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1,4,9,10-Anthradiquinone as precursor for antitumor compounds

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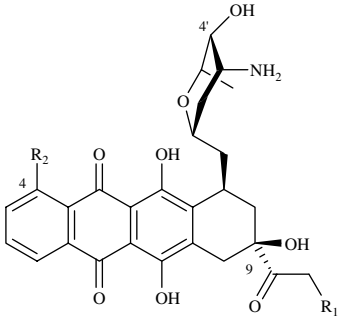
Abstract—1,4,9,10-Anthradiquinone **5** was reacted with enamines **6** in the Nenitzescu reaction to yield unexpected 3,3a,6,12-tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxo-naphtho[2,3-*d*]indol-1-carboxylates **8A**. However, anthracycline-like naphtho-condensed 5-hydroxyindoles were not obtained from this diquinone. It yielded similar reaction products of the Nenitzescu reaction like other quinones activated by two electron-withdrawing groups. Furthermore, these new compounds **8A** were found to constitute precursors for the synthesis of azonines. The conversion to dibenzoazonines **13** occurred in an unusual and up to now unknown way consisting of isomerization, ring opening, and re-closure. 2-Chloro-anthradiquinone **19** reacted with enamines **6** as vinylogeous acid chloride to pyrroloanthraquinone **20**. No substitution of chlorine was observed. Naphtho-condensed indoles **26** were obtained by the reactions of unsubstituted 1,4-anthraquinone **25** with enamines **6** via the normal Nenitzescu route. Indoles **26** were converted to Mannich bases, reacting further to dimers by the Diels–Alder reaction of intermediate *o*-quinone methides. Most of the synthesized heterocycles were evaluated for their anticancer properties in the NCI's human-disease oriented in vitro anticancer screen. Particularly, carbinolamines **8A** exhibited inhibitory activity of tumor cell growth and thus they constitute a new class of lead structures for anticancer drug design.

1. Introduction

Anthracycline antibiotics (e.g., daunorubicin, doxorubicin, idarubicin, and epirubicin) represent an important class of antitumor drugs. They are among the most widely used drugs for cancer chemotherapy, characteristically consisting of a four-membered fused ring system derived from naphthacen and a *p*-quinone moiety (Fig. 1). Within our ongoing research a modified Nenitzescu reaction was developed,[1,5–7] with regard to the synthesis of new heterocyclic and cytotoxic compounds with similar structure and cytotoxic activity like anthracyclines and presumed to act via intercalation into DNA.[1–4] Aminomethyleneindanones **2**, completely substituted at position 2, were employed instead of utilizing conventional 3-aminocrotonates as enamine components. Their reaction with unsubstituted 1,4-benzoquinone **1** was accompanied by intramolecular rearrangement of a spiro-intermediate **3** and yielded quinonoid 5*H*-benzo[*b*]carbazoles **4** (Scheme 1).[2,5–7] Synthetic pathways, anticancer activities as well as structure–activity relationships for this series of compounds have recently been published.[3] Continuing this work, we now investigated the reaction of alkyl β-aminocrotonates **6** and 1,4,9,10-anthradiquinone **5**



R_1 = H, R_2 = OCH_3	**daunorubicin**
R_1 = OH, R_2 = OCH_3	**doxorubicin**
R_1 = H, R_2 = H	**idarubicin**
4'-epi-doxorubicin	**epirubicin**

Figure 1. Anthracycline antibiotics.

Keywords: Ring enlargement; Nenitzescu reaction; Quinones; Enamines, Azonine; Cytostatic activity.
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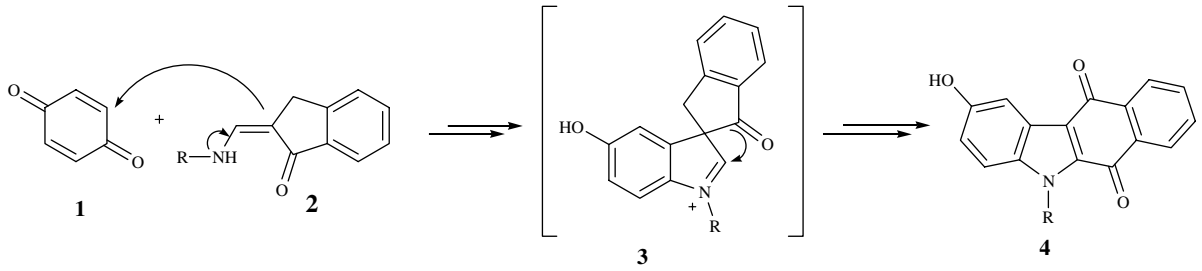
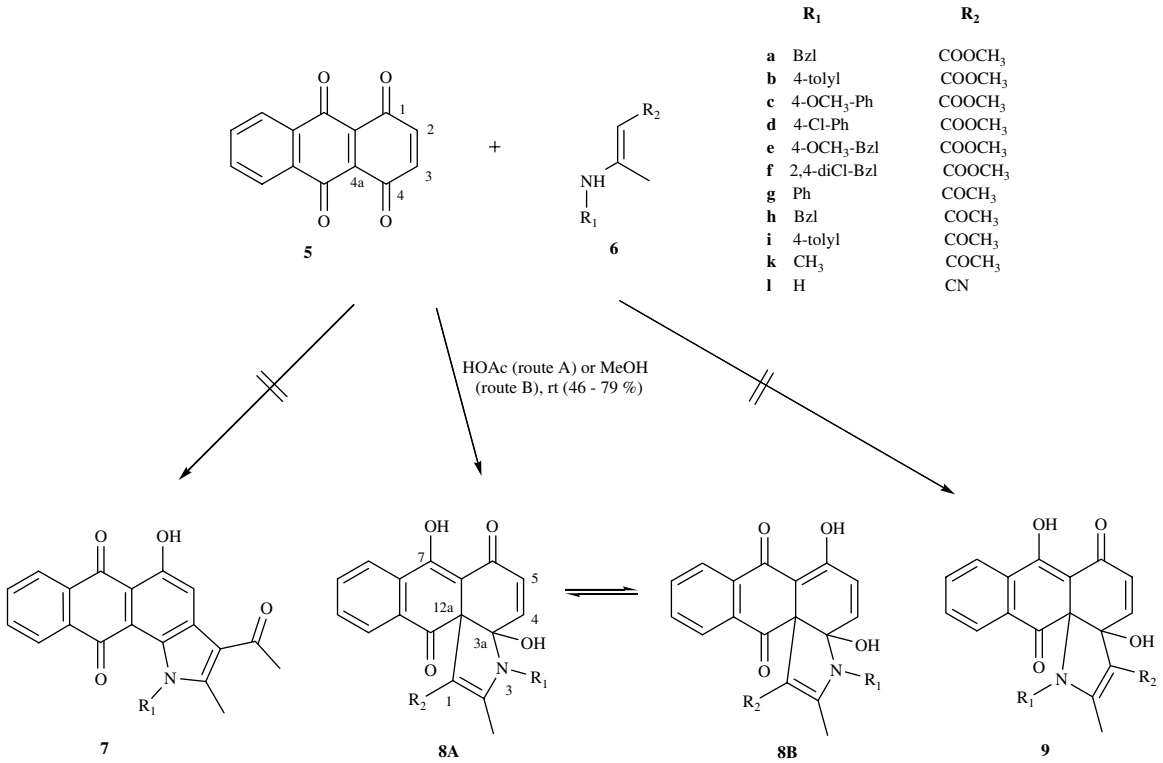


Scheme 1. Modified Nenitzescu reaction with *p*-benzoquinone **1** and aminomethyleneindanones **2** leading to benzocarbazolediones **4**.

with the aim to obtain indoles **7** via a 'normal' Nenitzescu route (Scheme 2). These compounds would consist of a fused heterocyclic ring system with a *p*-quinone substructure similar to that of anthracycline chromophores, which should be able to intercalate into DNA and therefore exhibit cytotoxic activity.

2. Chemistry

All Nenitzescu reactions of **5** with **6** were carried out either in glacial acetic acid (route A) or in dry methanol (route B) at room temperature. Main products were obtained in yields between 46% and 79%. They precipitated as solids after dissolving or suspending quinone **5**[8] in the appropriate solvent and subsequently adding an equimolar amount of a solution or suspension of the respective enamine **6** (Scheme 2). Product structures **8A** could be determined by NMR spectroscopic methods and X-ray analysis. The first step in the course of the Nenitzescu reaction normally consists of a nucleophilic attack of the β-carbon of the starting enamine to an electrophilic carbon atom of the quinone. In the case of the symmetric quinone **5**, there are different conceivable electrophilic positions for a nucleophilic addition: The attack at the activated carbon 2 should finally lead to typical Nenitzescu products **7**, containing a 5-hydroxyindol substructure and would be in accordance with the reaction mechanism proposed for aminomethyleneindanones **2** with *p*-benzoquinones **1** in Scheme 1. The addition at carbon 4a, activated by two carbonyl groups, however should lead to the formation of spirocyclic compounds **8A/B**. Additionally, it is also quite possible that the enamine β-carbon attacks the carbonyl C-4, which should lead to the formation of compounds **9**. Since the ^{1}H NMR spectra of all products still showed a coupling between the hydrogens in positions 2 and 3 of quinone **5** (AB-system), indoles **7** could thus be excluded. Moreover, ^{13}C NMR data for the benzyl-substituted compound revealed two additional sp^{3}-carbon atoms (93.86 and 59.05 ppm for **8Aa**), which is compatible with spirocyclic compounds **8** and **9**, respec-

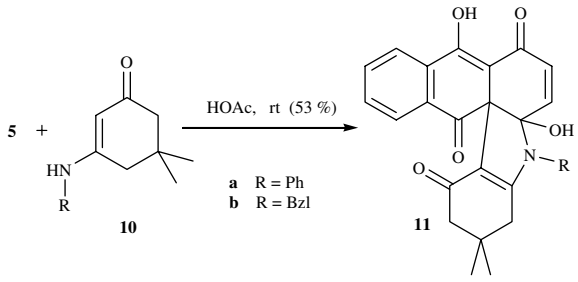


Scheme 2. Synthesis of compounds **8A** from quinone **5** and enamines **6**.

tively. Though the highly deshielded sp^3-carbon at 93.86 ppm would indicate carbinolamine structures **8**, their isomers **9** could not be excluded. Determination of the constitution of **8A** was made by X-ray analysis (Fig. 2). All enamines **6a**–**l** (aminocrotonates, aminopentenones, and aminocrotonitrile) utilized followed the same reaction pathway. Even cyclic enamines **10** within the dimedon series reacted analogously to yield the pentacyclic products **11** under the same conditions in 53% yield (Scheme 3).

In order to obtain the desired aromatic indoles, the acid-labile carbinolamines **8A** were then treated with methanolic hydrochloric acid (3.5 N) at room temperature. Complete disappearance of the starting material and formation of a new main product was observed after 1 h. But surprisingly, though the sp^3-signals for carbons 3a and 12a of **8A** disappeared in the ^{13}C NMR spectrum, indicating a complete rearrangement, indoles were not obtained. Mass spectra as well as elemental analysis provided evidence of an isomeric structure. Since ring opening of carbinolamine **8A** and re-closure to the isomeric carbinolamine **12** seemed to be possible under these conditions, a reaction pathway from **8A** via **12** leading to dibenzo[*c*,*f*]azonine derivatives **13** was developed (Scheme 4). Indeed, the hydroquinonoid substructure in **13a**–**c** was proven by acetylation to **14a**–**c**, utilizing acetic anhydride and catalytic amounts of pyridine (61–65% yield), and oxidation to the corresponding *p*-quinones **15** with silver(I)oxide in diethyl ether (64–74% yield). Due to the unusual and strange formation of an unsaturated nine-membered ring system, which was up to that time unknown in the literature, an additional X-ray crystal structure determination of the acetone solvate of **13d** was performed (Fig. 3). The azonine ring nearly adopts a boat conformation stabilized by an intramolecular hydrogen bond between its carbonyl oxygen and the phenolic hydrogen.

Since the new heterocyclic quinones **15** were now easily accessible and the antitumor activity of azonines **13**, **14**, and **15** was not satisfactory, we tried to modify the structure by reaction with enamines **6 a**,**b**,**d**,**e**,**g** to indoles **16**. However, not the desired indoles **16** were produced, but benzofuranes **17** or **18** were isolated (Scheme 5). Comparison of ^1H NMR-spectra of benzofuranes with those of the other azonines **13**, **14**, and **15** led to benzofurane structure **17**. This was in agreement with the expected chemical properties of quinone **15**. Due to conjugation of nitrogen with 12-C-carbonyl, the higher electrophilic activity in position 11 favors the addition of enamine **6** with subsequent ring closure to furane.



Scheme 3. Synthesis of compounds **11a** and **11b**.

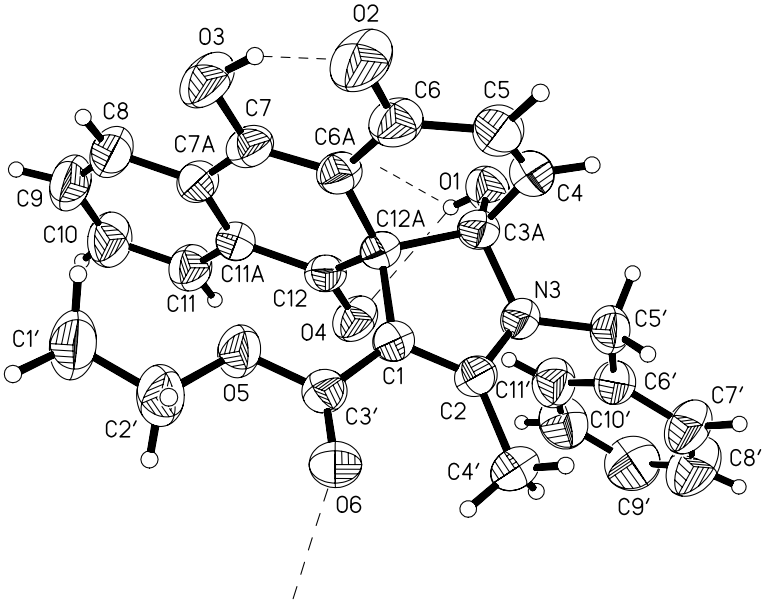
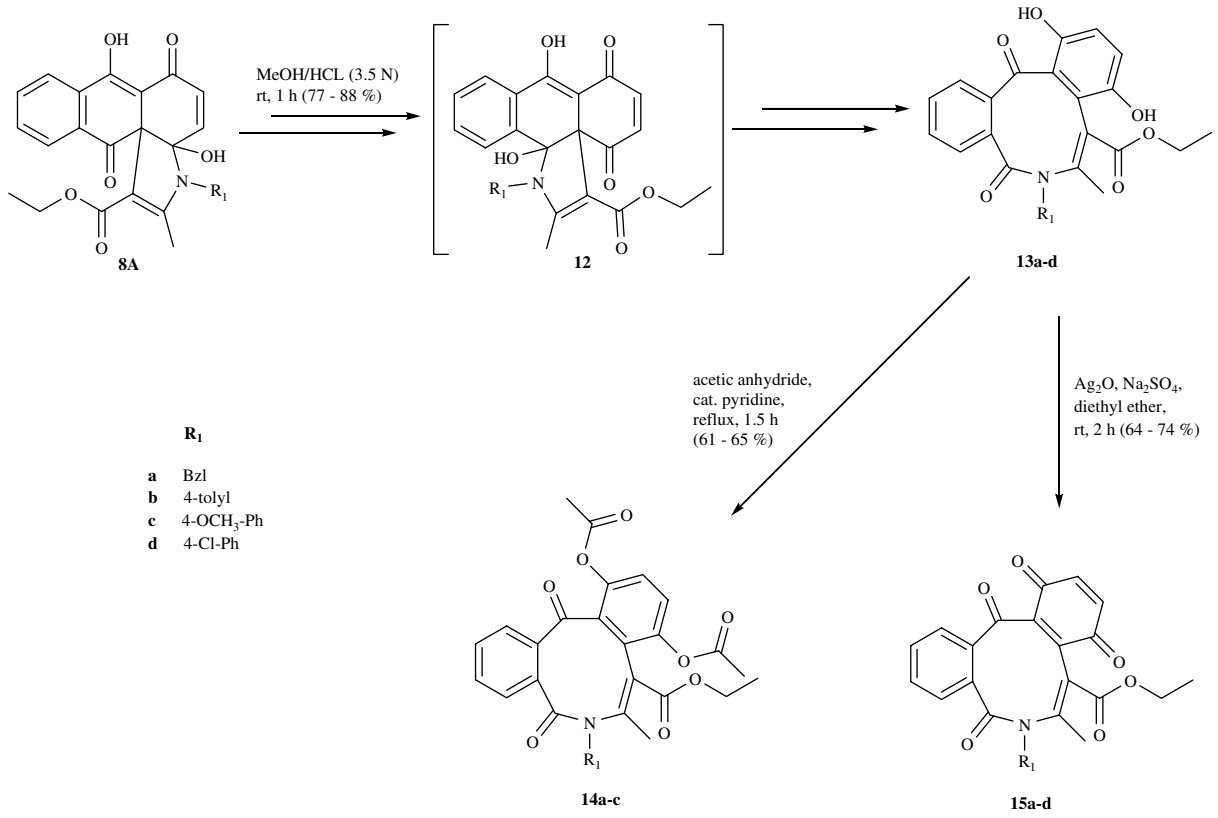


Figure 2. Diagram of **8Aa**. Displacement ellipsoids are drawn at the 30% probability level, radii of hydrogen atoms are chosen arbitrarily, and the hydrogen atom labels are omitted for clarity. Selected geometric features [Å; °]: C1–C2 1.366(2), C1–C12A 1.535(2), C2–C4′ 1.486(2), C2–N3 1.339(2), N3–C3A 1.483(2), N3–C5′ 1.458(2), C3A–C12A 1.564(2), C3A–C4 1.494(3), C4–C5 1.317(3), C5–C6 1.449(3), C6–C6A 1.418(3), C6–O2 1.260(2), C6A–C12A 1.516(2), C6A–C7 1.368(2), C7–C7A 1.439(3), C7–O3 1.325(2), C7A–C11A 1.396(2), C11A–C12 1.484(2), C12–C12A 1.526(2), C12–O4 1.211(2), O1–H1 0.84(2), H1···O4 2.33(2), O1···O4 2.941(2), H1···O6# 2.03(2); O1···O6# 2.738(2), O3–H3 1.01(3), H3···O2 1.56(3), O3···O2 2.480(2); C2–N3–C5′–C6′ 85.6(2), C4–C3A–C12A–C6A 32.0(2), C4–C3A–C12A–C1 −89.67(17), C4–C3A–C12A–C12 159.41(15), C5–C4–C3A–C12A −9.2(3), C12A–C1–C3′–O6 −172.27(18); symmetry code #: $-x$, $-y+1.5$, $z-0.5$. Dashed lines are indicating intra- and intermolecular hydrogen bonds.



Scheme 4. Synthesis of compounds **13**–**15**.

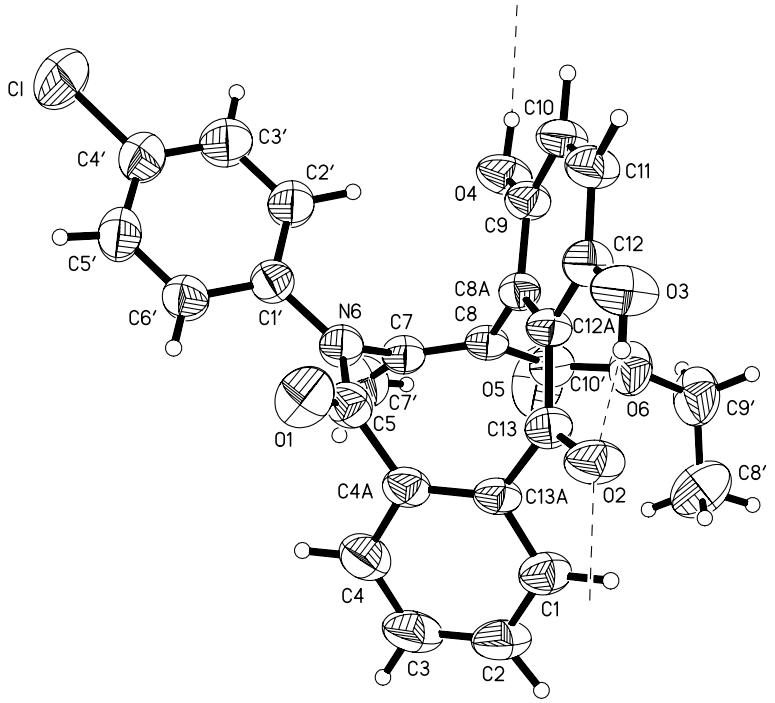
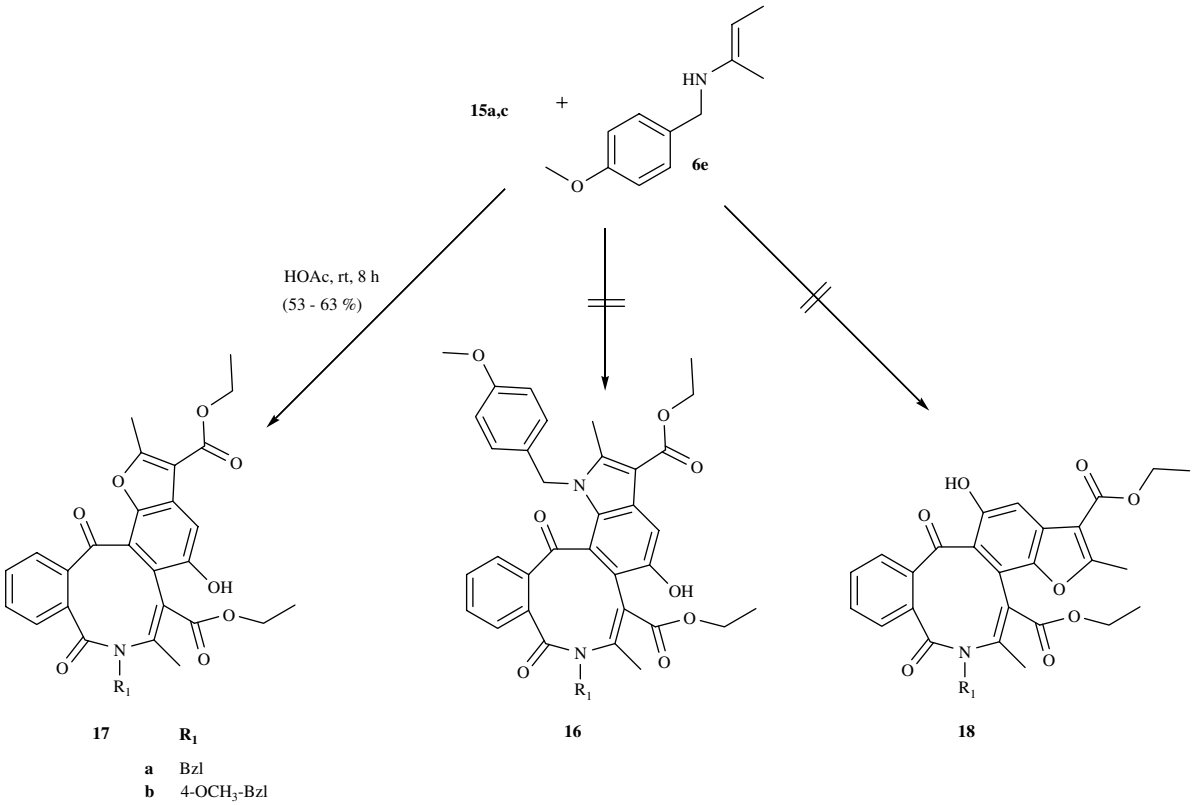
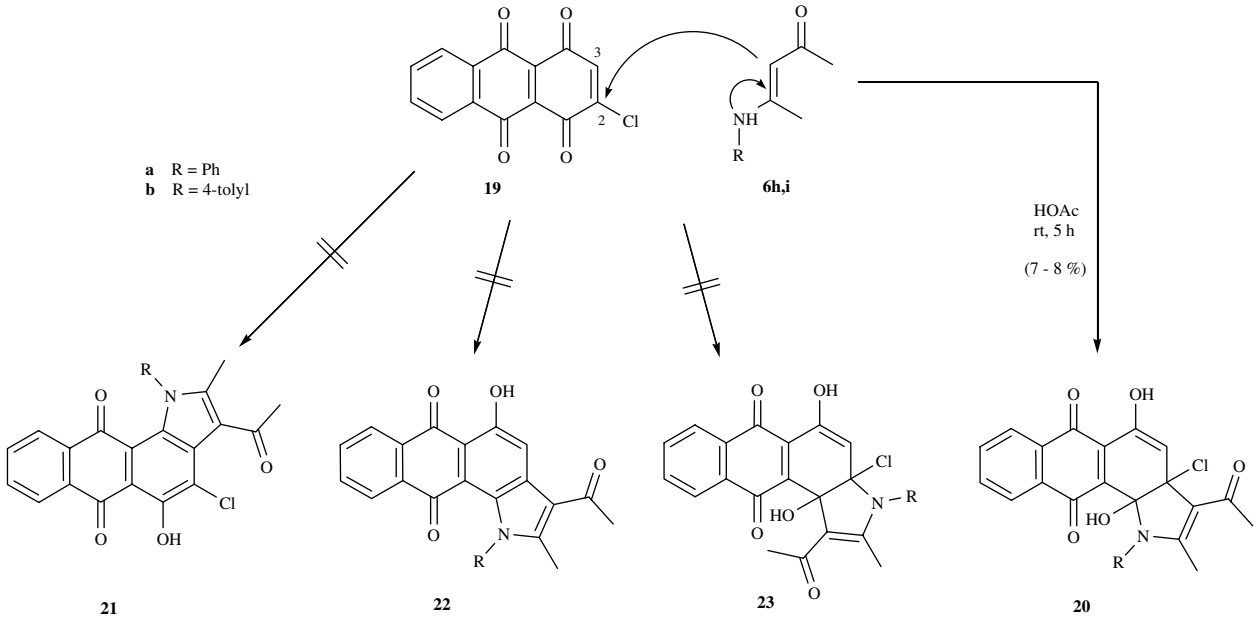


Figure 3. Diagram of **13d** in **13d** × C_3H_6O. Displacement ellipsoids are drawn at the 30% probability level, radii of hydrogen atoms are chosen arbitrarily, and the hydrogen atom labels are omitted for clarity. Selected geometric features [Å; °]: C5–O1 1.212(3), C5–N6 1.374(3), N6–C1′ 1.423(3), N6–C7 1.431(3), C7–C8 1.324(4), C8–C8A 1.507(3), C8A–C9 1.377(4), C12A–C13 1.448(4), C13–O2 1.241(3), C13–C13A 1.492(4), C13A–C4A 1.376(4), C4A–C5 1.499(4), C9–O4 1.361(3), C12–O3 1.349(3), O3–H30 0.79(4), H30···O2 1.84(4), O3···O2 2.523(3), O4–H40 0.85(4), H40···O2# 1.93(4), O4···O2# 2.756(3); C2′–C1′–N6–C7 −35.6(4), C5–N6–C7–C8 −60.9(3), N6–C7–C8–C8A −19.8(4), C7–C8–C8A–C12A 94.9(3), C8–C8A–C12A–C13 −0.9(4), C8A–C12A–C13–C13A −15.0(2), C12A–C13–C13A–C4A −53.2(4), C13–C13A–C4A–C5 6.8(4), C13A–C4A–C5–N6 98.9(3), C4A–C5–N6–C7 −17.1(3); symmetry code #: $x + 1$, y, z. Dashed lines are indicating intra- and intermolecular hydrogen bonds.



Scheme 5. Synthesis of compounds **17**.



Scheme 6. Synthesis of compounds **20** from quinone **19** and enaminones **6h**,**i**.

Since the reactions of quinone **5** with enamines **6** did not produce the desired and pharmacologically interesting indoles **7**, two other quinones **19** and **25** were tested under the conditions of the modified Nenitzescu reaction.

The additional 2-chloro substituent of 2-chloroanthradiquinone **19**, easily accessible from **5**,[9] should lead to a more electrophilic carbon at position 3.

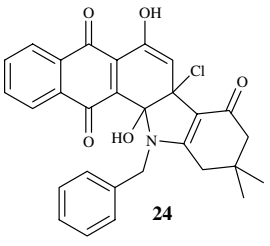
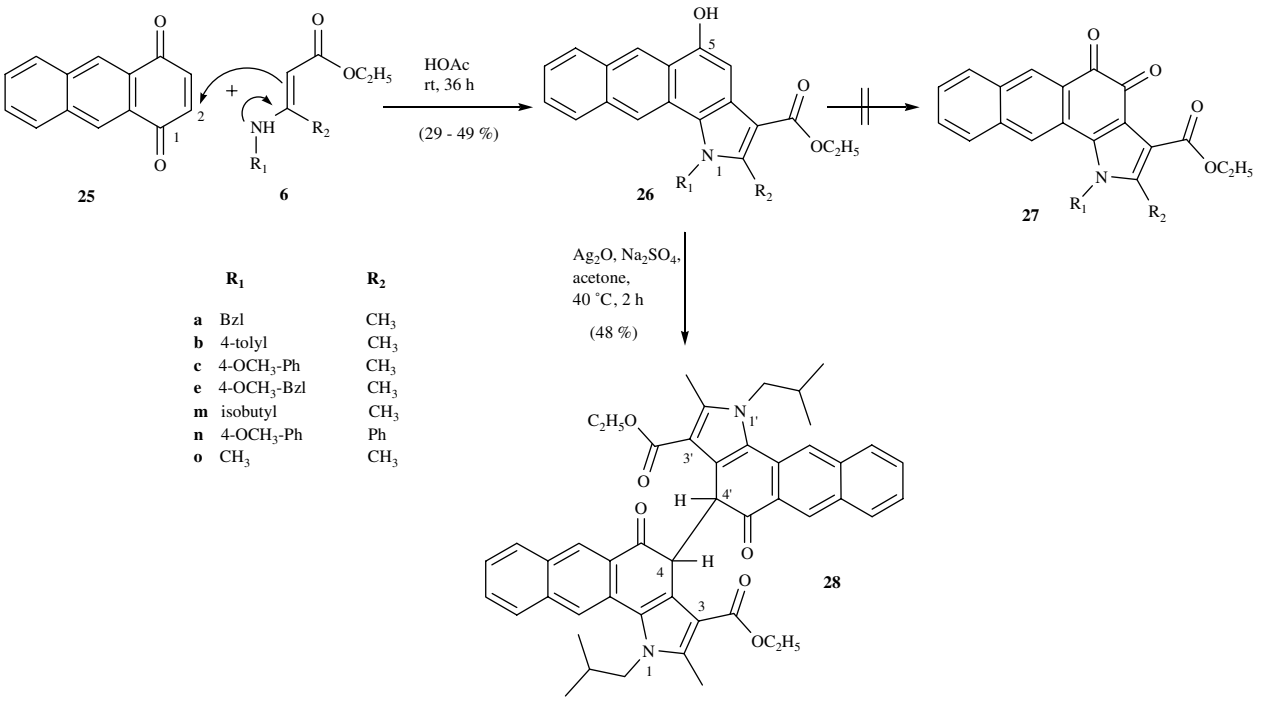
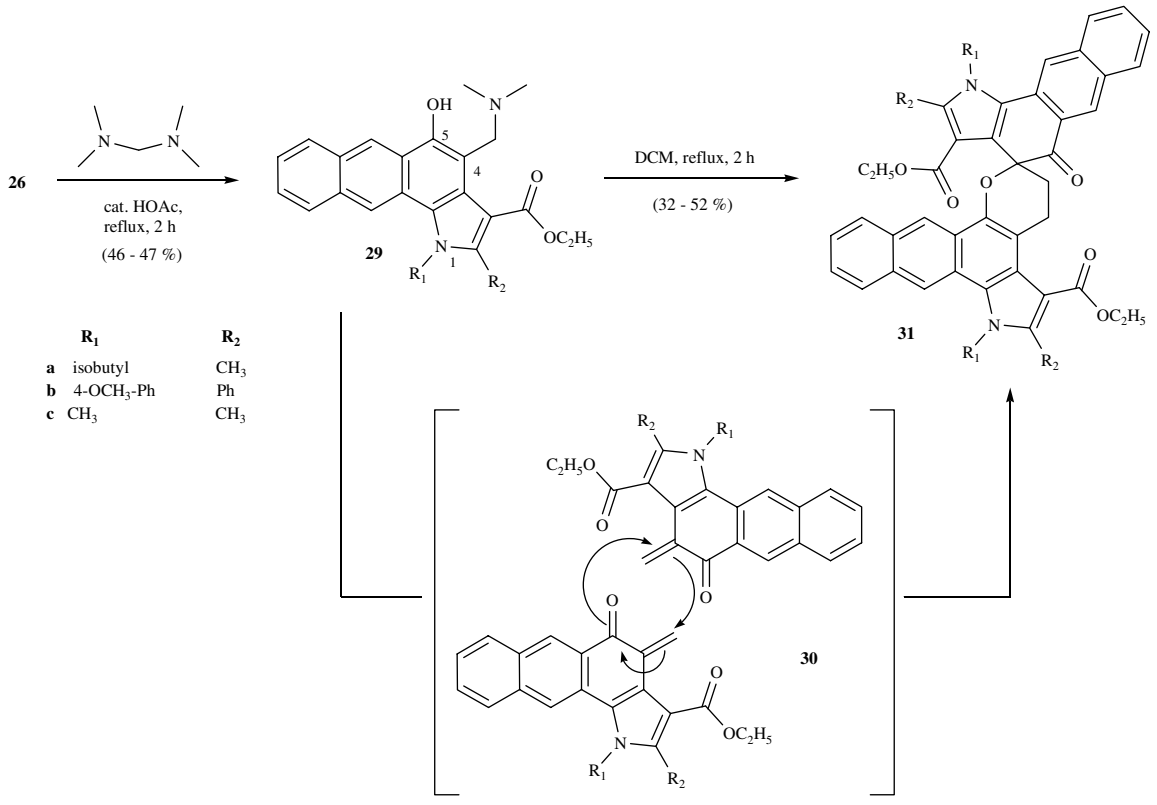


Figure 4.

However, under the same conditions as described in Scheme 2, reactions with enamines **6h/k** yielded carbinolamines **20a/b** (8% and 7% yield, respectively), which were in this case the result of an addition to the enamine β-carbon at position 2 of **19** (Scheme 6). Compound **19** reacted as vinylogeous acid chloride, though no substitution of chlorine was observed. The target indol **21** and the chlorine-free indol **22** could be excluded, since ^{13}C NMR spectra showed two singlets at 61.7 and 93.6 ppm for the two sp^3-carbons 3a and 11b of **20a**.



Scheme 7. Synthesis of compounds **26** and **28**.



Scheme 8. Synthesis of the phenolic Mannich bases **29** and Diels–Alder dimerization of intermediate *o*-quinone methides **30** to **31.**

We assume that the carbocyclus and the heterocyclus are cis-connected, that is, the 3a-chlorine and the 11b-hydroxyl group positioned on the same side. No split off of water is possible to yield indol **21**. Quinone **19** reacted with enaminone **10b** analogously to **24** (Fig. 4).

As a consequence of the fact that anthradiquinone reacts irregularly in the Nenitzescu reaction, we used a procedure described by Lepage[10] to synthesize unsubstituted 1,4-anthraquinone **25**. When utilizing this quinone, the desired indol derivatives **26** were now obtained as a result of a primary attack of the β-carbon of enamines **6** at carbon 2 of quinone **25** with yields between 29% and 49% (Scheme 7). Because many of the well-established antitumor agents (e.g., anthracyclines) contain a quinone moiety, which at least partially contributes to their activity, the *o*-quinonoid compounds **27** seemed to be an attractive target. Various conditions and oxidizing agents were examined. But instead of the monomeric target *o*-quinone **27** we were only able to isolate the dimeric indol **28** as the main product by reaction of **26m** with silver(I)oxide in acetone at 40 °C (48% yield). Accordingly, the ^{13}C NMR-spectrum shows signals of two carbonyl groups at 199.5 ppm (s, CO) and 165.2 ppm (s, COOR) as well as a doublet for C-4 at 53.3 ppm ($J = 110$ Hz). Similar observations were made by Diepenbrock[11] and Teuber and Thaler who oxidized 5-hydroxyindoles with Fremy's salt.[12]

Another interesting and promising idea to modify indoles **26** was to investigate the reaction with bisdimethylaminomethane in order to obtain ortho-phenolic Mannich bases **29**. The incorporation of a dimethylaminomethyl substituent should not only lead to a more water-soluble derivative under physiological conditions, but it should also improve the anticancer activity, as it is known from the drug topotecan used clinically. Heating of 5-hydroxyindoles **26** for 2 h in bisdimethylaminomethane with catalytic amounts of acetic acid yielded the ortho-phenolic Mannich bases **29** (46–47% yield) (Scheme 8). Interestingly, further heating of compounds **29** under reflux in dichloromethane for 2 h led to the spirocyclic dimers **31** as a result of a Diels–Alder dimerization of intermediate *o*-quinone methides **30**. These were formed after thermal desamination of **29** (32–52% yield). A similar reaction has been known for piperidinomethylcycloheptanone for a long time.[13] The ^{13}C NMR-spectrum of **31c** exhibited singlets at 199.50 ppm (CO group), as well as at 167.05 and 166.10 ppm of the ethoxycarbonyl groups. The singlet for the spiro-carbon was observed at 81.82 ppm and two triplets were registered at 28.82 and 21.49 ppm ($J = 130$ and 131 Hz) for the ethylene bridge in the spiro-pyrane ring. Thus, the structure of compounds **31** was proven.

In the case of the reaction of **26o** with bisdimethylaminomethane, we were not able to isolate the Mannich base **29c**, but the dimer **31c**. The easy dimerization of **29** via *o*-quinone methides stimulated the idea that the ortho-phenolic Mannich bases **29** could show antitumor activity, since some cytostatics such as mitomycin C or even the anthracyclines are known to exhibit their activity partly via an intermediate quinone methide species.[14]

3. In vitro anticancer activity

Most of the synthesized new heterocycles were evaluated in the anticancer screen for human disease-oriented tumor cell line developed at the NCI.[15,16] This in vitro screen is subdivided into a pre-test and a main test. Within the one-dose pre-test consisting of three tumor cell lines (MCF7 (breast), NCI-H460 (lung), and SF-268 (CNS)) test agents are added at only one concentration (10^{-4} M) to each cell line inoculated and preincubated on a microtiter plate, and the culture is then incubated for 48 h. End-point determinations are made with alamar blue.[17] Results for each test compound are reported as the percentage of growth of the treated cells in comparison with that of the untreated control cells. Negative numbers indicate cell death. Compounds reducing the growth of any one of the three cell lines by 32% or less are called 'active' and subsequently passed on for evaluation in the main test, this time consisting of approxi-

Table 1. In vitro anticancer activity—NCI's 3 cell line pre-test[a]

Compound	NCI-H460	MCF7	SF-268	Result[b]
8Aa	0	0	0	Active
8Ab	0	22	6	Active
8Ac	−43	−90	−47	Active
8Ad	−32	−61	−81	Active
8Af	0	0	1	Active
8Ag	0	0	0	Active
8Ah	1	1	1	Active
8Ai	0	0	1	Active
8Al	1	1	1	Active
11a	6	33	9	Active
13a	0	12	0	Active
13b	61	11	66	Active
13c	24	76	65	Active
14a	0	1	0	Active
14b	50	27	64	Active
15a	0	0	0	Active
15b	3	0	5	Active
17a	100	83	83	Inactive
20a	0	0	0	Active
20b	59	30	17	Active
26a	92	72	76	Inactive
26b	98	83	89	Inactive
26c	86	98	122	Inactive
26e	97	88	97	Inactive
26f	91	122	145	Inactive
26g	95	65	59	Inactive
28	67	64	104	Inactive
29a	79	118	145	Inactive
29b	59	112	111	Inactive
31a	92	92	84	Inactive
31b	77	122	139	Inactive
31c	79	99	82	Inactive

[a] Data were obtained from the NCI's in vitro anticancer 3 cell line pre-test (for details see Refs. 15 and 16). Negative numbers indicate cell kill. Each cell line was inoculated and preincubated on a microtiter plate. Test agents (10^{-4} M) were added and the culture incubated for 48 h. End-point determinations were made with alamar blue. Results for each test agent were reported as the percentage of growth of the treated cells when compared to untreated control cells.

[b] Compounds which reduce the growth of any one of the cell lines to 32% or less are called 'active' and passed on for evaluation in the main test.

mately 60 cell lines over a 5-log dose range (10^{-4}–10^{-8} M). Within the main test the antitumor activity of a test compound is expressed by three different dose–response parameters for each of the 60 cell lines derived from nine different types of cancer: GI_{50} (molar concentration required for half-growth inhibition), TGI (molar concentration leading to total growth inhibition), and LC_{50} (molar concentration required for 50% cell death). Moreover, a mean graph midpoint (MGM) is calculated for each of the above-mentioned parameters, which displays an averaged activity parameter over all cell lines.

The results of the pre-test for each tested compound are presented in Table 1. The azonine derivative **17a**, the 5-hydroxyindoles **26**, the ortho-phenolic Mannich bases **29**, and the dimers **28** and **31** were found to be inactive, whereas particularly the enamine–anthradiquinone adducts **8A** and the hydroquinonoid and quinonoid azonine derivatives **13**–**15** exhibited growth inhibitory activity. Moreover, the 4-methoxyphenyl- and the 4-chlorophenyl-substituted compounds **8Ac** and **8Ad** even led to a cytotoxic effect. In Table 2, MGM $\log GI_{50}$, $\log TGI$, and $\log LC_{50}$ values over all cell lines for each tested compound are given. Among this series of heterocycles, the most active ones were at the nitrogen unsubstituted nitril derivative **8Al** (MGM $\log GI_{50} = -5.55$) and the N-4-chlorophenyl-substituted derivative **8Ad** (MGM $\log GI_{50} = -5.39$), however, the inhibition was weaker than that obtained for mitomycin C (MGM $\log GI_{50} = -6.13$). Nitril **8Ak** showed some selectivity for the subpanel of leukemia cell lines (MGM $\log GI_{50} = -6.32$). This value was better than that of mitomycin C (MGM $\log GI_{50} = -6.09$) for the same subpanel.

Table 2. In vitro anticancer activity—NCI's 60 cell line main test[a]

Compound	MGM $\log GI_{50}$[b]	MGM $\log TGI$[c]	MGM $\log LC_{50}$[d]
8Aa	−4.98	−4.50	−4.14
8Ab	−5.13	−4.22	−4.01
8Ac	−4.87	−4.64	−4.19
8Ad	−5.39	−4.85	−4.34
8Ag	−4.93	−4.32	−4.06
8Ai	−4.93	−4.25	−4.01
8Al	−5.55	−4.68	−4.17
11a	−4.58	−4.12	>−4.00[e]
13a	−4.17	−4.04	>−4.00[e]
13b	−4.71	−4.28	−4.04
14a	−4.31	−4.03	>−4.00[e]
14b	−4.77	−4.23	−4.02
15a	−4.27	−4.06	−4.01
15b	−4.76	−4.34	−4.07
20a	−5.27	−4.43	−4.03
20b	−4.86	−4.18	−4.01

[a] Data were obtained from the NCI's in vitro anticancer 60 cell line main screen (for details see Refs. 15 and 16).
[b] Averaged log molar concentration for all tested cancer cell lines which led to 50% growth inhibition.
[c] Averaged log molar concentration for all tested cancer cell lines which led to total growth inhibition.
[d] Averaged log molar concentration for all tested cancer cell lines which led to 50% cell death.
[e] The highest tested concentration (10^{-4} M) of the drug did not lead to 50% cell death.

4. Conclusion

Anthracycline-like naphtho-condensed indoles **7** were not obtained from 1,4,9,10-anthradiquinone **5**. This diquinone reacted with enamines by addition to the doubly activated C=C-bond in 4a-position and not by reaction at the quinone in 2-position. Diquinone **5** therefore reacts comparably to other quinones activated by two electron-withdrawing groups.[21,22] The synthesized condensed spirocyclic carbinolamines **8A** are absolutely new lead structures for antitumor compounds. The reaction of compounds **8A** with methanolic hydrochloric acid resulting in an isomerization and ring opening to dibenzoazonine **13** is very surprising and interesting. This is with no equivalent in the literature. Thus, a new synthetic route to azonines **13** was found. 2-Chloro-anthradiquinone **19** reacted as vinylogeous carboxylic acid chloride, however, no substitution of the chlorine atom was observed. Naphtho-condensed indoles **26** were available from 1,4-anthraquinone **25** in a normal Nenitzescu reaction. The phenolic Mannich bases **29** of **25** were unstable further reacting via a Diels–Alder pathway.

5. Experimental

Melting points were determined with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded as frequency in cm^{-1} on a Perkin Elmer 1600 series FT-IR spectrometer in KBr. UV–vis spectra were obtained on a Perkin Elmer Lamda 16 spectrometer. NMR spectra were obtained on Bruker AC 200 in DMSO-d_6 or $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. The chemical shifts are reported in parts per million, in δ units. Mass spectra were recorded on Finnigan MAT 8200 or MAT 311A MAT (EI, 70 eV). Elemental analyses were performed with a Perkin Elmer PE 2400 CHN elemental analysator. Commercially available solvents and reagents were used without further purification unless otherwise mentioned.

5.1. General procedure for the preparation of 3,3a,6,12-tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxonaphtho[2,3-*d*]indol-1-carboxylates (8A), 1,2,3,4,5,5a,8,14-octahydro-5a,9-dihydroxy-3,3-dimethyl-naphtho[2,3-*k*]carbazole-1,8,14-triones (11) 9,14-dihydro-5-hydroxy-2,7-dimethyl-9,14-dioxo-8-*H*-benzo[*c*][1]-benzofuro[6,7-*f*]azonine-3,6-dicarboxylates (17), 3-acetyl-3a-chloro-3a,11b-dihydro-5,11b-dihydroxy-2-methyl-naphtho[2,3-*g*]indol-6,11-diones (20), 12-benzyl-7-chloro-7,8,9,10,11,12,12a,13-octahydro-6,12a-dihydroxy-10,10-dimethyl-5*H*-naphtho[2,3-*a*]carbazol-5,8,13-trione (24), and 5-hydroxy-2-methyl-1*H*-naphtho[2,3-*g*]indol-3-carboxylates (26)

The amount of quinone was dissolved or suspended in glacial acetic acid or dry methanol (1 ml corresponding to 100 mg quinone) and mixed with a solution or suspension of the appropriate enamine **6** in acetic acid or

methanol (1 ml corresponding to 100 mg enamine) at room temperature. The mixture was stirred for the time indicated and the obtained solid was collected and treated as indicated followed by recrystallization from isopropanol (compounds **8A**), dichloromethane/hexanes (40:60) (compounds **17**), dichloromethane/hexanes (20:80) (compounds **20** and compound **24**) or dichloromethane (compounds **26**).

5.1.1. Ethyl-3-benzyl-3,3a,6,12-tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxo-naphtho[2,3-*d*]indol-1-carboxylate (8Aa). Route A: 228 mg (1.2 mmol) ethyl-3-benzylaminocrotonate **6a**, 286 mg (1.2 mmol) **5**, acetic acid, 3 h, 365 mg (67%), route B: 228 mg (1.2 mmol) ethyl-3-benzylaminocrotonate **6a**, 286 mg (1.2 mmol) **5**, methanol, 7 h, 402 mg (73%), mp 181 °C (yellow crystals), IR 3422, 1670, 1652, 1592, MS (EI) 457 (22; M^+), 440 (13), 385 (6), 368 (47), 277 (59), 250 (65), 225 (22), 165 (12), 138 (30), 91 (100), 64 (53), ^{1}H NMR ($CDCl_3$) δ 15.92 (s, 1H, 7-OH), 8.16 (mc, 1H) and 8.04 (mc, 1H, 8-H, 11-H), 7.75 (mc, 1H) and 7.59 (mc, 1H, 9-H, 10-H), 7.57 (mc, 5H, arom. H), 6.30 (d, 1H) and 6.25 (d, 1H, 4-H, 5-H, J = 10.2 Hz), 5.50 (s, 1H, 3a-OH), 4.86 (d, 1H) and 4.56 (d, 1H, phe-CH_2, J = 16.8 Hz), 3.70 (mc, 2H, O–CH_2), 2.16 (s, 3H, 2-CH_3), 0.78 (t, 3H, O–C–CH_3, J = 7.2 Hz), ^{13}C NMR ($CDCl_3$) δ 198.25 (s, C=O (carbonyl)), 183.02 (s, C=O (carbonyl)); 173.83 (s, C=O (ester)), 164.72 (s, C-2), 163.43 (br s, C-7, C–OH), 137.89, 135.73, 135.65, 134.75, 132.84, 131.95, 128.97, 127.49, 127.43, 127.01, 126.40, 125.09, 102.52 (s, C-1), 100.59 (s, C-6a), 93.86 (s, C-3a, C–OH), 59.05 (s, C-12a), 58.72 (t, O–CH_2, $^1J_{C/H}$ = 138.4 Hz), 44.53 (t, N–CH_2, $^1J_{C/H}$ = 136.4 Hz), 14.35 (q, 2-CH_3, $^1J_{C/H}$ = 130.0 Hz), 13.90 (q, CH_3-ester, $^1J_{C/H}$ **= 129.3 Hz), UV–vis (MeOH) 274 (4.22), 316 (4.06), 388 (3.76). Anal. Calcd for $C_{27}H_{23}NO_6$ (457.46): C, 70.89; H, 5.07; N, 3.06. Found: C, 70.67; H, 5.07; N, 2.92.**

5.1.2. Crystal structure determination of compound 8Aa[18]. Crystals of **8Aa**, suitable for X-ray study, were selected by means of a polarization microscope. One was investigated on a Stoe Imaging Plate Diffraction System, using graphite monochromatized Mo Kα radiation (λ = 0.71073 Å). Unit cell parameters were determined by a least-squares refinement on the positions of 8000 strong reflections distributed equally in reciprocal space. A monoclinic lattice was found, and space group $P2_1/c$ was uniquely determined. Crystal data of **8Aa**: M_r ($C_{27}H_{23}NO_6$) = 457.46, a = 14.4890(14) Å, b = 10.4297(5) Å, c = 14.4691(13) Å, β = 90.392(11)°, V = 2186.5(3) Å^3, Z = 4, D_x = 1.390 g cm^{-3}, μ = 0.099 mm^{-1}, T = 291 K, orange crystal of dimensions 0.8 mm × 0.6 mm × 0.3 mm. 25470 intensity data (Θ_{min} = 2.41°, Θ_{max} = 27.49°) were collected and Lp corrections were applied. The structure was solved by direct methods,[19] and approximate positions of all hydrogen atoms were found via difference Fourier synthesis. Refinement (379 parameters, all of 5006 unique reflections used, 0 restraints) by full-matrix least-squares calculations on F^2,[20] converged to the following final indicators: $R_1[F_o^2 > 2\sigma(F_o^2)] = 0.047$, wR_2 = 0.098 (all data), $w = 1/[\sigma^2(F_o^2) + (0.7P)^2 + 0.1P]$ where $P = (F_o^2 + 2F_c^2)/3$, S = 1.109, and[20] largest peak and hole in the final difference map are 0.200 e/Å^2 and −0.167 e/Å^3, respectively. Anisotropic displacement parameters were used for all non-hydrogen atoms. Individual isotropic displacement parameters were refined for all H atoms, individual coordinates for all but the H atoms of methyl and methylen groups. The H atoms of CH_3 groups were allowed to ride on their parent carbon atom and to move collectively around the neighboring C–C axis. Furthermore, the C–H distances were allowed to vary, the same shifts being applied along the three C–H bonds of a group. Together with their parent carbon atom the H atoms of the CH_2 groups were treated as rigid groups with idealized geometry, allowed for rotational movement.

5.1.3. Ethyl-3,3a,6,12-tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxo-3-(4-tolyl)-naphtho[2,3-*d*]indol-1-carboxylate (8Ab). 228 mg (1.2 mmol) ethyl-3-(4-tolylamino)-crotonate **6b**, 286 mg (1.2 mmol) **5**, acetic acid, 3 h, 450 mg (79%), mp 160 °C (yellow crystals), IR 3262 m, 1678, 1591, 1568, MS (EI) 457 (8; M^+), 368 (100), 338 (5), 280 (42), 251 (32), 223 (15), 168 (13), 131 (83), 91 (86), 64 (63), ^{1}H NMR ($CDCl_3$) δ 15.87 (s, 1H, 7-OH), 8.17 (mc, 1H) and 8.02 (mc, 1H, 8-H, 11-H), 7.80 (mc, 1H) and 7.62 (mc, 1H, 9-H, 10-H), 7.26 (mc, 4H, arom. H), 6.29 (d, 1H) and 6.22 (d, 1H, 4-H, 5-H, J = 10.2 Hz), 5.54 (s, 1H, 3a-OH), 3.74 (mc, 2H, O–CH_2), 2.43 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 0.81 (t, 3H, O–C–CH_3, J = 7.1Hz), UV–vis (MeOH) 234 (4.54), 277 (4.24), 315 (4.40), 377 (3.85). Anal. Calcd for $C_{27}H_{23}NO_6$ (457.48): C, 70.89; H, 5.07 N: 3.06. Found: C: 70.66 H: 5.03 N: 2.87.

5.1.4. Ethyl-3-(4-methoxyphenyl)-3,3a,6,12-tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxo-naphtho[2,3-*d*]indol-1-carboxylate (8Ac). 282 mg (1.2 mmol) ethyl-3-(4-methoxyphenylamino)crotonate **6c**, 286 mg (1.2 mmol) **5**, acetic acid, 8 h, 440 mg (78%), mp 180 °C (yellow crystals), IR 3439, 1676, 1591, 1568, MS (EI) 473 (9; M^+), 418 (1), 384 (100), 356 (4), 280 (44), 223 (18), 147 (82), 121 (70), 77 (39), 43 (11), ^{1}H NMR($CDCl_3$) δ 15.86 (s, 1H, 7-OH), 8.17 (mc, 1H) and 8.02 (mc, 1H, 8-H, 11-H), 7.77 (mc, 1H) and 7.62 (mc, 1H, 9-H, 10-H), 7.15 (mc, 4H, arom. H), 6.29 (d, 1H) and 6.21 (d, 1H, 4-H, 5-H, J = 10.2 Hz), 5.55 (s, 1H, 3a-OH), 3.87 (s, 3H, OCH_3), 3.73 (mc, 2H, O–CH_2), 2.08 (s, 3H, 2-CH_3), 0.81 (t, 3H, O–C–CH_3, J = 7.0 Hz), UV–vis (MeOH) 232 (4.30), 277 (3.99), 316 (4.15), 377 (3.70). Anal. Calcd for $C_{27}H_{23}NO_7$ (473.48): C, 68.49; H, 4.90; N, 2.96. Found: C, 68.23; H, 5.04; N, 3.04.

5.1.5. Ethyl-3-(4-chlorphenyl)-3,3a,6,12-tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxo-naphtho[2,3-*d*]indol-1-carboxylate (8Ad). Route A: 287 mg (1.2 mmol) ethyl-3-(4-chlorophenylamino)crotonate **6d**, 286 mg (1.2 mmol) **5**, acetic acid, 3 h, 375 mg (65%), route B: 287 mg (1.2 mmol) ethyl-3-(4-chlorophenylamino)crotonate **6d**, 286 mg (1.2 mmol) **5**, methanol, 6 h, 450 mg (79%), mp 172 °C (yellow crystals from isopropanol), IR 3266, 1678, 1592, 1568, MS (EI) 477 (3; M^+), 431 (1), 388 (30), 351 (10), 280 (22), 250 (27), 224(9), 152 (100), 111 (36), 75 (48), 41

(16), ^{1}H NMR ($CDCl_3$) δ 15.85 (s, 1H, 7-OH), 8.18 (mc, 1H) and 8.03 (mc, 1H, 8-H, 11-H), 7.78 (mc, 1H) and 7.62 (mc, 1H, 9-H, 10-H), 7.35 (m, 4H, arom. H), 6.28 (d, 1H) and 6.17 (d, 1H, 4-H, 5-H), 5.55 (s, 1H, 3a-OH), 3.75 (mc, 2H, O–CH_2), 2.09 (s, 3H, 2-CH_3), 0.83 (t, 3H, O–C–CH_3), UV–vis (MeOH) 234 (4.54), 314 (4.40), 377 (3.97). Anal. Calcd for $C_{26}H_{20}ClNO_6$ (477.90): C, 65.35; H, 4.22; N, 2.93. Found: C, 65.23; H, 4.06; N, 2.93.

5.1.6. Ethyl-3,3a,6,12-tetrahydro-3a,7-dihydroxy-3-(4-methoxybenzyl)-2-methyl-6,12-dioxo-naphtho[2,3-*d*]indol-1-carboxylate (8Ae). 298 mg (1.2 mmol) ethyl-3-(4-methoxybenzylamino)crotonate **6e**, 286 mg (1.2 mmol) **5**, acetic acid, 3 h, 430 mg (74%), mp 170 °C (yellow crystals), IR 3444, 1654, 1632, 1592, 1558. MS (EI) 487 (4; M^+), 398 (4), 339 (1), 280 (8), 240 (18), 180 (4), 136 (6), 121 (100), 77 (9), 51 (4), ^{1}H NMR ($CDCl_3$) δ 15.92 (s, 1H, 7-OH), 8.15 and 8.02 (mc, 2H, 8-H, 11-H), 7.76 and 7.63 (mc, 1H, 9-H, 10-H), 7.2 (mc, 4H, arom. H), 6.29 (d, 1H) and 6.22 (d, 1H, 4-H, 5-H, J = 10.2 Hz), 5.50 (s, 1H, 3a-OH), 4.78 (d, 1H) and 4.56 (d, 1H, phe-CH_2, J = 16.4 Hz), 3.84 (s, 3H, OCH_3), 3.70 (mc, 2H, O–CH_2), 2.17 (s, 3H, 2-CH_3), 0.78 (t, 3H, CH_3–C–O), UV–vis (MeOH) 215 (4.53), 261 (4.17), 303 (4.29), 364 (3.88). Anal. Calcd for $C_{28}H_{25}NO_7$ (487.50): C, 68.98; H, 5.17; N, 2.87. Found: C, 68.70; H, 5.03; N, 2.78.

5.1.7. Ethyl-3-(2,4-chlorbenzyl)-3,3a,6,12-tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxo-naphtho[2,3-*d*]indol-1-carboxylate (8Af). 343 mg (1.2 mmol) ethyl-3-(2,4-dichlorbenzylamino)crotonate **6f**, 286 mg (1.2 mmol) **5**, acetic acid, 5 h, 490 mg (78%), mp 186 °C (yellow crystals), IR 3424, 1713, 1666, 1592, 1562, MS (EI) 526 (17; M^+), 508 (35), 452 (27), 436 (10), 379 (3), 320 (12), 279 (14), 251 (30), 200 (4), 159 (100), 139 (5), 89 (4), ^{1}H NMR ($CDCl_3$) δ 15.91 (s, 1H, 7-OH), 8.17 (mc, 1H) and 8.04 (mc, 1H, 8-H, 11-H), 7.78 (mc, 1H) and 7.62 (mc, 1H, 9-H, 10-H), 7.42 (mc, 3H. arom. H), 6.33 (d, 1H) and 6.32 (d, 1H, 4-H, 5-H, J = 10.2 Hz), 5.36 (s, 1H, 3a-OH), 4.66 (s, 2H, CH_2–phe), 3.73 (mc, 2H, O–CH_2), 2.13 (s, 3H, 2-CH_3), 0.79 (t, 3H, O–C–CH_3), UV–vis (MeOH) 227 (4.48), 314 (4.26), 376 (3.87). Anal. Calcd for $C_{27}H_{21}Cl_2NO_6$ (477.90): C, 61.61; H, 4.02; N, 2.66. Found: C, 61.12; H, 3.80; N, 2.59.

5.1.8. 1-(3,3a,6,12a-Tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxo-1-phenyl-naphtho[2,3-*d*]indol-1-yl)-ethanone (8Ag). 210 mg (1.2 mmol) 4-phenylamino-pent-3-en-2-one **6g**, 286 mg (1.2 mmol) **5**, acetic acid, 8 h, 330 mg (67%), mp 172 °C (yellow crystals), IR 3440, 1683, 1640, 1593, 1569, MS (EI) 413 (3; M^+), 371 (15), 353 (100), 278 (47), 240 (27), 193 (12), 140 (32), 119 (70), 107 (16), 93 (82), ^{1}H NMR ($CDCl_3$) δ 15.82 (s, 1H, 7-OH), 8.32 (mc, 1H) and 8.06 (mc, 1H, 8-H, 11-H), 7.85 (mc, 1H) and 7.68 (mc, 1H, 9-H, 10-H), 7.53 (mc, 5H, arom. H), 6.37 (d, 1H) and 6.28 (d, 1H, 4-H, 5-H, J = 10.2 Hz), 5.50 (s, 1H, 3a-OH), 2.17 (s, 3H, CH_3), 2.13 (s, 1H, CH_3), UV–vis (MeOH) 228 (4.53), 309 (4.46). Anal. Calcd for $C_{25}H_{19}NO_5$ (423.42): C, 72.63; H, 4.63; N, 3.39. Found: C, 72.41; H, 4.58; N, 3.24.

5.1.9. 1-(3-Benzyl-3,3a,6,12a-tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxo-naphtho[2,3-*d*]indol-1-yl)-ethanone (8Ah). 227 mg (1.2 mmol) 4-benzylaminopent-3-en-2-one **6h**, 286 mg (1.2 mmol) **5**, acetic acid, 8 h, 350 mg (68%), mp 170 °C (yellow crystals), IR 3429, 1685, 1647, 1593, 1568, MS (EI) 427 (5; M^+), 385 (25), 368 (11), 278 (38), 251 (29), 225 (16), 149 (12), 91 (100), 65 (21), 43 (40), ^{1}H NMR ($CDCl_3$) δ 15.79 (s, 1H, 7-OH), 8.23 (m, 1H) and 7.99 (m, 1H, 8-H, 11-H), 7.77 (mc, 1H) and 7.60 (mc, 1H, 9-H, 10-H), 7.44 (mc, 5H, arom. H), 6.21 (d, 1H) and 6.30 (d, 1H, 4-H, 5-H, J = 10.2 Hz), 5.40 (s, 1H, 3a-OH), 4.91 (d, 1H) and 4.64 (d, 1H, CH_2–phe, J = 16.9 Hz), 2.11 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), UV–vis (MeOH) 215 (4.34), 309 (4.29). Anal. Calcd for $C_{26}H_{21}NO_5$ (427.45): C, 73.06; H, 4.95; N, 3.28. Found: C, 72.81; H, 5.16; N, 3.13.

5.1.10. 1-(3,3a,6,12a-Tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxo-1-(4-tolyl)-naphtho[2,3-*d*]indol-1-yl)-ethanone (8Ai). 227 mg (1.2 mmol) 4-(4-tolylamino)pent-3-en-2-one **6i**, 286 mg (1.2 mmol) **5**, acetic acid, 8 h, 350 mg (68%), mp 181 °C (yellow crystals), IR 429, 1641, 1593, 1569, MS (EI) 427 (3; M^+), 384 (25), 356 (100), 338 (9), 278 (47), 240 (54), 190 (15), 175 (31), 133 (84), 108 (75), ^{1}H NMR ($CDCl_3$) δ 15.75 (s, 1H, 7-OH), 8.23 (mc, 1H) and 7.97 (mc, 1H, 8-H, 11-H), 7.77 (mc, 1H) and 7.59 (mc, 1H, 9-H, 10-H), 7.28 (mc, 4H, arom.H), 6.29 (d, 1H) and 6.20 (d, 1H, 4-H, 5-H), 5.39 (s, 1H, 3a-OH), 2.44 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), UV–vis (MeOH), 216 (4.47), 310 (4.45). Anal. Calcd for $C_{26}H_{21}NO_5$ (427.45): C, 73.06; H, 4.95; N, 3.28. Found C, 73.01; H, 4.75; N, 3.06.

5.1.11. 1-(3,3a,6,12a-Tetrahydro-3a,7-dihydroxy-2,3-dimethyl-6,12-dioxo-naphtho[2,3-*d*]indol-1-yl)-ethanone (8Ak). 136 mg (1.2 mmol) 4-methylaminopent-3-en-2-one **6k**, 286 mg (1.2 mmol) **5**, acetic acid, 9 h, 195 mg (46%), mp 167 °C (yellow crystals), IR 3430, 1681, 1640, 1594, 1570, MS (EI) 351 (14; M^+), 309 (90), 278 (25), 251 (71), 221 (48), 195 (5), 165 (46), 139 (27), 76 (35), ^{1}H NMR ($CDCl_3$) δ 15.75 (s, 1H, 7-OH), 8.22 (mc, 1H) and 7.91 (mc, 1H, 8-H, 11-H), 7.76 (mc, 1H) and 7.58 (mc, 1H, 9-H, 10-H), 6.26 (d, 1H) and 6.21 (d, 1H, 4-H, 5-H, J = 10.2 Hz), 5.25 (s, 1H, 3a-OH), 3.11 (s, 3H, N–CH_3), 2.25 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), UV–vis (MeOH) 217 (4.33), 264 (4.05), 309 (4.30), 364 (3.79). Anal. Calcd for $C_{20}H_{17}NO_5$ (351.35): C, 68.37; H, 4.88; N, 3.99. Found: C, 68.22; H, 4.88; N, 3.79.

5.1.12. 1-Cyano-3,3a,6,12-tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxo-naphtho[2,3-*d*]indol (8Al). 97.5 mg (1.2 mmol) 3-aminocrotonitrile **6l**, 286 mg (1.2 mmol) **5**, acetic acid, 5 h, 190 mg (49%), mp 196 °C (yellow crystals), IR 3430, 2188, 1678, 1650, 1592, 1565, MS (EI) 320 (21; M^+), 302 (100), 273 (52), 240 (55), 190 (44), 174 (16), 136 (41), 95 (44), 76 (53), 53 (70), ^{1}H NMR ($CDCl_3$) δ 15.83 (s, 1H, 7-OH), 8.15 (mc, 1H) and 8.02 (mc, 1H, 8-H, 11-H), 7.82 (mc, 1H) and 7.68 (mc, 1h, 9-H, 10-H), 6.45 (s, 1H, NH), 6.28 (d, 1h) and 6.21 (d, 1H, 4-H, 5-H, J = 10.2 Hz), 4.79 (s, 1H, 3a-OH), 2.02 (s, 3H, 2-CH_3), UV–vis (MeOH) 231

(4.47), 286 (4.25), 377 (3.88). Anal. Calcd for $C_{18}H_{12}N_2O_4$ (320.30): C, 67.50; H, 3.78; N, 8.75. Found: C, 67.09; H, 4.11; N, 8.43.

5.1.13. 1,2,3,4,5,5a,8,14-Octahydro-5a,9-dihydroxy-3,3-dimethyl-5-phenyl-naphtho[2,3-*k*]carbazole-1,8,14-trione (11a). 258 mg (1.2 mmol) 5,5-dimethyl-3-phenylamino-cyclohex-2-enone **10a**, 286 mg (1.2 mmol) **5**, acetic acid, 24 h, 290 mg (53%), mp 220 °C (yellow crystals from isopropanole), IR 3416, 1684, 1629, 1592, 1561, MS (EI) 453 (27; M^+), 408 (24), 379 (30), 290 (8), 249 (18), 176 (13), 147 (15), 116 (17), 83 (100), 53 (56), ^{1}H NMR ($CDCl_3$) δ 15.88 (s, 1H, 9-OH), 8.25 (mc, 1H) and 7.96 (mc, 1H, 10-H, 13-H), 7.80 (mc, 1H) and 7.60 (mc, 1H, 11-H, 12-H), 7.42 (mc, 5H, arom. H), 5.45 (s, 1H, 5a-OH), 6.27 (d, 1H) and 6.17 (d, 1H, 6-, 7-H, J = 10.3 Hz), 2.20 (mc, 2H, 2-CH_2), 1.89 (mc, 2H, 4-CH_2), 0.97 (s, 3H, 3-CH_3), 0.83 (s, 3H, 3-CH_3), UV–vis (MeOH) 242 (4.39), 317 (4.36), 381 (3.73). Anal. Calcd for $C_{28}H_{23}NO_5$ (453.49): C, 74.16; H, 5.11; N, 3.09. Found: C, 74.07; H, 5.08; N, 2.86.

5.1.14. 5-Benzyl-1,2,3,4,5,5a,8,14-octahydro-5a,9-dihydroxy-3,3-dimethyl-naphtho[2,3-*k*]carbazole-1,8,14-trione (11b). 275 mg (1.2 mmol) 3-benzylamino-5,5-dimethyl-cyclohex-2-enone **10b**, 286 mg (1.2 mmol) **5**, acetic acid, 24 h, 295 mg (53%), mp 189 °C (yellow crystals), IR 3420, 1682, 1623, 1592, 1568, MS (EI) 467 (28; M^+), 393 (30), 376 (31), 320 (8), 274 (8), 251 (10), 165 (6), 139 (6), 83 (100), 44 (7), ^{1}H NMR ($CDCl_3$) δ 15.90 (s, 1H, 9-OH), 8.23 (mc, 1H) and 7.98 (mc, 1H, 10-H, 13-H), 7.78 (mc, 1H) and 7.59 (mc, 1H, 11-H, 12-H), 7.41 (mc, 5H, arom. H), 6.28 (d, 1H) and 6.23 (d, 1H, 6-H, 7-H, J = 10.5 Hz), 6.25 (s, 1H, 5a-OH), 4.84 (d, 1H) and 4.58 (d, 1H, CH_2–phe, J = 16.7 Hz), 2.00 (mc, 4H, 2-CH_2, 4-CH_2), 0.92 (s, 3H, 3-CH_3), 0.80 (s, 3H, 3-CH_3), UV–vis (MeOH) 231 (4.34), 304 (4.25), 366 (3.71). Anal. Calcd for $C_{29}H_{25}NO_5$ (467.52): C, 74.50; H, 5.39; N, 3.00. Found: C, 74.26; H, 5.68; N, 2.82.

5.2. General procedure for the preparation of 6,13-dihydro-9,12-dihydroxy-7-methyl-5,13-dioxo-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylates (13)

Ethyl 3,3a,6,12-tetrahydro-3a,7-dihydroxy-2-methyl-6,12-dioxo-naphtho[2,3-*d*]indol-1-carboxylates **8A** were dissolved in 250 ml of 3.5 N methanolic HCl at room temperature for 1 h and then diluted with 250 ml of water. The precipitate was collected, dried, and recrystallized from dichloromethane/hexanes (35:65).

5.2.1. Ethyl-6-benzyl-6,13-dihydro-9,12-dihydroxy-7-methyl-5,13-dioxo-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylate (13a). 457 mg (1 mmol) **8Aa**, 400 mg (88%), mp 188 °C (yellow crystals), IR 3208, 1716, 1624, 1590, MS (EI) 457 (19; M^+), 411 (20), 356 (12), 320 (9), 279 (14), 251 (22), 223 (1), 132 (2), 106 (21), 91 (100), 45 (25), ^{1}H NMR ($CDCl_3$) δ 10.87 (s, 1H, 12-OH), 8.23 (s, 1H, 9-OH), 7.26–7.84 (m, 9H, arom. H), 7.17 (d, 1H) and 6.92 (d, 1H, 10-H, 11-H, J = 9.0 Hz), 4.92 (d, 1H) and 4.18 (d, 1H, CH_2–phe, J = 15 Hz), 3.95 (mc, 2H, O–CH_2), 1.93 (s, 3H, 7-CH_3), 1.02 (t, 3H, O–C–CH_3), ^{13}C NMR ($CDCl_3$) δ 198.33 (s, C-13), 169.03 (s, C-5), 165.91 (s, $COOC_2H_5$), 157.89 (s, C-12), 150.56 (s, C-9), 145.02 (s, C-7), 137.16, 136.90, 136.33, 131.97, 129.32, 129.25, 128.75, 128.72, 128.44, 127.83, 125.65, 125.13 (s), 121.88 (d), 119.98 (s), 119.07 (s, C-8), 61.44 (t, $COOCH_2$), 48.24 (t, N–CH_2), 19.73 (q, 7-CH_3), 13.83 (q, O–C–CH_3), UV–vis (MeOH) 385 (3.39). Anal. Calcd for $C_{27}H_{23}NO_6$ (457.48): C, 70.89; H, 5.07; N, 3.06. Found: C, 70.74; H, 4.96; N, 2.87.

5.2.2. Ethyl-6,13-dihydro-9,12-dihydroxy-7-methyl-5,13-dioxo-6-(4-tolyl)-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylate (13b). 457 mg (1 mmol) **8Ab**), 350 mg (77%), mp 193 °C (yellow crystals), IR 3305, 1724, 1681, 1644, 1588, 1512, MS (EI) 457 (9; M^+), 411 (6), 366 (8), 350 (6), 286 (22), 245 (14), 213 (14), 149 (48), 132 (100), 91 (42), 44 (68), ^{1}H NMR ($CDCl_3$) δ 11.74 (s, 1H, 12-OH), 7.76 (mc, 1H, arom. H), 7.54 (mc, 2H, arom. H), 7.11–7.60 (m, 6H, arom. H), 6.96 (d, 1H, 10-H, or 11-H, J = 9.0 Hz), 5.76 (s, 1H, 9-OH), 4.03 (mc, 2H, O–CH_2), 2.32 (s, 3H, CH_3–tol), 1.92 (s, 3H, 7-CH_3), 1.00 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{27}H_{23}NO_6$ (457.48): C, 70.89; H, 5.07; N, 3.06. Found: C, 70.70; H, 4.74; N, 3.03.

5.2.3. Ethyl-6,13-dihydro-9,12-dihydroxy-6-(4-methoxybenzyl)-7-methyl-5,13-dioxo-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylate (13c). 488 mg (1 mmol) **8Ae**, 410 mg (84%), mp 184 °C (yellow crystals), IR 3166, 1716, 1632, 1590, 1514, MS (EI) 487 (4; M^+), 441 (1), 353 (1), 303 (4), 279 (2), 251 (1), 136 (7), 121 (100), 91 (3), 77 (3), 44 (1), ^{1}H NMR ($CDCl_3$) δ 11.57 (s, 1H, 12-OH), 7.72 (mc, 1H, arom. H), 7.48 (mc, 2H, arom. H), 7.12 (mc, 6H, arom. H), 6.82 (d, 1H, J = 8.5 Hz), 4.84 (d, 1H) and 4.12 (d, 1H, CH_2–phe, J = 14.6 Hz), 4.81 (s, 1H, 9-OH), 3.99 (mc, 2H, O–CH_2), 3.81 (s, 3H, OCH_3), 1.76 (s, 3H, 7-CH_3), 1.05 (t, 3H, O–C–CH_3), UV–vis (MeOH) 397 (3.47). Anal. Calcd for $C_{28}H_{25}NO_7$ (487.50): C, 68.98; H, 5.17; N, 2.87. Found: C, 68.72; H, 4.92; N, 2.74.

5.2.4. Ethyl-6-(4-chlorphenyl)-6,13-dihydro-9,12-dihydroxy-7-methyl-5,13-dioxo-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylate (13d). 478 mg (1 mmol) **8Ad**, 400 mg (84%), mp 215 °C (yellow crystals), IR 3384, 1719, 1684, 1646, 1589, 1492, MS (EI) 477 (6; M^+), 387 (14), 358 (9), 305 (38), 249 (16), 152 (100), 111 (32), 75 (34), 44 (15), ^{1}H NMR ($CDCl_3$) δ 11.71 (s, 1H, 12-OH), 7.77 (mc, 1H, arom. H), 7.57 (mc, 2H, arom. H), 7.23–7.41 (m, 5H, arom. H), 7.10 (d, 1H) and 6.96 (d, 1H, 10-H, 11-H, J = 9.1 Hz), 5.88 (s, 1H, 9-OH), 4.04 (mc 2H, O–CH_2), 1.93 (s, 3H, 7-CH_3), 1.10 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{26}H_{20}ClNO_6$ (477.90): C, 65.35; H, 4.22; N, 2.93. Found: C, 65.16; H, 4.32; N, 2.85.

5.2.5. Crystal structure determination of compound 13d ×. C_3H_6O.[18] Only relatively weak diffracting crystals of limited quality were available. Some were selected by means of a polarization microscope and investigated on a Stoe Imaging Plate Diffraction System using graphite monochromatized Mo Kα radiation (λ = 0.71073 Å). Unit cell parameters were determined by a least-squares refinement on the positions of 8000 reflections, distributed equally in reciprocal space. An anorthic lattice was

found compatible with space groups $P1$ and $P\bar{1}$. The latter was confirmed in the course of the structure refinement. Crystal data: M_r ($C_{29}H_{26}ClNO_7$) = 535.96, a = 8.3481(7) Å, b = 11.3715(11) Å, c = 13.6753(13) Å, α = 87.145(11)°, β = 88.903(11)°, γ = 89.437(11), V = 1296.3(2) Å^3, Z = 2, D_x = 1.373 g cm^{-3}, μ = 0.197 mm^{-1}, T = 291 K, yellow crystal of dimensions 0.7 mm × 0.25 mm × 0.15 mm. 18866 intensity data (Θ_{min} = 2.39°, Θ_{max} = 26.11°) were collected and Lp corrections were applied. The structure was solved by direct methods,[19] and approximate positions of all but the hydrogen atoms of the solvent acetone molecule were found *via* difference Fourier syntheses. Refinement (401 parameters, all of 4799 unique reflections used, five restraints idealizing acetone geometry) by full-matrix least-squares calculations on F,[2,20] converged to the following final indicators: $R_1[F_o^2 > 2\sigma(F_o^2)] = 0.050$, $wR_2 = 0.100$ (all data), $w = 1/[\sigma^2(F_o^2) + (0.007P)^2 + 1.0P]$ where $P = (F_o^2 + 2F_c^2)/3$, $S = 1.033$,[20] and largest peak and hole in the final difference map are 0.400 e/Å^2 and −0.313 e/Å^3, respectively. Anisotropic displacement parameters were used for all non-hydrogen atoms. Individual isotropic displacement parameters were refined for all H atoms with the exception of methyl group hydrogen atoms of the acetone molecule, The isotropic displacement parameters of these H atoms were kept equal to 150% of the equivalent isotropic displacement parameters of the parent primary carbon atom. Individual coordinates were refined for all but the H atoms of methyl groups that were allowed ride on their parent carbon atom and to move collectively around the neighboring C–C axis. For the methyl groups of **13d** itself also the C–H distances were allowed to vary, the same shifts being applied along the three C–H bonds of a group.

5.3. General procedure for the synthesis of ethyl-9,12-diacetoxy-7-methyl-5,13-dioxo-6,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylates (14)

Ethyl-6,13-dihydro-9,12-dihydroxy-7-methyl-5,13-dioxo-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylates (**13**) were heated for 90 min in acetic anhydride (10 ml) with catalytic amounts of pyridine under reflux followed by evaporation and recrystallization from water/methanol (60:40).

5.3.1. Ethyl-9,12-diacetoxy-6-benzyl-7-methyl-5,13-dioxo-6,13-tetrahydro-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylate (14a). 457 mg (1 mmol) **13a**, 350 mg (65%), mp 142 °C (white powder), IR 3064, 1770, 1719, 1661, 1593, MS (EI) 542 (21; M^++H), 500 (11), 434 (4), 392 (6), 352 (10), 304 (6), 279 (6), 253 (6), 136 (16), 91 (100), 77 (21), ^{1}H NMR ($CDCl_3$) δ 8.24 (mc, 1H, arom. H), 7.61 (mc, 2H, arom. H), 7.38 (mc, 8H, arom. H), 5.19 (d, 1H) and 3.84 (d, 1H, CH_2–phe, J = 15.0 Hz), 4.05 (mc, 2H, O–CH_2), 2.36 (s, 3H, CH_3CO), 2.35 (s, 3H, CH_3CO), 1.82 (s, 3H, 7-CH_3), 1.16 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{31}H_{27}NO_8$ (541.55): C, 68.75; H, 5.03; N, 2.59. Found: C, 68.58; H, 5.04; N, 2.52.

5.3.2. Ethyl-9,12-diacetoxy-6,13-dihydro-7-methyl-5,13-dioxo-6-(4-tolyl)-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylate (14b). 45 mg (1 mmol) **13b**, 340 mg (63%), mp 208 °C (white powder), IR 3060, 1775, 1718, 1676, 1590, 1510, MS (EI) 541 (23; M^+), 499 (16), 457 (16), 411 (2), 350 (3), 305 (2), 251 (2), 132 (100), 91 (20), 43 (15), ^{1}H NMR ($CDCl_3$) δ 8.18 (mc, 1H, arom. H), 7.57 (mc, 2H, arom. H), 7.13–7.36 (m, 7H, arom. H), 4.00 (mc, 2H, O–CH_2), 2.33 (s, 3H, CH_3–tol), 2.24 (s, 3H, CH_3CO), 2.24 (s, 3H, CH_3CO), 2.00 (s, 3H, 7-CH_3), 1.07 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{31}H_{27}NO_8$ (541.55): C, 68.75; H, 5.03; N, 2.59. Found: C, 68.63; H, 4.71; N, 2.57.

5.3.3. Ethyl-9,12-diacetoxy-6,13-dihydro-6-(4-methoxybenzyl)-7-methyl-5,13-dioxo-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylate (14c). 488 mg (1 mmol) **13c**, 350 mg (61%), mp 208 °C (white powder), IR 3070, 1774, 1719, 1661, 1592, 1514, MS (EI) 571 (1; M^+), 512 (1), 455 (2), 395 (18), 352 (27), 321 (12), 279 (18), 178 (3), 121 (100), 43 (23), ^{1}H NMR ($CDCl_3$) δ 8.15 (m, 1H, arom. H), 7.52 (mc, 2H, arom. H), 7.25 (m, 5H, arom. H), 6.87 (mc, 2H, 10-H, 11-H), 5.06 (d, 1H) and 3.67 (d, 1H, CH_2–phe, J = 14.5 Hz), 4.00 (mc, 2H, O–CH_2), 3.81 (s, 3H, O–CH_3), 2.28 (s, 3H, CH_3CO), 2.20 (s, 3H, CH_3CO), 1.72 (s, 3H, 7-CH_3), 1.08 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{32}H_{29}NO_9$ (571.58): C, 67.24; H, 5.11; N, 2.45. Found: C, 67.09; H, 4.98; N, 2.31.

5.4. General procedure for the preparation of ethyl-6,9,12,13-tetrahydro-7-methyl-5,9,12,13-tetraoxo-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylates (15)

Ethyl-6,13-dihydro-9,12-dihydroxy-7-methyl-5,13-dioxo-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylates (**13**) were dissolved in 250 ml of diethyl ether. Anhydrous sodium sulfate and silver(I)oxide were then added and the reaction mixture was stirred for 2 h at room temperature. After filtration and concentration in vacuo, quinones **15** were obtained and recrystallized from diethyl ether.

5.4.1. Ethyl-6-benzyl-6,9,12,13-tetrahydro-7-methyl-5,9,12,13-tetraoxo-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylate (15a). 457 mg (1 mmol) **13a**, 1.4 g sodium sulfate, 4.1 g silver(I)oxide, 320 mg (70%), mp 144 °C (yellow powder), IR 1724, 1678, 1666, 1592, MS (EI) 455 (1; M^+), 411 (4), 382 (2), 364 (3), 322 (31), 250 (30), 204 (1), 133 (6), 106 (4), 91 (100), 43 (2), ^{1}H NMR ($CDCl_3$) δ 8.20 (mc, 1H, 1-H), 7.60 (mc, 2H, arom. H), 7.30 (mc, 6H, arom. H), 6.75 (d, 1H) and 6.86 (d, 1H, 10-H and 11-H, J = 10.2 Hz), 4.10 (d, 1H) and 5.00 (d, 1H, CH_2–Phe, J = 14.8 Hz), 4.05 (q, 2H, O–CH_2), 1.11 (t, 3H, O–C–CH_3), UV–vis (MeOH) 231 (4.35). Anal. Calcd for $C_{27}H_{21}NO_6$ (455.46): C, 71.20; H, 4.65; N, 3.08. Found: C, 71.04; H, 4.90; N, 2.92.

5.4.2. Ethyl-6,9,12,13-tetrahydro-7-methyl-5,9,12,13-tetraoxo-6-(4-tolyl)-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylate (15b). 457 mg (1 mmol) **13b**, 1.4 g sodium sulfate, 4.1 g silver(I)oxide, 315 mg (69%), mp 131 °C (yellow powder), IR 1724, 1682, 1590, MS (EI) 455 (47; M^+), 411 (8), 382 (12), 322 (9), 249 (56), 165 (9), 132 (100), 91 (43), 65 (9), 44 (6) ^{1}H NMR ($CDCl_3$) δ 8.25 (mc, 1H, 1-H), 7.64 (mc. 2H, arom. H), 7.27 (mc, 5H, arom. H), 6.81 ('s,' 2H, 10-H and 11-H), 4.09 (m, 2H, O–CH_2), 2.34 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 1.15 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{27}H_{21}NO_6$ (455.46):

C, 71.20; H, 4.65; N, 3.08. Found: C, 71.03; H, 4.56; N, 3.01.

5.4.3. Ethyl-6,9,12,13-tetrahydro-7-methyl-6-(4-methoxybenzyl)-5,9,12,13-tetraoxo-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylate (15c). 488 mg (1 mmol) **13c**, 1.4 g sodium sulfate, 4.4 g silver(I)oxide, 310 mg (64%), mp 128 °C (yellow powder), IR 1722, 1677, 1666, 1591, MS (EI) 485 (2; M^+), 398 (1), 353 (1), 277 (1), 249 (4), 191 (2), 121 (100), 77 (6), 44 (3). ^{1}H NMR ($CDCl_3$) δ 8.19 (m, 1H, 1-H), 7.57 (mc, 2H, arom. H), 7.26 (mc, 3H, arom. H), 6.86 (mc, 2H, arom. H), 6.73 (d, 1H) and 6.88 (d, 1H, 10-H, 11-H, J = 10.2 Hz), 4.94 (d, 1H) and 4.08 (d, 1H, –CH_2–phe, J = 14.5 Hz), 4.05 (mc, 2H, O–CH_2), 3.82 (s, 3H, OCH_3), 2.03 (s, 3H, 7-CH_3), 1.10 (t, 3H, O–C–CH_3). Anal. Calcd from $C_{28}H_{23}NO_7$ (485.49): C, 69.27; H, 4.78; N, 2.89. Found: C, 69.01; H, 4.99; N, 2.88.

5.4.4. Ethyl-6-(4-chlorphenyl)-6,9,12,13-tetrahydro-7-methyl-5,9,12,13-tetraoxo-5*H*-dibenzo[*c*,*f*]azonine-8-carboxylate (15d). 478 mg (1 mmol) **13d**, 1.4 g sodium sulfate, 4.3 g silver(I)oxide, 350 mg (74%), mp 160 °C, IR 1724, 1683, 1669, 1590, MS (EI) 475 (5; M^+), 402 (12), 348 (13), 322 (14), 249 (98), 165 (18), 152 (100), 104 (21), 75 (18), 44 (16), ^{1}H NMR ($CDCl_3$) δ 8.26 (mc., 1H, 1-H), 7.66 (mc, 2H, arom. H), 7.31 (mc, 5H, arom. H), 6.82 (d, 1H) and 6.84 (d, 1H, 10-H, 11-H, J = 10.2 Hz), 4.10 (m, 2H, O–CH_2), 2.11 (s, 3H, 7-CH_3), 1.15 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{26}H_{18}ClNO_6$ (475.88): C, 65.62; H, 3.81; N, 2.94. Found: C, 65.52; H, 3.78; N, 2.86.

5.4.5. Diethyl-8-benzyl-9,14-dihydro-5-hydroxy-2,7-dimethyl-9,14-dioxo-8-*H*-benzo[*c*]benzo[*b*]furo[6,7-*f*]azonine-3,6-dicarboxylate (17a). 455mg (1 mmol) **15a**, 250 mg (1 mmol) ethyl-3-(4-methoxy-benzylamino)crotonate **6e**, acetic acid, 8 h, 356 mg (63%), mp 211 °C (white powder from dichloromethane/hexane), IR 3403, 1716, 1674, 1662, 1592, MS (EI) 567 (12; M^+), 521 (16), 476 (9), 414 (14), 389 (8), 307 (7), 176 (12), 154 (71), 136 (58), 91 (100), 65 (13), ^{1}H NMR ($CDCl_3$) δ 8.23 (mc, 1H, 13-H), 7.69 (s, 1H, 4-H), 7.58 (mc, 2H, arom. H), 7.30 (mc, 6H, arom. H), 6.09 (s, 1H, OH), 5.01 (d, 1H) and 3.84 (d, 1H, CH_2–phe, J = 14.7 Hz), 4. 42 (q, 2H, O–CH_2), 4.08 (mc, 2H, O–CH_2), 2.74 (s, 3H, 2-CH_3), 1.71 (s, 3H, 7-CH_3), 1.46 (t, 3H, O–C–CH_3), 1.11 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{33}H_{29}NO_8$ (567.59): C, 69.83; H, 5.15; N, 2.47. Found: C, 69.76; H, 5.25; N, 2.36.

5.4.6. Diethyl-9,14-dihydro-5-hydroxy-8-(4-methoxybenzyl)-2,7-dimethyl-9,14-dioxo-8-*H*-benzo[*c*][1]-benzofuro[6,7-*f*]azonine-3,6-dicarboxylate (17b). 485mg (1 mmol) **15c**, 250 mg (1 mmol) ethyl-3-(4-methoxy-benzylamino)crotonate **6e**, acetic acid, 8 h, 315 mg (53%), mp 156 °C, IR 3297, 1715, 1660, 1642, 1592, MS (EI) 597 (1; M^+), 551 (1), 462 (6), 414 (43), 389 (81), 361 (12), 149 (4), 121 (100), 91 (5), 45 (9), ^{1}H NMR ($CDCl_3$) δ 8.22 (mc, 1H, 13-H), 7.70 (s, 1H, 4-H), 7.55 (mc, 2H, arom. H), 7.24 (mc, 3H, arom. H), 6.84 (mc, 2H, arom. H), 6.50 (s, 1H, 5-OH), 3. 78 (d, 1H) and 4.96 (d, 1H, CH_2–phe, J = 14.5 Hz), 4.40 (q, 2H, O–CH_2), 4.11 (mc, 2H, O–CH_2), 3.80 (s, 3H, OCH_3), 2.71 (s, 3H, 2-CH_3), 1.72 (s, 3H, 7-CH_3), 1.44 (t, 3H, O–C–CH_3), 1.07 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{34}H_{31}NO_9$ (597.62): C, 68.33; H, 5.23; N, 2.34. Found: C, 68.54; H, 4.98; N, 2.37.

5.4.7. 3-Acetyl-3a-chloro-3a,11b-dihydro-5,11b-dihydroxy-2-methyl-1-phenyl-naphtho[2,3-*g*]indol-6,11-dione (20a). 210 mg (1.2 mmol) 4-phenylaminopent-3-en-2-one **6g**, 286 mg (1.2 mmol) 2-chloro-1,4,9,10-anthradiquinone **19**, acetic acid, 5 h, 41.0 mg (8%), mp 139 °C (yellow crystals), IR 3420, 1663, 1684,1592, 1564, MS 447 (28; M^+), 405 (19), 371 (10), 314 (7), 274 (14), 240 (11), 175 (5), 133 (9), 118 (100), 77 (60), 44 (21), ^{1}H NMR ($CDCl_3$) δ 15.49 (s, 1H, 5-OH), 8.23 (mc, 1H) and 7.97 (mc, 1H, 7-H, 10-H), 7.80 (mc, 1H, arom. H), 7.66–7.36 (m, 6H, arom. H), 6.45 (s, 1H, 4-H), 5.29 (s, 1H, 11b-OH), 2.11 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), ^{13}C NMR ($CDCl_3$) δ 198.60 (s, C=O (carbonyl)), 190.04 (s, C=O (carbonyl)), 178.51 (s, C=O (carbonyl)), 172.30 (s, C-2), 158.61 (s, br, C-5, C–OH), 135.09, 134.80, 133.14, 132.87, 132.79, 132.42, 132.16, 131.47, 131.12, 126.68, 126.54, 125.66, 125.39, 124.26, 116.37, 102.53 (s, C-3), 93.62 (s, C-11b, C–OH), 61.69 (s, C-3a), 30.08 (q, CH_3, $^1J_{C/H}$ = 127.5 Hz), 16.37 (q, CH_3, $^1J_{C/H}$ = 130.1 Hz). Anal. Calcd for $C_{25}H_{18}ClNO_5$ (447.87): C, 67.04; H, 4.05; N, 3.13. Found: C, 66.77; H, 3.78; N, 3.05.

5.4.8. 3-Acetyl-3a-chloro-3a,11b-dihydro-5,11b-dihydroxy-2-methyl-1-(4-tolyl)-naphtho[2,3-*g*]indol-6,11-dione (20b). 210 mg (1.2 mmol) 4-(4-tolylamino)pent-3-en-2-one **6i**, 286 mg (1.2 mmol) 2-chloro-1,4,9,10-anthradiquinone **19**, acetic acid, 5 h, 38 mg (7%), mp 223 °C (yellow crystals), IR 3269, 1693, 1644, 1585, 1511, MS (EI) 462 (9; M^+), 418 (2), 374 (1), 307 (14), 289 (11), 242 (2), 176 (15), 154 (100), 77 (54), ^{1}H NMR ($CDCl_3$) δ 10.14 (s, 1H, 5-OH), 9.64 (s, 1H, 11b-OH), 8.06 (mc, 1H) and 7.77 (mc, 1H, 7-H, 10-H), 7.60 (mc, 2H, 8-H, 9-H), 7.38–7.17 (m, 4H, arom. H), 7.06 (s, 1H, 4-H), 2.31 (s, 3H, CH_3–tol), 1.92 (s, 3H, CH_3), 1.78 (s, 3H, CH_3). Anal. Calcd for $C_{26}H_{20}ClNO_5$ (461.90): C, 67.61; H, 4.36; N, 3.03. Found: C, 67.42; H, 3.67; N, 2.91.

5.4.9. 12-Benzyl-7-chloro-7,8,9,10,11,12,12a,13-octahydro-6,12a-dihydroxy-10,10-dimethyl-5*H*-naphtho[2,3-*a*]carbazol-5,8,13-trione (24). 210 mg (1.2 mmol) 3-benzylamino-5,5-dimethylcyclohex-2-enone **10b**, 286 mg (1.2 mmol) 2-chloro-1,4,9,10-anthradiquinone **19**, acetic acid, 5 h, 180 mg (30%), mp 209 °C (yellow crystals), IR 3416, 1682, 1625, 1590, 1566, MS (EI) 501 (25; M^+), 467 (13), 410 (17), 374 (7), 336 (2), 290 (2), 249 (5), 83 (100), 55 (9), ^{1}H NMR ($CDCl_3$) δ 15.71 (s, 1H, 5-OH), 8.22 (mc, 1H) and 7.97 (mc, 1H, 7-H, 10-H), 7.82 (mc, 1H) and 7.62 (mc, 1H, 8-H, 9-H), 7.57–7.32 (m, 5H, arom. H), 6.50 (s, 1H, 4-H), 6.19 (s, 1H, 12b-OH), 4.83 (d, 1H) and 4.60 (d, 1H, CH_2–phe, J = 16.6 Hz), 2.18 (mc, 4H, 2× CH_2), 0.94 (s, 3H, CH_3), 0.79 (s, 3H, CH_3), UV–vis (MeOH) 232 (3.99), 258 (3.94), 323 (3.86), 387 (3.45). Anal. Calcd for $C_{29}H_{24}ClNO_5$ (501.96): C, 69.39; H, 4.82; N, 2.79. Found: C, 69.27; H, 4.79; N, 2.79.

5.4.10. Ethyl-1-benzyl-5-hydroxy-2-methyl-1*H*-naphtho[2,3-*g*]indol-3-carboxylate (26a). 263 mg (1.2 mmol) ethyl-3-benzylaminocrotonate **6a**, 250 mg (1.2 mmol) 1,4-anthraquinone **25**, acetic acid, 36 h, 180 mg (37%), mp 263 °C, IR 3272, 1654, 1584, 1521, MS (EI) 409 (100; M^+), 364 (11), 318 (19), 290 (32), 272 (17), 216 (16), 152 (12), 91 (14), 49 (11), 44 (11) ^{1}H NMR (DMSO-d_6) δ 10.03 (s, 1H, OH), 8.81 (s, 1H, 6-H), 8.06 (m, 1H) and 7.80 (m, 1H, 7-H, 10-H), 7.71 (s, 1H, 4-H), 7.43 (mc, 2H, 8-H, 9-H), 7.26 (m, 5H, arom. H), 6.04 (s, 2H, CH_2–phe), 4.36, (q, 2H, O–CH_2), 2.80 (s, 3H, 2-CH_3), 1.43 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{27}H_{23}NO_3$ (409.48): C, 79.20; H, 5.66; N, 3.42. Found: C, 78.97; H, 5.81; N, 3.27.

5.4.11. Ethyl-5-hydroxy-2-methyl-1-(4-tolyl)-1*H*-naphtho[2,3-*g*]indol-3-carboxylate (26b). 263 mg (1.2 mmol) ethyl-3-(4-tolylamino)crotonate **6b**, 250 mg (1.2 mmol) 1,4-anthraquinone **25**, acetic acid, 36 h, 185 mg (38%), mp 251 °C, IR 3304, 1662, 1621, 1514, MS (EI) 409 (100; M^+), 381 (34), 320 (16), 291 (16), 245 (14), 182 (21), 149 (10), 91 (10), 57 (10), 43 (10), ^{1}H NMR (DMSO-d_6) δ 10.06 (s, 1H, OH), 8.81 (s, 1H, 6-H), 8.06 (m, 1H, 7-H), 7.69 (s, 1H, 4-H), 7.42 (mc, 8H, arom. H), 4.36 (q, 2H, O–CH_2), 2.59 (s, 3H, 2-CH_3), 2.46 (s, 3H, CH_3), 1.41 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{27}H_{23}NO_3$ (409.48): C, 79.20; H, 5.66; N, 3.42. Found: C, 79.07; H, 5.37; N, 3.21.

5.4.12. Ethyl-5-hydroxy-1-(4-methoxyphenyl)-2-methyl-1*H*-naphtho[2,3-*g*]indol-3-carboxylate (26c). 282 mg (1.2 mmol) ethyl-3-(4-methoxyphenylamino)crotonate **6c**, 250 mg (1.2 mmol) 1,4-anthraquinone **25**, acetic acid, 36 h, 150 mg (29%), mp 263 °C, IR 3236, 1664, 1619, 1512, MS (EI) 425 (100; M^+), 397 (26), 380 (7), 352 (7), 320 (8), 308 (7), 190 (9), 140 (6), 126 (4), 43 (12), ^{1}H NMR (DMSO-d_6) δ 10.06 (s, 1H, OH), 8.82 (s, 1H, 6-H), 8.06 (m, 1H, arom. H), 7.70 (s, 1H, 4-H), 7.45 (mc, 8H, arom. H), 4.35 (q, 2H, O–CH_2), 3.98 (s, 3H, OCH_3), 2.46 (s, 3H, 2-CH_3), 1.41 (t, 3H, O–C–CH_3), UV–vis (MeOH) 289 (4.36). Anal. Calcd for $C_{27}H_{23}NO_4$ (425.48): C, 76.22; H, 5.45; N, 3.29. Found: C, 75.97; H, 5.72; N, 3.12.

5.4.13. Ethyl-5-hydroxy-1-(4-methoxybenzyl)-2-methyl-1*H*-naphtho[2,3-*g*]indol-3-carboxylate (26e). 248 mg (1.2 mmol) ethyl-3-(4-methoxybenzylamino)crotonate **6e**, 250 mg (1.2 mmol) 1,4-anthraquinone **25**, acetic acid, 36 h, 260 mg (49%), mp 199 °C, IR 3272, 1666, 1584, 1513, MS (EI) 439 (36; M^+), 394 (1), 318 (2), 290 (4), 272 (6), 216 (5), 189 (4), 152 (5), 121 (100), 91 (5), 44 (10), ^{1}H NMR (DMSO-d_6): δ 10.04 (s, 1H, OH), 8.83 (s, 1H) and 8.69 (s, 1H, 6-H, 11-H), 8.07 (mc, 1H) and 7.84 (mc, 1H, 7-H, 10-H), 7.72 (s, 1H, 4-H), 7. 46 (mc, 2H, 8-H, 9-H), 6.98 (mc, 4H, arom. H), 5.94 (s, 2H, CH_2–phe), 4.36 (q, 2H, O–CH_2), 3.64 (s, 3H, OCH_3), 2.79 (s, 3H, 2-CH_3), 1.44 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{28}H_{25}NO_4$ (439.51) C, 76.52; H, 5.73; N, 3.19. Found: C, 76.46; H, 5.49; N, 3.10.

5.4.14. Ethyl-5-hydroxy-1-isobutyl-2-methyl-1-*H*-naphtho[2,3-*g*]indol-3-carboxylate (26m). 221 mg (1.2 mmol) ethyl-3-isobutylaminocrotonate **6m**, 250 mg (1.2 mmol) 1,4-anthraquinone **25**, acetic acid, 20 h, 210 mg (46%), mp 282 °C, IR 3254, 1658, 1584, 1519, MS (EI) 375 (100; M^+), 346 (8), 290 (16), 259 (13), 216 (10), 189 (5), 149 (4), 119 (2), 57 (6), 41 (9), ^{1}H NMR (DMSO-d_6) δ 10.01 (s, 1H, OH), 8.87 (s, 1H) and 8.74 (s, 1H, 6-H, 11-H), 8.12 (mc, 2H, 7-H, 10-H), 7.67 (s, 1H, 4-H), 7.50 (mc, 2H, 8-H, 9-H), 4.52 (br, 2H, CH_2–isobu), 4.31 (q, 2H, O–CH_2), 2.77 (s, 3H, 2-CH_3), 2.28 (m, 1H, CH–isobu), 1.40 (t, 3H, O–C–CH_3), 0.94 ('s,' 6H, $(CH_3)_2$–isobu), UV–vis (MeOH) 291 (4.22). Anal. Calcd for $C_{24}H_{25}NO_3$ (375.46): C, 76.77; H, 6.71; N, 3.73. Found: C, 76.54; H, 6.71; N, 3.72.

5.4.15. Ethyl-5-hydroxy-1-(4-methoxyphenyl)-2-phenyl-1*H*-naphtho[2,3-*g*]indol-3-carboxylate (26n). 356 mg (1.2 mmol) ethyl-3-(4-methoxyphenylamino)cinnamate **6n**, 250 mg (1.2 mmol) 1,4-anthraquinone **25**, acetic acid, 36 h, 270 mg (46%), mp 282 °C, IR 3244, 1650, 1584, 151, MS (EI) 487 (100; M^+), 459 (10), 414 (3), 341 (6), 221 (5), 170 (22), 149 (36), 91(16), 57 (40), 43 (80), ^{1}H NMR (DMSO-d_6): δ 10.18 (s, 1H, OH), 8.86 (s, 1H, 6-H), 8.09 (m, 1H, arom. H), 7.76 (s, 1H, 4-H), 7.25 (mc, 13H, arom. H), 4.07 (q, 2H, O–CH_2), 3.85 (s, 3H, O–CH_3), 1.03 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{32}H_{25}NO_4$ (487.55): C, 78.83; H, 5.17; N, 2.87. Found: C, 78.75; H, 5.12; N, 2.65.

5.4.16. Ethyl-5-hydroxy-1,2-dimethyl-1*H*-naphtho[2,3-*g*]indol-3-carboxylate (26o). 172 mg (1.2 mmol) ethyl-3-methylaminocrotonate **6o**, 250 mg (1.2 mmol) 1,4-anthraquinone **25**, acetic acid, 36 h, 180 mg (45%), mp 286 °C, IR 3257, 1643, 1582, 1518, MS (EI) 333 (100; M^+), 304 (54), 259 (12), 231 (8), 216 (7), 152 (5), 144 (7), 95(3), 44 (4) ^{1}H NMR (DMSO-d_6) δ 9.96 (s, 1H, OH), 9.06 (s, 1H) and 8.86 (s, 1H, 6-H, 11-H), 8.15 (mc, 2H, 7-H, 10-H), 7.65 (s, 1H, 4-H), 7.50 (mc, 2H, 8-H, 9-H), 4.28 (m, 5H, O–CH_2, N–CH_3), 2.77 (s, 3H, 2-CH_3), 1.41 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{21}H_{19}NO_3$ (333.38): C, 75.66; H, 5.74; N, 4.20. Found: C, 75.40; H, 5.79; N, 4.23.

5.4.17. Diethyl-4,4′,5,5′-tetrahydro-1,1′-diisobutyl-2,2′-dimethyl-5,5′-dioxo-1*H*,1′*H*-4,4′binaphtho[2,3-*g*]indol-3,3′-dicarboxylate (28). 250 mg (0.67 mmol) of **26m** was dissolved in 15 ml of acetone and treated with 9 g of silver(I)oxide and 3 g of anhydrous sodium sulfate for 2 h at 40 °C. Recrystallization after evaporation in vacuo afforded **28**. 120 mg (48%), mp 276 °C (from dichlormethane/hexane (70:30)), IR 1694, 1598, 1515, MS (EI) 748 (7; M^+), 703 (2), 629 (3), 570(1), 397 (15), 374 (100), 330 (9), 307 (13), 290 (12), 272 (11), 230 (6), ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 2H, 6-H, 6′-H), 7.77 (mc, 4H, 7-H, 7′-H, 10-H, 10′-H), 7.53 (m, 4H, 8-H, 8′-H, 9-H, 9′-H), 7.43 (s, 2H, 11-H, 11′-H), 4.84 (s, 2H, 4-H, 4′-H), 4.10 (m, 2H, O–CH_2), 4.30 (m, 2H, OCH_2), 3.70 and 3.40 (m, 4H, 2× CH_2–isobut), 2.36 (s, 6H, 2× 2-CH_3), 1.83 (m, 2H, 2× CH–isobu), 1.42 (t, 6H, 2× O–C–CH_3), 0.80 and 0.65 (d, 6H, $(CH_3)_2$–isobu, $J = 6.6$ Hz). Anal. Calcd for $C_{48}H_{48}N_2O_6$ (748.91): C, 76.98; H, 6.46; N, 3.74. Found: C, 76.75; H, 6.60; N, 3.70.

5.5. General procedure for the preparation of ethyl-4-[(dimethylamino)methyl]-5-hydroxy-2-methyl-1*H*-naphtho[2,3-*g*]indol-3-carboxylates (29)

Ethyl-5-hydroxy-2-phenyl-1*H*-naphtho[2,3-*g*]indol-3-carboxylates **26** were heated in bisdimethylaminomethane (2 ml) with catalytic amounts of acetic acid (2 ml) under reflux for 2 h. After evaporation in vacuo, the obtained residue was recrystallized from dichloromethane/hexanes (40:60).

5.5.1. Ethyl-4-[(dimethylamino)methyl]-5-hydroxy-1-isobutyl-2-methyl-1*H*-naphtho[2,3-*g*]indol-3-carboxylate (29a). 450 mg (1.2 mmol) **26m**, 200 mg (46%), mp 149 °C, IR 1690, 1617, 1533, MS (EI) 432 (11; M^+), 387 (100), 375 (23), 342 (16), 286 (19), 230 (10), 154 (47), 77(36), 50 (38), ^{1}H NMR ($CDCl_3$) δ 11.0 (br, 1H, OH), 8.98 (s, 1H) and 8.61 (s, 1H, 6-H, 11-H), 8.00 (m, 2H, 7-H, 10-H), 7.48 (m, 2H, 8-H, 9-H), 4.41 (m, 4H, O–CH_2, N–CH_2–C), 4.05 (s, 2H, $(CH_3)_2$N–CH_2), 2.65 (s, 3H, 2-CH_3), 2.53 (m, 1H, CH–isobu), 2.41 (s, 6H, N$(CH_3)_2$), 1.45 (t, 3H, O–C–CH_3), 1.05 (d, 6H, $(CH_3)_2$–C), UV–vis (MeOH) 299 (4.29). Anal. Calcd for $C_{27}H_{32}N_2O_3$ (432.56): C, 74.97; H, 7.46; N, 6.48. Found: C, 74.86; H, 7.58; N, 6.38.

5.5.2. Ethyl-4-[(dimethyl-amino)-methyl]-5-hydroxy-1-(4-methoxy-phenyl)-2-phenyl-1*H*-naphtho[2,3-*g*]indol-3-carboxylate (29b). 406 mg (1.2 mmol) **26n**, 310 mg (47%), mp 285 °C, IR 1700, 1617, 1512, MS 544 (5; M^+), 499 (42), 454 (16), 352 (4), 329 (24), 176 (100), 136 (33), 77(41), 50 (40), ^{1}H NMR ($CDCl_3$) 10.5 (br, 1H, OH), 8.91 (s, 1H, 6-H), 8.00 (m, 1H, 7-H), 7.43–6.92 m, 13H, arom. H), 4.20 (s, 2H, $(CH_3)_2$N–CH_2), 4.11 (q, 2H, O–CH_2), 3.88 (s, 3H, OCH_3), 2.50 (s, 6H, N$(CH_3)_2$), 0.98 (s, 3H, O–C–CH_3). Anal. Calcd for $C_{35}H_{32}N_2O_4$ (544.65): C, 77.18; H, 5.92; N, 5.14. Found: C, 76.91; H, 5.96; N, 5.37.

5.6. General procedure for the preparation of spiro[ethyl-4,5-dihydro-2-methyl-5-oxo-1*H*-naphtho[2,3-*g*]indol-3-carboxylat-4,2′-ethyl-2′,3′,4′,7′-tetrahydro-6′-methyl-naphtho[2′,3′-*g*]pyrano[3′,2′-*e*]indol-5′-carboxylates (31)

Ethyl-4-[(dimethylamino)methyl]-5-hydroxy-2-methyl-1*H*-naphtho[2,3-*g*]indol-3-carboxylates **29** were heated in dichlormethane under reflux for 2 h. Evaporation of the reaction mixture and recrystallization of the obtained residue from dichloromethane/hexanes (30:70) yielded compounds **31**.

5.6.1. Spiro[ethyl-4,5-dihydro-1-isobutyl-2-methyl-5-oxo-1*H*-naphtho[2,3-*g*]indol-3-carboxylat-4,2′-ethyl-2′,3′,4′,7′-tetrahydro-7′-isobutyl-6′-methyl-naphtho[2′,3′-*g*]pyrano[3′,2′-*e*] indol-5′-carboxylate (31a). 432 mg (1.0 mmol) **29a**, 150 mg (39%), mp 272 °C, IR 1700, 1622, 1520, MS (EI) 775 (14; M^+), 682 (4), 410 (4), 387 (100), 358 (4), 342 (12), 302 (6), 285 (15), 270 (5), 244 (6), 228 (4), 202 (4), UV–vis (MeOH) 258 (3.66), 315 (3.37), 346 (3.85). Anal. Calcd for $C_{50}H_{50}N_2O_6$ (774.95): C, 77.49; H, 6.50; N, 3.61. Found: C, 77.50; H, 6.58; N, 3.46.

5.6.2. Spiro[ethyl-4,5-dihydro-1-(4-methoxyphenyl)-5-oxo-2-phenyl-1*H*-naphtho[2,3-*g*]indol-3-carboxylat-4,2′-ethyl-2′,3′,4′,7′-tetrahydro-7′-(4′-methoxyphenyl)-6′-phenyl-naphtho[2′,3′-*g*]pyrano[3′,2′-*e*]indol-5′-carboxylate (31b). 544 mg (1.0 mmol) **29b**, 160 mg (32%), mp 300 °C, IR 3051, 1703, 1622, 1519, MS (EI) 499 (100), 455 (8), 426 (8), 383 (4), 354 (6), 306 (2), 252 (2), 235 (7), 177 (2), 109 (1), 77 (1), 44 (4). Anal. Calcd for $C_{66}H_{50}N_2O_8$ (999.13): C, 79.18; H, 5.04; N, 2.80. Found: C, 78.73; H, 4.98; N, 2.81.

5.6.3. Spiro[ethyl-4,5-dihydro-1,2-dimethyl-5-oxo-1*H*-naphtho[2,3-*g*]indol-3-carboxylat-4,2′-ethyl-2′,3′,4′,7′-tetrahydro-6′,7′-dimethyl-naphtho[2′,3′-*g*]pyrano[3′,2′-*e*]indol-5′-carboxylate (31c). 26o was brought to reaction like **26m** and **26n**. Mannich-base **29c** was not isolable and directly reacted to spiro-compound **31c**, 180 mg (52%), mp 287 °C, IR 1698, 1621, 1522, MS (EI) 690 (7; M^+), 490 (5), 460 (10), 345 (22), 329 (31), 307 (100), 289 (53), 272 (11), 202 (6), 159 (6), 109 (4), 44 (5), ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1H, arom. H), 8.77 (s, 1H, arom. H), 8. 46 (s, 1H, arom. H), 7.90 (mc, 5H, arom. H), 7.47 (mc, 4H, arom. H), 4.25 (mc, 2H, O–CH_2), 4.16 (s, 3H, N–CH_3), 3.95 (s, 3H, N–CH_3), 3.63 (mc, 1H) and 2.93 (mc, 4H, pyran-H, O–CH_2me), 2.56 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.24 (mc, 1H, pyran-H), 1.30 (t, 3H, O–C–CH_3), 0.35 (t, 3H, O–C–CH_3). Anal. Calcd for $C_{44}H_{38}N_2O_6$ (690.79): C, 76.50; H, 5.54; N, 4.06. Found: C, 76.43; H, 5.48; N, 4.32.

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References and notes

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