, 1H), 5.48 (m, 1H), 6.99–7.04 (m, 2H), 7.23–7.26 (m, 2H), 7.25 (d, *J*=8.1 Hz, 1H), 7.30–7.34 (m, 2H), 7.84 (d, *J*=8.1 Hz, 1H), 8.05–8.08 (m, 2H), 12.62 (s, 1H). Exact mass (EI^+) *m/z* calcd for $C_{35}H_{27}^{79}BrClNO_6$ (M^+): 671.0710. Found: 671.0710.

4.5.29. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-10-Bromo-2-(4-bromophenyl)-6-(4-fluorophenyl)-11-hydroxy-6a,12a-dimethyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 183 {A3,B6,C7}. MS *m/z* 693 (M^+ $^{79}Br/^{81}Br$). ^1H NMR (600 MHz, $CDCl_3$): δ 1.38 (s, 3H), 2.25 (m, 1H), 2.62 (ddd, *J*=14.8 Hz, 8.3 Hz, 6.4 Hz, 1H), 2.73 (ddd, *J*=15.8 Hz, 7.1 Hz, 1.4 Hz, 1H), 2.87 (m, 1H), 3.02 (ddd, *J*=14.8 Hz, 9.0 Hz, 6.1 Hz, 1H), 3.30 (ddd, *J*=9.1 Hz, 8.4 Hz, 1.4 Hz, 1H), 3.34 (dd, *J*=6.4 Hz, 6.1 Hz, 1H), 3.36 (dd, *J*=8.4 Hz, 5.3 Hz, 1H), 3.43 (br s, 1H), 5.46 (m, 1H), 6.83–6.89 (m, 2H), 7.00–7.05 (m, 2H), 7.04–7.08 (m, 2H), 7.25 (d, *J*=8.1 Hz, 1H), 7.58–7.63 (m, 2H), 7.83 (d, *J*=8.1 Hz, 1H), 12.63 (s, 1H). Exact mass (EI^+) *m/z* calcd for $C_{33}H_{24}^{79}Br_2FNO_5$ (M^+): 691.0005. Found: 691.0019.

4.5.30. (3a*RS*,6*SR*,6a*RS*,12a*SR*,13a*RS*,13b*SR*)-2-Benzyl-10-bromo-6-(4-fluorophenyl)-11-hydroxy-6a,12a-dimethyl-3a,4,6,6a,12a,13,13a,13b-octahydro-1*H*-anthra[2,3-*e*]isoindole-1,3,7,12(2*H*)-tetrone 184 {A3,B6,C8}. MS *m/z* 627 (M^+ ^{79}Br). ^1H NMR (600 MHz, $CDCl_3$): δ 1.25 (s, 3H), 2.13 (m, 1H), 2.25 (ddd, *J*=14.7 Hz, 8.6 Hz, 6.4 Hz, 1H), 2.65 (br dd, *J*=15.8 Hz, 7.3 Hz, 1H), 2.75 (m, 1H), 2.95 (ddd, *J*=14.7 Hz, 8.8 Hz, 6.1 Hz, 1H), 3.13–3.19 (3H), 3.27 (dd, *J*=6.4 Hz, 6.1 Hz, 1H), 4.59 (d, *J*=14.1 Hz, 1H), 4.63 (d, *J*=14.1 Hz, 1H), 5.30 (m, 1H), 6.77–6.82 (m, 2H), 6.84–6.88 (m, 2H), 7.19 (d, *J*=8.1 Hz, 1H), 7.25–7.31 (m, 5H), 7.81 (d, *J*=8.1 Hz, 1H), 12.62 (s, 1H). Exact mass (EI^+) *m/z* calcd for $C_{34}H_{27}^{79}BrFNO_5$ (M^+): 627.1057. Found: 627.1059.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.04.092.

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