Synthesis, Antitumor Activity, and Mechanism of Action of Benzo[*a*]pyrano[3,2-*h*]acridin-7-one Analogues of Acronycine

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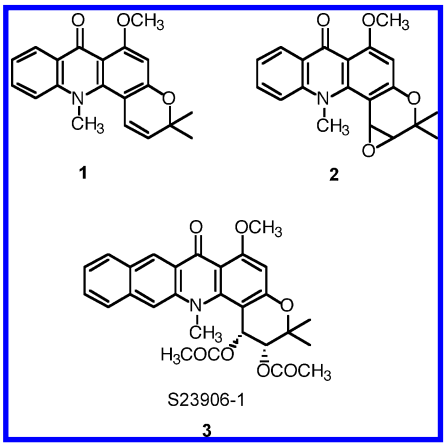
Twenty-two derivatives belonging to the *cis*-1,2-diacyloxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one series were synthesized in nine steps starting from 3,5-dimethoxyacetanilide (**5**) and 2-methoxy-1-naphthalenecarboxylic acid (**7**). Most of them exhibited submicromolar cytotoxicity when tested against murine leukemia (L1210) and human epidermoid carcinoma (KB-3-1) cell lines. The cytotoxic activity correlated strongly with the ability of the compounds to form covalent adducts with purified DNA. Among the most active compounds, **25**, with IC_{50} values of 0.7 and 0.15 μM against L1210 and KB-3-1, respectively, was selected for evaluation in vivo against Colon 38 adenocarcinoma implanted in mice. This compound was active at 3 mg/kg iv (day 12 and 24) with 3/7 tumor free mice by day 80.

Introduction

The natural pyranoacridone acronycine (**1**, Chart 1), first isolated from *Acronychia baueri* Schott (Rutaceae) in 1948,[1,2] was subsequently shown to exhibit a broad spectrum of activity against numerous experimental tumor models, including sarcoma, myeloma, carcinoma, and melanoma.[2,3] Nevertheless, the moderate potency and very low solubility in aqueous solvents of this alkaloid severely hampered the subsequent clinical trials, which gave only poor results.[4]

Following the isolation of the unstable acronycine epoxide (**2**) from several New-Caledonian *Sarcomelicope* species, efforts toward the design of more potent derivatives were guided by a hypothesis of bioactivation of the 1,2-double bond of acronycine into the corresponding oxirane in vivo.[2,5] Significant improvements in terms of potency were obtained with derivatives modified in the pyran ring, which had a similar reactivity toward nucleophilic agents as acronycine epoxide but an improved chemical stability. Such compounds are exemplified by diesters of *cis*-and *trans*-1,2-dihydroxy-1,2-dihydroacronycine, which exhibited marked antitumor properties, with a broadened spectrum and increased potency when compared to acronycine.[6] Further on, structural analogues in the related benzo[*b*]acronycine series, including an additional aromatic ring linearly fused on the natural alkaloid skeleton, were developed, and several *cis*-1,2-dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one esters and diesters proved even more potent.[7,8] A representative of this latter series, diacetate **3**, currently under phase I clinical trials under the code S23906-1, displayed a particularly impressive broad preclinical antitumor spectrum. Indeed, when evaluated against aggressive orthotopic models of human ovarian, lung, and colon cancers, compound **3** demonstrated comparable and/or better activity than paclitaxel, vinorelbine, and irinotecan, respectively.[9] The mechanism of its action was shown to imply alkylation of the 2-amino group of DNA guanine residues by the carbocation resulting from the elimination of the ester leaving group at position 1 of the drug.[8,10]

Chart 1. Acronycine (**1**), Acronycine Epoxide (**2**), and (±)-*cis*-1,2-Diacetoxy-1,2-dihydrobenzo[*b*]acronycine (**3**)



In a continuation of our studies on the structure−activity relationships in the acronycine series,[11] we describe here the synthesis and the biological properties of 6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (**4**) and of related *cis*-1,2-dihydro-1,2-diol esters and diesters. The aim of the present work is to determine the influence of the mode of fusion of the additional aromatic ring onto the natural acronycine tetracyclic core on DNA alkylation and cytotoxic and antitumor properties.

Chemistry

The well-documented facile decarboxylation of 2-amino-1-naphthalenecarboxylic acid derivatives[12] and the toxicity of 2-naphthylamine, which had to be avoided as starting material

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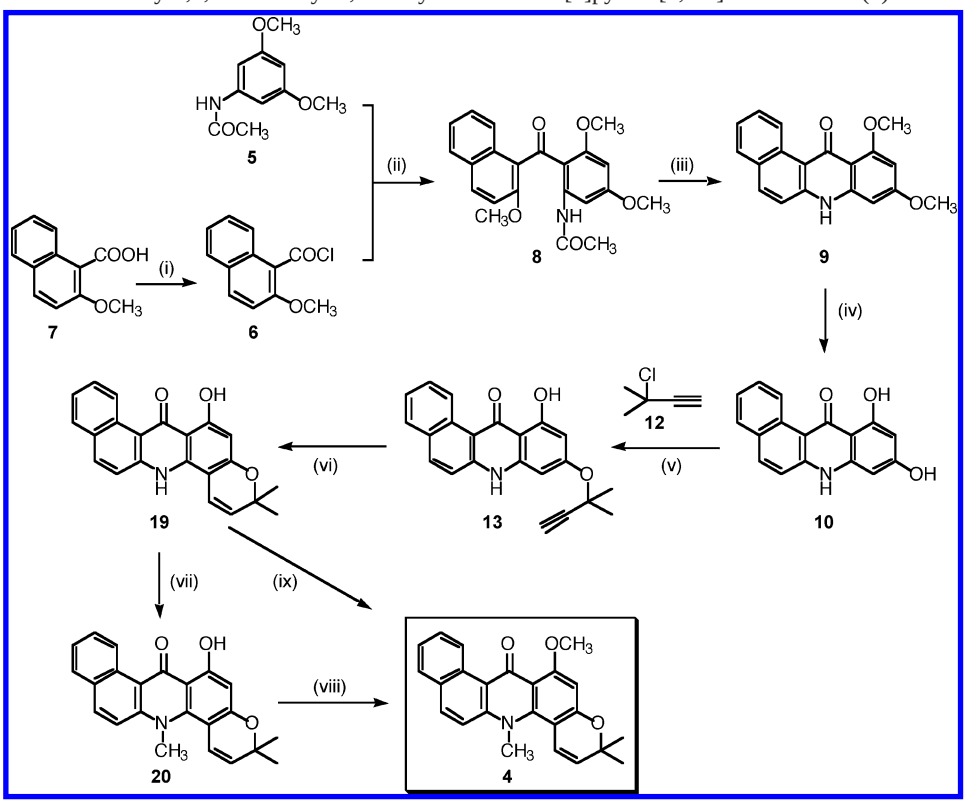
Scheme 1. Synthesis of 6-Methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (**4**)[a]



[a] Reagents and conditions: (i) $SOCl_2$, 60 °C; (ii) $AlCl_3$, CH_2Cl_2, 3 h at 0 °C, and 12 h at rt, (55%); (iii) NaH, DMF, rt (95%); (iv) $HBr/H_2O/CH_3COOH$, reflux (94%); (v) K_2CO_3/KI, DMF, 65 °C (40 °C); (vi) DMF, 130 °C (95%); (vii) K_2CO_3/MeI, Me_2CO, reflux (90%); (viii), NaH/MeI, Me_2CO, reflux (75%); (ix) NaH/$(CH_3)_2SO_4$, DMF, rt (65%).

in the case of a large-scale synthesis, did not permit us to build up the pentacyclic basic benzo[*a*]pyrano[3,2-*h*]acridin-7-one core using a strategy similar to those previously developed in the isomeric benzo[*b*]pyrano[3,2-*h*]acridin-7-one series.[7,8] Consequently, the general approach was inspired by the synthesis of acronycine developed by Lewis et al.,[13] which involved base-catalyzed cyclization of an intermediate diphenyl ketone to construct the acridone skeleton (Scheme 1).[14]

Friedel−Crafts reaction of 3,5-dimethoxyacetanilide (**5**)[15] with 2-methoxy-1-naphthoyl chloride (**6**), prepared extemporaneously by treatment of 2-methoxy-1-naphthalenecarboxylic acid (**7**)[16] with thionyl chloride, afforded 2-methoxy-1-naphthyl (6-acetamido-2,4-dimethoxy)phenyl ketone (**8**) in 55% yield. Cyclization of **8** to 9,11-dimethoxybenzo[*a*]acridin-12(7*H*)-one (**9**) was achieved in 95% yield by the use of sodium hydride in dimethylformamide. Treatment of **9** with hydrogen bromide in acetic acid gave the required 9,11-dihydroxybenzo[*a*]acridin-12(7*H*)-one (**10**) in 94% yield, accompanied by minute amounts of 11-hydroxy-9-methoxybenzo[*a*]acridin-12(7*H*)-one (**11**, Chart 2). Construction of the dimethylpyran ring onto the phenol at 9-position of **10** was performed by a Claisen rearrangement of the corresponding dimethylpropargyl ether.[7a,17] Treatment of **10** with 3-chloro-3-methylbut-1-yne (**12**)[18] at 65 °C in dimethylformamide, in the presence of potassium carbonate and potassium iodide, gave the desired 11-hydroxy-9-(1,1-dimethylpropyn-1-oxy)benzo[*a*]acridin-12(7*H*)-one (**13**) isolated in 40% yield after purification by column chromatography. This compound was accompanied by 3% of 11-hydroxy-9-(6-hydroxy-1,1,6-trimethylhepta-2,4-diynyloxy)-12*H*-benzo[*a*]acridin-12(7*H*)-one (**14**, Chart 2), 2% of 10,12-dihydroxy-9,9-dimethyl-8-methylidene-8,9-dihydro-15*H*-benzo[*a*]pyrrolo[1, 2,3-*fg*]acridin-13-one (**15**), and 9% of 12-hydroxy-9,9-dimethyl-8-methylidene-8,9-dihydro-10-(1,1-dimethylpropyn-1-oxy)-15*H*-benzo[*a*]pyrrolo[1,2,3-*fg*]acridin-15-one (**16**). In addition, a fifth compound was obtained in mixture with **16**, and the two compounds could only be separated as their methylated derivatives **17** and **18**. All these secondary products resulted from the C-alkylation of **10** or **13** by 3-chloro-3-methylbut-1-yne, eventually followed by subsequent cyclization in alkaline medium.[19] As expected, Claisen rearrangement of **13** by heating at 130 °C in dimethylformamide gave the required 6-hydroxy-3,3-dimethyl-3,14-dihydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (**19**) in 95% yield.

Methylation of **19** in acetone, using potassium carbonate as base and methyl iodide as alkylating agent, gave 6-hydroxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (**20**) in almost quantitative yield. In contrast, when the reaction was carried out with dimethyl sulfate in dimethylformamide, in the presence of an excess of sodium hydride, the desired 6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*a*]-pyrano[3,2-*h*]acridin-7-one (**4**) was obtained in 65% yield, together with smaller amounts of 6,7-dimethoxy-3,3-dimethyl-3*H*-benzo[*a*]pyrano[3,2-*h*]acridin (**21**, Chart 2) and 6-methoxy-3,3-dimethyl-3,14-dihydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (**22**). In a similar way, the unresolved mixture obtained in the course of the synthesis of **13** was converted into the corresponding *O*-methyl derivatives **17** and **18**. A phase-sensitive NOESY experiment performed on **18** permitted us to ascribe unambiguously the linear fusion of the dihydrofuran to the benzo[*a*]acridinone core.

The (±)-*cis*-diol **23**, accompanied by small amounts of the corresponding keto alcohol **24** (Chart 3),[8] was conveniently obtained by catalytic osmium tetroxide oxidation of **4** using *N*-methylmorpholine *N*-oxide to regenerate the oxidizing agent (Scheme 2).[7a,20] Treatment of diol **23** with an excess of acylating reagent, acyl anhydride, or acyl chloride afforded the corre-

Chart 2. Compounds **11**, **14**−**18**, and **20**−**22**

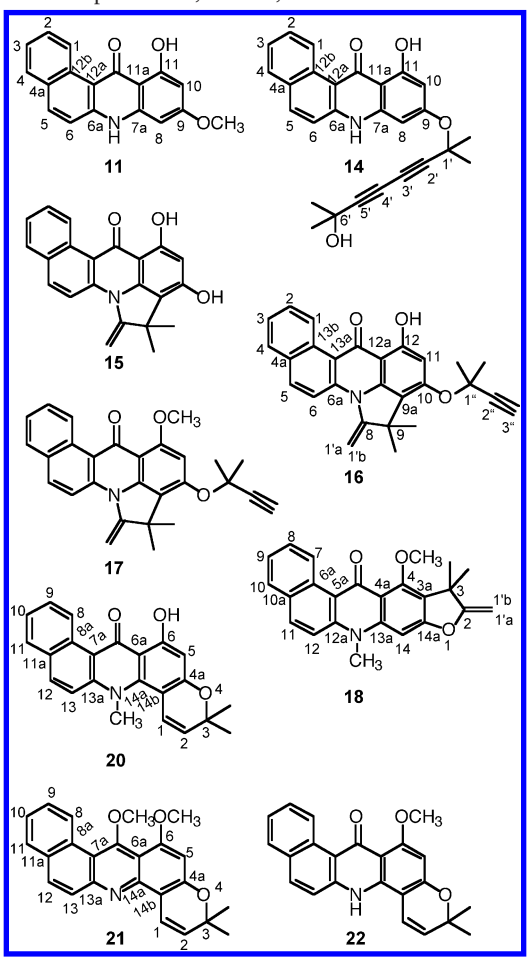
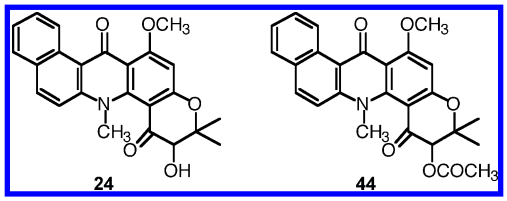


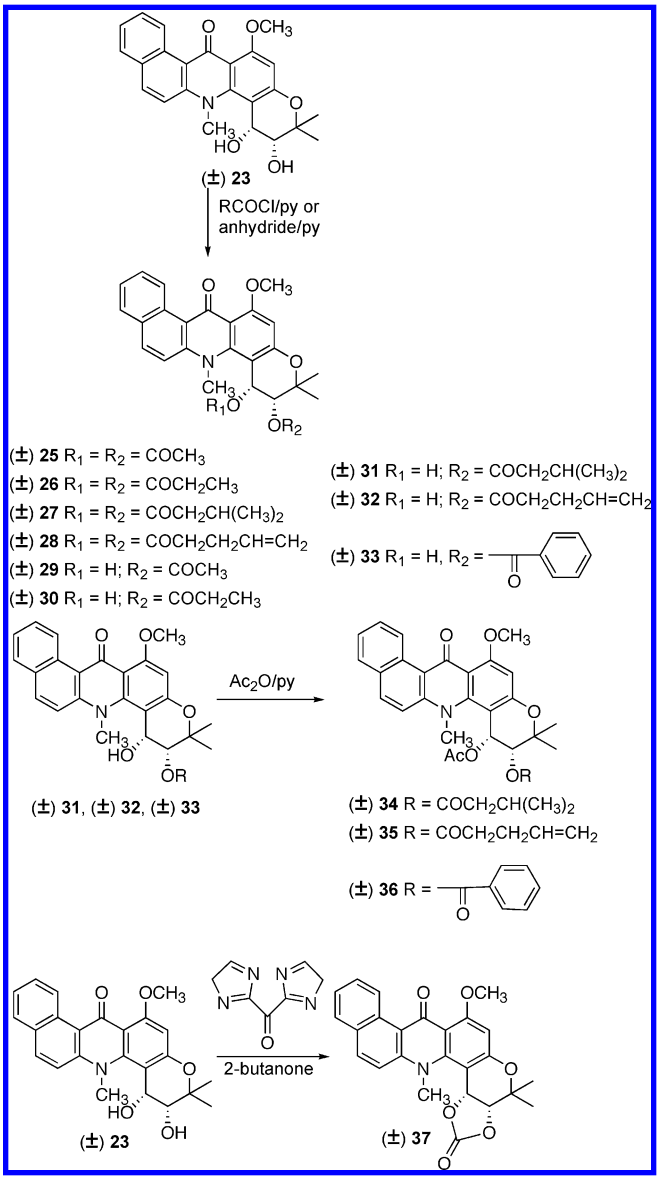
Chart 3. Compounds **24** and **44**



sponding diesters exemplified by diacetate **25**, dipropionate **26**, diisovalerate **27**, and dipentenoate **28**. Under controlled conditions, monoesters at the less hindered 2-position, **29**−**33**, were obtained. Treatment of monovalerate **31**, monopentenoate **32**, and monobenzoate **33** with excess acetic anhydride led to the mixed esters **34**, **35**, and **36**, respectively. The reaction of diol **23** with *N*,*N*′-carbonyldiimidazole in 2-butanone under reflux afforded the cyclic carbonate **37**. Finally, di-*N*,*N*-diethylcarbamate **38** and mono-*N*,*N*-dimethylcarbamate **39**, whose counterparts in the benzo[*b*]pyrano[3,2-*h*]acridin-7-one series had been recently prepared,[7b] were obtained upon treatment of diol **23** with *N*,*N*-diethylcarbamoyl and *N*,*N*-dimethylcarbamoyl chloride, respectively, in tetrahydrofuran, in the presence of potassium hydride (Scheme 3).

To better investigate the structure−activity relationships, the diacetate analogous to **25** was prepared in the isomeric benzo[*a*]pyrano[3,2-*h*]acridin series (Scheme 4). For this purpose, 6,7-dimethoxy-3,3-dimethyl-3*H*-benzo[*a*]pyrano[3,2-*h*]acridin (**21**) was submitted to catalytic osmium tetroxide oxidation. The expected *cis*-diol **40** was obtained in a moderate 15% yield under those conditions, accompanied by the keto alcohol **41** and the diol **42** (Chart 4), both isolated in 16% yield from the reaction

Scheme 2. Synthesis of (±)-*cis*-1,2-Dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one Esters and Diesters

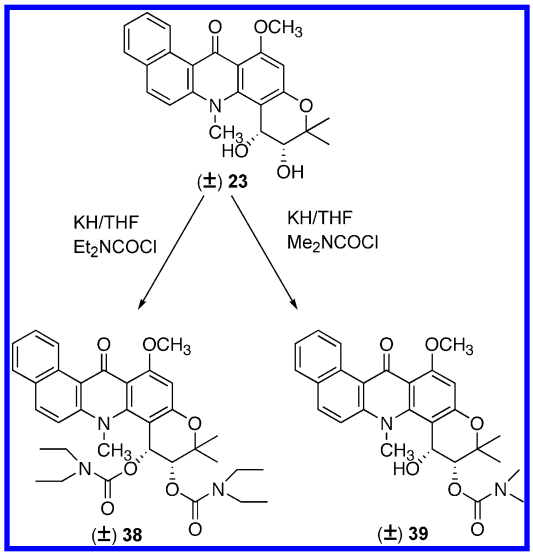


mixture. Acetylation of **40** with acetic anhydride afforded the desired (±)-*cis*-1,2-Diacetoxy-6,7-dimethoxy-3,3-dimethyl-3*H*-benzo[*a*]pyrano[3,2-*h*]acridine (**43**). Similarly, acetylation of **24** gave 2-acetoxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-1,7-dione (**44**, Chart 3).

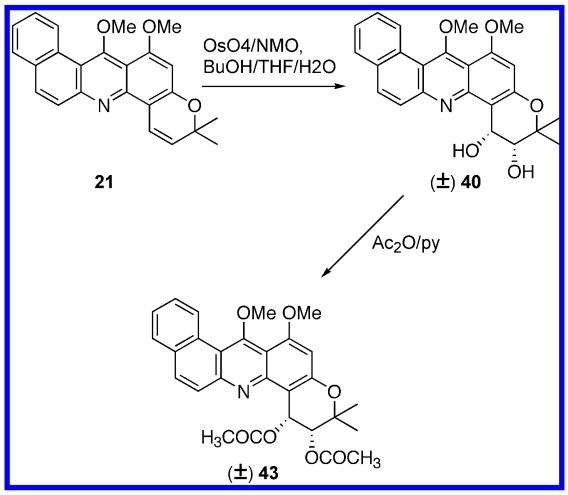
Results and Discussion

All the new benzo[*a*]acronycine derivatives were first evaluated in vitro for their cytotoxicity against two tumor cell lines, a murine leukemia cell line (L1210) and a human epidermoid carcinoma cell line (KB-3-1). The results (IC_{50}) are reported in Table 1. As expected, all (±)-*cis*-1,2-dihydroxy-6-methoxy-3,3,-14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one esters and diesters **25**−**35**, as well as the cyclic carbonate **37** and the carbamates **38** and **39**, exhibited cytotoxic properties, with submicromolar IC_{50} (between 0.06 and 1 μM) against L1210 cells. It is worth noticing that these compounds were significantly more potent on the solid tumor KB-3-1 cell line than on the L1210 leukemia (8-fold increase for compound **34**, 0.1 versus 0.8μM), as previously observed for their

Scheme 3. Synthesis of (±)-*cis*-1,2-Dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one Carbamates



Scheme 4. Synthesis of (±)-*cis*-1,2-Diacetoxy-6,7-dimethoxy-3,3-dimethyl-3*H*-benzo[*a*]pyrano[3,2-*h*]acridine 43



counterparts in the isomeric benzo[*b*]acronycine series.[8] In contrast, 6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo-[*a*]pyrano[3,2-*h*]acridin-7-one (benzo[*a*]acronycine) (**4**), diol **23**, keto alcohol **44**, and compounds **21**, **40**, and **43**, with an aromatized C ring, only displayed marginal cytotoxic activity or were found to be inactive. Therefore, the structure−cytotoxicity relationships observed within the benzo[*a*]acronycine series are comparable to those previously established in the benzo[*b*]acronycine series.[7a,8] The presence of an ester leaving group on the pyran ring appears as an important structural requirement to observe significant cytotoxic activity in both series.

The perturbation of the cell cycle induced by the new benzo-[*a*]acronycine derivatives was studied on L1210 cell line. As previously observed in the isomeric benzo[*b*]acronycine series, all active compounds induced accumulation in the S phase.

The compounds were also evaluated for their ability to form covalent complexes with DNA using gel shift assay.[8] As shown in Figure 1, the various benzo[*a*]acronycine derivatives were used at a fixed concentration (50 μM) and incubated with the radiolabeled 117-bp DNA fragment for a fixed short time (2 h,

Chart 4. Compounds **41** and **42**

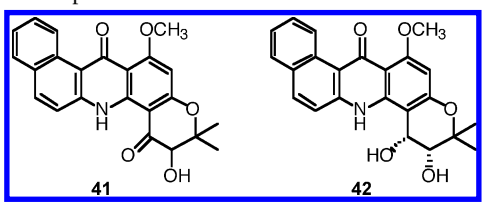


Table 1. Cytotoxicity of Compounds **4**, **21**, **23**, **25**-**41**, **43**, and **44** in Comparison with Acronycine (**1**) and S 23906-1 (**3**)

compound	cytotoxicity, IC_{50}, μM[a] L1210 cells	KB-3-1 cells	% of L1210 cells in S phase [concn, μM][b]	in vitro DNA alkylation[c]
1 (acronycine)	23	3.7		nt
3 (S 23906-1)	0.7	0.1	73 [5]	++[e]
4	2.5	8.6	na	nt
21	28	33	nt	nt
23	49	32	nt	0
25	0.7	0.15	68 [5]	++
26	0.5	0.1	70 [5]	+
27	0.7	0.15	60 [10]	++
28	0.5	0.13	66 [10]	++
29	0.7	0.2	76 [5]	++
30	0.5	0.1	69 [5]	++
31	1.0	0.2	73 [5]	+
32	0.8	0.25	70 [5]	0
33	0.8	0.3	73 [2.5]	+
34	0.8	0.1	76 [5]	++
35	0.7	0.1	78 [5]	++
36	insoluble	insoluble	insoluble	nt
37	0.06	0.015	64 [0.25]	0
38	0.9	0.8	43 [10]	+
39	0.5	0.1	73 [10]	++
40	1.4	6.3	nt	0
41	0.5	2.0	na	0
43	8.0	7.2	nt	0
44	2.0	6.3	nt	0

[a] Inhibition of cell proliferation measured by the MTT assay (mean of at least three values obtained in separate experiments). [b] Highest percentage of L1210 cells arrested in S phase after a 21 h exposure to the indicated concentration. Untreated control: 32% on average; na: inactive; nt: not tested. [c] The capacity of the tested compounds to form complexes with purified DNA was investigated by a gel shift assay. Symbols ++ and + refer to strong and weak alkylation, respectively, whereas 0 means no DNA alkylation at all.

Figure 1A) or a longer delay (24 h, Figure 1B).[8] This result clearly identifies some compounds as efficient DNA binding agents with the most efficient one at 2 h being the diacetate derivative **25**. Inactive DNA binding molecules were also identified (see compounds **23**, **44**, **41**, **40**, and **37**). Indeed, compounds **44** and **41** are not able to react with DNA, in full agreement with the data previously published for their benzo-[*b*]acronycine counterparts.[8] Similarly, the diols **23** and **40** failed to react with DNA, since they do not bear any reactive group on the pyran ring, which is a major requisite element for the alkylating reaction.[10] Surprisingly, the benzo[*a*]acronycine monoacetate **29** binds DNA less efficiently than the benzo[*a*]-acronycine diacetate **25**, by contrast with the higher reactivity of benzo[*b*]acronycine monoacetate previously shown to be more reactive than compound **3**.[8] In the same manner, the monopentenoate **32** totally failed to supershift DNA, whereas the corresponding diesters bearing an additional acetate (**35**) or a second pentenoate group (**28**) efficiently delayed the DNA migration as a marker of DNA binding. The same observation was done using the isovalerate derivatives **27**, **34**, and **31**. In term of kinetic of reaction, some compounds achieve their maximum of reactivity after 2 h, and further incubation for 24 h did not allow additional binding/bonding of the compounds

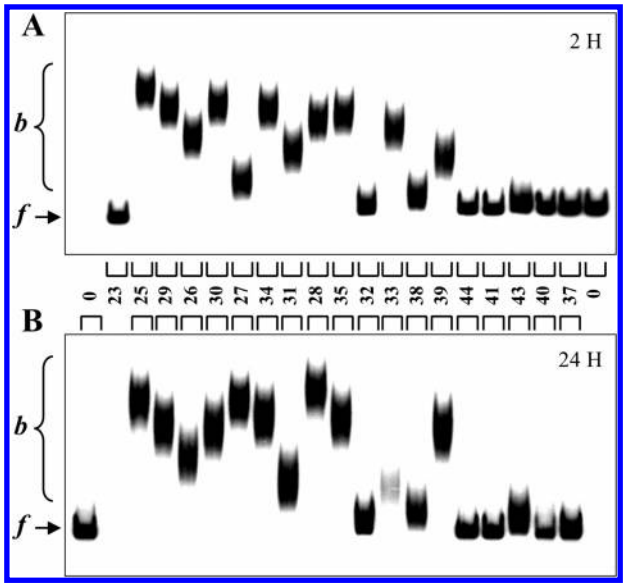


Figure 1. DNA bonding analysis by benzo[*a*]acronycine derivatives using gel shift experiments. The various compounds (50 μM) were incubated for 2 h (panel A) or 24 h (panel B) with the 117-bp radiolabeled DNA substrate in 1 mM Na cacodylate buffer prior to be subjected to electrophoresis on a 10% native polyacrylamide gel. The lane "0" refers to the control DNA fragment alone. Bound and free DNA fragments are referred as "*b*" and "*f*", respectively.

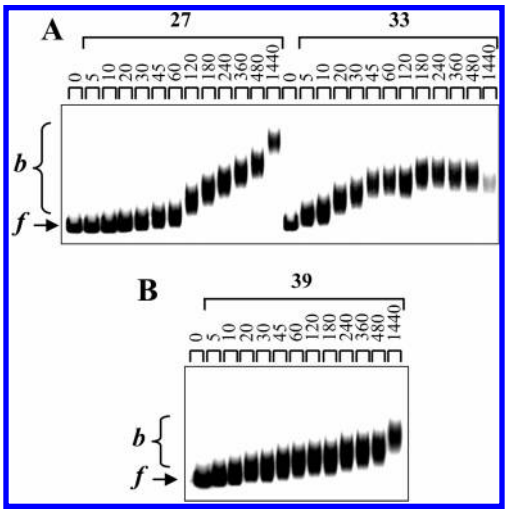


Figure 2. Kinetics of DNA bonding using electromobility shift assay. The radiolabeled 117-bp DNA fragment was incubated with 50 μM of **27**, **33**, or **39** derivatives for the appropriate time indicated on the top of the lanes (min). Bound and free DNA fragments are referred as "*b*" and "*f*", respectively.

to the DNA fragment (see the diacetate **25** and monoacetate **29**, the di- and monopropionate **26** and **30**, the acetate−isovalerate **34** and the acetate−pentenoate **35**), whereas other derivatives presented delayed reaction, as shown by comparing the 2 h (Figure 1, panel A) with the overnight (Figure 1, panel B) incubation time. This is notably the case for compounds **27** and **39**, the latter one clearly presenting a slow and progressive alkylation process as revealed by kinetics measurements (Figure 2B). Kinetics of alkylation reaction using the diisovalerate **27** (Figure 2A) reveals a slow reactivity with nearly no gel shift after 1 h of incubation. However, this compound appears to be a very efficient DNA alkylating agent after a 24-h incubation, suggesting a very slow isovalerate release and/or transesterification process. By contrast, the monobenzoate derivative **33** quickly reacted with DNA with a maximum of alkylation observed after 2 to 3 h, but a small decrease in the alkylation efficiency from 3 to 24 h suggested the release of the adduct from DNA.

Finally, compound **25** was selected for an in vivo evaluation, comparatively with compound **3**, on an established C38 colon adenocarcima (sc implantation) in mice. Although less potent than compound **3** (Figure 3), compound **25** administered twice (day 12, day 24) by the iv route at the optimal dose of 4 mg/kg proved to be significantly active, inhibiting tumor growth by more than 80% and with three of seven mice tumor-free on day 80.

Conclusion

In summary, 1,2-dihydroxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one esters and diesters were markedly more potent than acronycine in terms of cytotoxicity, when tested against L1210 and KB-3-1 cell lines. As previously observed in the isomeric benzo[*b*]acronycine series, the cytotoxic activity appeared to be strongly correlated with the ability of the compounds to give covalent adducts with DNA. Compound **25**, although less potent than its benzo[*b*]-pyrano[3,2-*h*]acridin-7-one counterpart **3**, proved to be significantly active in vivo on the murine C38 colon adenocarcinoma model. The new benzo[*a*]acronycine series appears very promising, and various pharmacomodulations are currently being carried out.

Experimental Section

Chemistry. Melting points were determined on a hot stage Reichert microscope and are uncorrected. Mass spectra were recorded with ZQ 2000 Waters and Q-Tof1 Micromass spectrometers using electrospray ionization (ESI-MS; Vc = 30 V) or with a Nermag R-10-10C spectrometer using desorption-chemical ionization (DCI-MS; reagent gas: NH_3). UV spectra (λ_{max} in nm) were recorded in spectroscopic grade MeOH on a Beckman Model 34 spectrophotometer. IR spectra (ν_{max} in cm^{-1}) were obtained from potassium bromide pellets or sodium chloride films on a Perkin-Elmer 257 instrument. ^1H NMR [δ (ppm), J (Hz)] spectra were run at 400 MHz and ^{13}C NMR spectra at 75 MHz, using Bruker AVANCE-400 and AC-300 spectrometers, respectively. When necessary, the structures of the novel compounds were ensured and the signals unambiguously assigned by 2D NMR techniques: $^1H-^1H$ COSY, $^1H-^1H$ NOESY, $^{13}C-^1H$ HMQC, and $^{13}C-^1H$ HMBC. These experiments were performed using standard Bruker microprograms. Column chromatographies were carried out with silica gel 20−45 μm. Flash column chromatographies were conducted using silica gel 60 Merck (35−70 μm) with an overpressure of 300 mbars. Microanalyses were in agreement with calculated values ±0.4%.

Cell Culture and Cytotoxicity. Cell Culture and Cytotoxicity. L1210 and KB-3-1 cells were cultivated in RPMI 1640 or DMEM medium, respectively (Gibco) supplemented with 10% fetal calf serum, 2 mM L-glutamine, 100 units/mL penicillin, 100 μg/mL streptomycin, and 10 mM HEPES buffer (pH 7.4). Cytotoxicity was measured by the microculture tetrazolium assay (MTA) as described.[21] Cells were exposed to graded concentrations of drug (nine serial dilutions in triplicate) for four doubling times (48 h for L1210 cells and 96 h for KB-3-1 cells). Results are expressed as IC_{50}, the concentration that reduced by 50% the optical density of treated cells with respect to the optical density of untreated controls.

For the cell cycle analysis, L1210 cells (5×10^5 cells/mL) were incubated for 21 h with various concentrations of drugs. Cells were then fixed by 70% ethanol (v/v), washed, and incubated in PBS containing 100 μg/mL RNAse and 50 μg/mL propidium iodide for 30 min at 20 °C. For each sample, 10 000 cells were analyzed on an XLMCL flow cytometer (Beckman Coulter, France). Results are expressed as the percentage of cells in the S phase of the cell cycle.

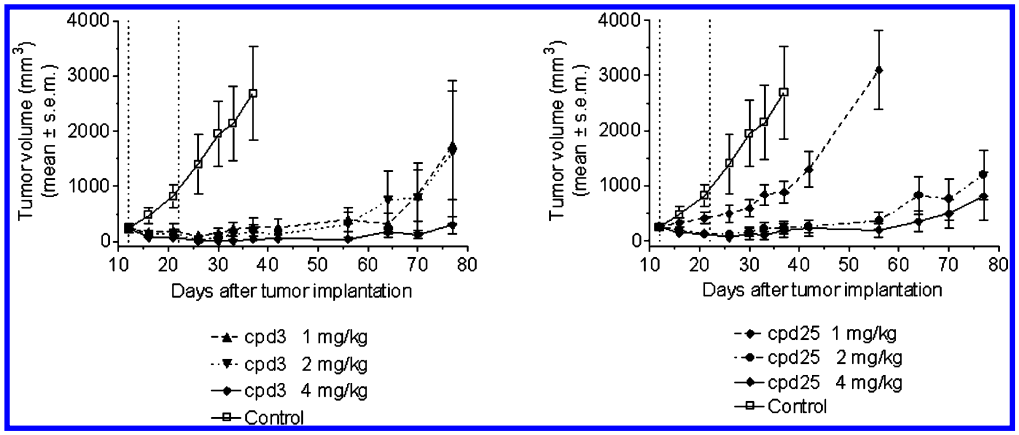


Figure 3. In vivo evaluation of compound **25** in comparison with compound **3**, on an established C38 colon adenocarcima (sc implantation) in mice.

Antitumor Activity. The antitumor activity of the compounds **3** and **25** was evaluated on the murine colon 38 adenocarcinoma implanted in B6D2F1 (C57B1/6 x DBA2) mice. The colon adenocarcinoma C38 (NCI, Frederick) was introduced by sc implantation of a tumor fragment into the dorsal flank. The compounds were solubilized in a preparation of cremophor ELP/ethanol (10% each in physiological saline) and administered by iv injection 12 and 22 days after the tumor graft. Compounds were administered at their maximal tolerated dose (MTD) of 3 mg/kg, which was the highest nontoxic dose, and at one-third of the MTD, 1 mg/kg. A dose is considered as toxic when the weight loss is higher than 20% or when it induces toxic deaths. Tumors were measured twice a week and tumor volumes (V_t) were calculated using the following formula: length (mm) × width^2 (mm^2)/2. At the end of the experiment, on day 80, mice were palpated and the number of tumor-free mice was recorded.

DNA Restriction Fragments. The 117-bp DNA fragment was obtained from the pBS plasmid digestion using *Eco* RI and *Pvu* II restriction enzymes in their respective digestion buffers and was then labeled at the *Eco* RI site using α-[^{32}P]dATP (Amersham) and AMV reverse transcriptase (Ozyme). The radiolabeled DNA was then purified by electrophoresis on a nondenaturing 10% (w/v) polyacrylamide gel with the desired 3′-end-labeled product being cut out of the gel and eluted overnight in 500 mM ammonium acetate, 10 mM magnesium acetate.

Gel Shift Studies. A typical cross-linking reaction consisted of incubating 50 μM of the drug with the radiolabeled DNA in 1 mM Na cacodylate, pH 7.0 (Tris buffer must be avoided due to the presence of reactive amine functions) and incubated in the dark at room temperature during the period specified in the legend. After the desired incubation time, 5 μL of a 50% glycerol containing tracking dyes solution was added to each DNA sample, which were then resolved by electrophoresis under nondenaturing conditions in 6% polyacrylamide gels for about 5 h at 300 V at room temperature in TBE buffer (89 mM boric acid, 2.5 mM Na_2EDTA, pH 8.3). Gels were transferred to Whatman 3MM paper, dried under vacuum at 80 °C, and then analyzed on a phosphorimager (Molecular Dynamics 445SI).

2-Methoxy-1-naphthyl (2-Acetamido-4,6-dimethoxy)phenyl Ketone (8). Thionyl chloride (60 mL, 405 mmol) was added dropwise to 2-methoxynaphthalene-1-carboxylic acid (**7**) (30.3 g, 150 mmol). The mixture was heated at 60 °C for 3 h, and the excess of thionyl chloride was evaporated under reduced pressure. The acyl chloride **6** obtained was immediately dissolved in dry CH_2Cl_2 (100 mL) and added to an iced-cooled suspension of 3,5-dimethoxyacetanilide (**5**) (25.4 g, 120 mmol) and anhydrous $AlCl_3$ (25 g, 186.6 mmol) in dry CH_2Cl_2 (100 mL). The mixture was stirred under argon at 0 °C for 3 h and then at room temperature for 12 h. The cooled reaction mixture was poured onto ice-cooled 1 N aqueous HCl (300 mL) and extracted with CH_2Cl_2 (5 × 250 mL). The combined organic layers were washed with 1 M $NaHCO_3$ solution (3 × 100 mL) and water (5 × 100 mL), dried over $NaSO_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography (solvent CH_2Cl_2 and then CH_2Cl_2/MeOH 99.5:0.5 to 95:5) gave **8** (25.1 g, 55%) as white crystals: mp 150 °C (crystallized from Me_2CO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H, NHCOCH_3), 3.02 (s, 3H, C_6-OCH_3), 3.81 (s, 3H, C_2-OCH_3), 3.88 (s, 3H, C_4-OCH_3), 5.99 (d, J = 2 Hz, 1H, H-5′), 7.27 (d, J = 9 Hz, 1H, H-8), 7.32 (td, J = 8, 1 Hz, 1H, H-7), 7.36 (td, J = 8, 1 Hz, 1H, H-6), 7.53 (dd, J = 8, 1 Hz, 1H, H-5), 7.79 (dd, J = 8, 1 Hz, 1H, H-8), 7.83 (d, J = 9 Hz, 1H, H-4), 8.17 (d, J = 2 Hz, 1H, H-3′), 12.27 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0 (NHCO*C*H$_3$), 55.7 (C_5-O*C*H$_3$ + C_3-O*C*H$_3$), 57.0 (C_2-O*C*H$_3$), 94.6 (C-5′), 96.9 (C-3′), 109.8 (C-1′), 113.7 (C-3), 123.8 (C-7 + C-5), 126.9 (C-6), 128.0 (C-8), 128.9 (C-4a + C-1), 129.8 (C-4), 130.8 (C-8a), 144.7 (C-2′), 152.8 (C-2), 163.6 (C-4′), 165.9 (C-6′), 170.1 (NH*C*OCH$_3$), 198.3 (CO); DCI-MS m/z 380 [MH]$^+$; IR (KBr) ν 3196, 3138, 3006, 2944, 2839, 1693, 1612, 1507, 1448, 1297, 1200, 1107, 889, 823, 757 cm^{-1}; UV λ (MeOH) (log ϵ) 230 (4.90), 250 (sh) (4.48), 306 nm (4.24). Anal. ($C_{22}H_{21}NO_5$) C, H, N.

9,11-Dimethoxybenzo[*a*]acridin-12(7*H*)-one (9). Sodium hydride (4.95 g of 80% oil dispersion, 165 mmol) was added to an ice-cooled solution of **8** (12.50 g, 33 mmol) in dry *N*,*N*-dimethylformamide (150 mL). The mixture was stirred under nitrogen for 30 min at 0 °C and then for 15 h at room temperature and poured onto ice water (1 L). The precipitate was filtered, washed with water (4 × 200 mL), and dried in a vacuum over P_2O_5 to afford **9** (9.6 g, 95%) as a white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 6H, 2 × OCH_3), 6.34 (d, J = 2 Hz, 1H, H-10), 6.50 (d, J = 2 Hz, 1H, H-8), 7.48 (td, J = 8, 1 Hz, 1H, H-3), 7.51 (d, J = 9 Hz, 1H, H-6), 7,62 (td, J = 8, 1 Hz, 1H, H-2), 7.90 (dd, J = 8, 1 Hz, 1H, H-4), 8.08 (d, J = 9 Hz, 1H, H-5), 10.06 (dd, J = 8, 1 Hz, 1H, H-1), 11.68 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.6 (OCH_3), 56.8 (OCH_3), 91.4 (C-8), 94.7 (C-10), 95.4 (C-11a), 110.0 (C-12a), 118.6 (C-6), 125.5 (C-3), 126.7 (C-1), 129.2 (C-2), 129.4 (C-4), 129.9 (C-4a), 132.6 (C-12b), 135.2 (C-5), 141.7 (C-7a), 144.0 (C-6a), 162.8 (C-9), 163.6 (C-11), 178.3 (C-12); DCI-MS m/z 306 [MH]$^+$; IR (KBr) ν 3421, 3283, 2994, 2955, 1639, 1584, 1452, 1410, 1161, 1130, 823, 749 cm^{-1}; UV λ (MeOH) (log ϵ) 233 (4.07), 288 (4.67), 368 (3.69), 386 nm (3.66). Anal. ($C_{19}H_{15}NO_3$) C, H, N.

9,11-Dihydroxybenzo[*a*]acridin-12(7*H*)-one (10) and 11-Hydroxy-9-methoxybenzo[*a*]acridin-12(7*H*)-one (11). To a solution of **9** (2.5 g, 8.2 mmol) in acetic acid (90 mL) was added 48% hydrogen bromide aqueous solution (90 mL). The reaction mixture was stirred and refluxed for 4 days. The cooled mixture was poured onto ice water (500 mL). The brown precipitate was filtered, washed with water (4 × 100 mL), and dried in a vacuum over P_2O_5. Column chromatography on silica gel (solvent, CH_2Cl_2 and then CH_2Cl_2/MeOH, 99:1 to 90:10) gave **10** (2.14 g, 94%) as yellow sheets and **11** (0.071 g, 3%) as a yellow amorphous solid.

Compound **10**: mp 312 °C (crystallized from acetone/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.05 (s, 1H, H-10), 6.39 (s, 1H, H-8), 7.53 (td, J = 8, 1 Hz, 1H, H-3), 7.57 (d, J = 9

Hz, 1H, H-6), 7.70 (td, $J = 8$, 1 Hz, 1H, H-2), 7.96 (dd, $J = 8$, 1 Hz, 1H, H-4), 8.16 (d, $J = 9$ Hz, 1H, H-5), 10.02 (dd, $J = 8$, 1 Hz, 1H, H-1), 10.47 (s, 1H, C_9-O*H*), 12.21 (s, 1H, NH), 15.00 (s, 1H, C_{11}-O*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 91.2 (C-8), 97.2 (C-10), 106.0 (C-11a), 110.8 (C-12a), 118.3 (C-6), 125.5 (C-3), 126.4 (C-1), 129.3 (C-2 + C-4), 129.4 (C-4a), 131.6 (C-12b), 136.1 (C-5), 142.0 (C-7a), 142.7 (C-6a), 163.9 (C-9), 164.2 (C-11), 182.5 (CO); DCI-MS *m*/*z* 278 $[MH]^+$; IR (KBr) ν 3344, 3048, 1639, 1584, 1506, 1460, 1421, 1270, 1208, 827 cm^{-1}; UV λ (MeOH) (log ϵ) 238 (5.22), 287 (5.54), 381 nm (5.44). Anal. ($C_{17}H_{11}NO_3$) C, H, N.

Compound **11**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.86 (s, 3H, C_9-OC*H*$_3$), 6.23 (d, $J = 2$, 1H, H-10), 6.47 (d, $J = 2$, 1H, H-8), 7.56 (td, $J = 8$, 1 Hz, 1H, H-3), 7.58 (d, $J = 9$ Hz, 1H, H-6), 7.73 (td, $J = 8$, 1 Hz, 1H, H-2), 7.99 (dd, $J = 8$, 1 Hz, 1H, H-4), 8.20 (d, $J = 9$ Hz, 1H, H-5), 10.02 (dd, $J = 8$, 1 Hz, 1H, H-1), 12.39 (s, 1H, NH), 14.98 (s, 1H, C_{11}-O*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 56.4 (OCH_3), 89.4 (C-8), 95.2 (C-10), 104.2 (C-11a), 114.4 (C-12a), 118.6 (C-6), 126.7 (C-1), 127.0 (C-1), 129.8 (C-2), 130.0 (C-4), 131.0 (C-4a), 131.7 (C-12b), 137.1 (C-5), 154.2 (C-7a), 157.1 (C-6a), 158.4 (C-9), 165.3 (C-11), 181.0 (CO); DCI-MS *m*/*z* 292 $[MH]^+$; IR (KBr) ν 3382, 3274, 2998, 2936, 1643, 1577, 1511, 1411, 1239, 1153, 823 cm^{-1}; UV λ (MeOH) (log ϵ) 213 (3.56), 251 (3.95), 285 (4.40), 299 (sh), 324 (sh), 378 nm (3.81). Anal. ($C_{18}H_{13}NO_3$) C, H, N.

Reaction of 10 with 3-Chloro-1-methylbut-1-yne (12). A solution of **10** (3 g, 10.8 mmol) in dry *N*,*N*-dimethylformamide (100 mL) was stirred and heated to 65 °C for 15 min, under nitrogen, in the presence of anhydrous potassium carbonate (4.47 g, 32.4 mmol). Then, dry potassium iodide (5.38 g, 32.4 mmol) and excess 3-chloro-3-methylbut-1-yne (6.64 g, 64.8 mmol) were added, and the mixture was stirred and heated at 65 °C for 24 h. After addition of cold water (200 mL), the reaction mixture was extracted with CH_2Cl_2 (4 × 250 mL). The combined organic layers were washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography (solvent, cyclohexane and then cyclohexane/acetone, 98:2 to 90:10) afforded successively **16** (0.4 g, 9%); an inseparable mixture, which was further methylated to **17** and **18** (0.2 g); **13** (1.5 g, 40%), **15** (0.07 g, 2%), and **14** (0.15 g, 3%) as yellow solid products.

11-Hydroxy-9-(1,1-dimethylpropyn-1-oxy)benzo[*a*]acridin-12-(7*H*)-one (13): yellow sheets; mp 212 °C (crystallized from CH_2Cl_2/acetone, 1:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.72 (s, 6H, 2 × CH_3), 3.89 (s, 1H, H-3′), 6.34 (d, $J = 2$ Hz, 1H, H-10), 6.92 (d, $J = 2$ Hz, 1H, H-8), 7.58 (td, $J = 8$, 1 Hz, 1H, H-3), 7.61 (d, $J = 9$ Hz, 1H, H-6), 7.73 (td, $J = 8$, 1 Hz, 1H, H-2), 8.00 (dd, $J = 8$, 1 Hz, 1H, H-4), 8.21 (d, $J = 9$ Hz, 1H, H-5), 10.02 (dd, $J = 8$, 1 Hz, 1H, H-1), 12.46 (s, 1H, NH), 14.90 (s, 1H, C_{11}-O*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 30.4 (2 × CH_3), 73.2 (C-1′), 78.9 (C-3′), 86.1 (C-2′), 95,2 (C-8), 100.3 (C-10), 107.6 (C-11a), 111.6 (C-12a), 118.9 (C-6), 126.2 (C-3), 127.0 (C-1), 129.8 (C-4), 129.9 (C-2), 130.0 (C-4a), 131.9 (C-12b), 137.0 (C-5), 141.6 (C-7a), 143.4 (C-6a), 161.6 (C-9), 164.0 (C-11), 183.2 (CO); DCI-MS *m*/*z* 344 $[MH]^+$; IR (KBr) ν 3340, 3048, 2971, 2924, 1639, 1588, 1550, 1499, 1359, 1173, 1142, 1126, 823, 746 cm^{-1}; UV λ (MeOH) (log ϵ) 221 (sh), 242 (3.42), 296 (3.82), 332 (sh), 399 nm (2.70). Anal. ($C_{22}H_{17}NO_3$) C, H, N.

11-Hydroxy-9-(6-hydroxy-1,1,6-trimethylhepta-2,4-diynyloxy)-12*H*-benzo[*a*]acridin-12(7*H*)-one (14): yellow amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 6H, $C_{6'}$-(CH_3)$_2$), 1.51 (s, 6H, $C_{1'}$-(CH_3)$_2$), 5.47 (s, 1H, $C_{6'}$-O*H*), 6.16 (s, 1H, H-10), 7.52 (s, 1H, H-8), 7.59 (td, $J = 8$, 1 Hz, 1H, H-3), 7.73 (td, $J = 8$, 1 Hz, 1H, H-2), 7.95 (d, $J = 9$ Hz, 1H, H-6), 7.99 (dd, $J = 8$, 1 Hz, 1H, H-4), 8.23 (d, $J = 9$ Hz, 1H, H-5), 10.25 (dd, $J = 8$, 1 Hz, 1H, H-1), 11.62 (br.s, 1H, NH), 15.58 (s, 1H, C_{11}-O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.3 [$C_{1'}$-(CH_3)$_2$], 32.7 [$C_{6'}$-(CH_3)$_2$], 64.4 (C-5′), 78.8 (C-1′), 78.9 (C-2′ + C-3′), 79.2 (C-4′), 98.2 (C-10), 99.3 (C-8), 99.9 (C-6′), 106.9 (C-11a), 111.4 (C-12a), 118.8 (C-6), 126.0 (C-3), 126.6 (C-1), 129.3 (C-4), 129.5 (C-2), 129.8 (C-4), 131.1 (C-12b), 137.0 (C-5), 143.7 (C-6a + C-7a), 158.7 (C-9), 165.8 (C-11), 183.4 (CO); ESI-MS *m*/*z* 426 $[MH]^+$, 448 $[MNa]^+$, 464 $[MK]^+$; IR (NaCl) ν 3428, 3204, 3078, 3055, 2921, 2849, 1630, 1600, 1583, 1492, 1361, 1155, 1024, 752 cm^{-1}; UV λ (MeOH) (log ϵ) 210 (4.41), 247 (4.15), 293 (4.45), 308 (4.44), 400 nm (3.52). Anal. ($C_{27}H_{23}NO_4$) C, H, N.

10,12-Dihydroxy-9,9-dimethyl-8-methylidene-8,9-dihydro-15*H*-benzo[*a*]pyrrolo[1,2,3-*fg*]acridin-13-one (15): yellow amorphous solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.56 (s, 6H, C_9-(CH_3)$_2$), 5.17 (d, $J = 3$ Hz, 1H, H-1′a), 5.76 (d, $J = 3$ Hz, 1H, H-1′b), 6.23 (s, 1H, H-11), 7.63 (td, $J = 8$, 1 Hz, 1H, H-3), 7.73 (td, $J = 8$, 1 Hz, 1H, H-2), 7.87 (dd, $J = 8$, 1 Hz, 1H, H-4), 8.31 (d, $J = 9$ Hz, 1H, H-5), 8.40 (d, $J = 9$ Hz, 1H, H-6), 10.16 (dd, $J = 8$, 1 Hz, 1H, H-1), 10.72 (s, 1H, C_{10}-O*H*), 12.94 (s, 1H, C_{12}-O*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 27.4 [C_9-(CH_3)$_2$], 46.5 (C-9), 92.6 (C-1′), 98.4 (C-11), 104.9 (C-12a), 110.3 (C-9a), 113.7 (C-13a), 115.9 (C-6), 126.1 (C-3), 127.4 (C-1), 128.6 (C-4a), 129.7 (C-4), 129.8 (C-2), 132.9 (C-13b), 137.0 (C-5), 141.1 (C-9b), 143.6 (C-6a), 158.9 (C-8), 160.0 (C-10), 161.8 (C-12), 182.9 (CO); ESI-MS *m*/*z* 344 $[MH]^+$, 366 $[MNa]^+$; IR (KBr) ν 3432, 2976, 2930, 2851, 1650, 1600, 1598, 1558, 1523, 1453, 1357, 1279, 1137, 1086, 1061, 825, 757 cm^{-1}; UV λ (MeOH) (log ϵ) 203 (4.34), 243 (4.31), 299 (4.50), 325 (4.21), 389 nm (3.77). Anal. ($C_{22}H_{17}NO_3$) C, H, N.

12-Hydroxy-9,9-dimethyl-8-methylidene-8,9-dihydro-10-(1,1-dimethylpropyn-1-oxy)-15*H*-benzo[*a*]pyrrolo[1,2,3-*fg*]acridin-15-one (16): yellow amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 6H, C_9-(CH_3)$_2$), 1.81 (s, 6H, $C_{1''}$-(CH_3)$_2$), 2.74 (s, 1H, H-3″), 4.99 (d, $J = 3$ Hz, 1H, H-1′a), 5.60 (d, $J = 3$ Hz, 1H, H-1′b), 7.14 (s, 1H, H-11), 7.58 (td, $J = 8$, 1 Hz, 1H, H-3), 7.74 (td, $J = 8$, 1 Hz, 1H, H-2), 7.87 (dd, $J = 8$, 1 Hz, 1H, H-4), 8.01 (d, $J = 9$ Hz, 1H, H-5), 8.25 (d, $J = 9$ Hz, 1H, H-6), 10.26 (dd, $J = 8$, 1 Hz, 1H, H-1), 13.05 (s, 1H, C_{12}-O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7 [C_9-(CH_3)$_2$], 29.8 [$C_{1''}$-(CH_3)$_2$], 46.9 (C-9), 72.3 (C-1″), 75.2 (C-3″), 85.2 (C-2″), 92.2 (C-1′), 99.1 (C-11), 104.6 (C-12a), 112.8 (C-9a), 115.4 (C-13a), 115.6 (C-6), 125.7 (C-3), 126.9 (C-1), 128.3 (C-4), 129.4 (C-2), 132.5 (C-13b + C-4a), 135.4 (C-5), 140.8 (C-9b), 142.5 (C-6a), 156.4 (C-10), 158.6 (C-8), 160.8 (C-12), 182.8 (C-13); ESI-MS *m*/*z* 410 $[MH]^+$, 432 $[MNa]^+$, 448 $[MK]^+$; IR (KBr) ν 3244, 2975, 2926, 2861, 1670, 1623, 1608, 1558, 1512, 1343, 1297, 1179, 1136, 1086, 1061, 825, 664 cm^{-1}; UV λ (MeOH) (log ϵ) 246 (4.32), 299 (4.53), 417 nm (3.61). Anal. ($C_{27}H_{23}NO_3$) C, H, N.

6-Hydroxy-3,3-dimethyl-3,14-dihydro-7*H*-benzo[*a*]pyrano-[3,2-*h*]acridin-7-one (19). A solution of **13** (3 g, 8.75 mmol) in dry *N*,*N*-dimethylformamide (100 mL) was heated at 130 °C for 3 h. The solvent was removed by evaporation under reduced pressure. Flash chromatography (solvent, cyclohexane and then cyclohexane/acetone, 98:2 to 90:10) gave **19** (2.85 g, 95%) as a yellow amorphous solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.47 (s, 6H, 2 × CH_3), 5.74 (d, $J = 10$ Hz, 1H, H-2), 6.12 (s, 1H, H-5), 7.17 (d, $J = 10$ Hz, 1H, H-1), 7.56 (td, $J = 8$, 1 Hz, 1H, H-10), 7.71 (td, $J = 8$, 1 Hz, 1H, H-9), 7.93 (d, $J = 9$ Hz, 1H, H-13), 7.97 (dd, $J = 8$, 1 Hz, 1H, H-11), 8.19 (d, $J = 9$ Hz, 1H, H-12), 10.19 (dd, $J = 8$, 1 Hz, 1H, H-8), 11.46 (s, 1H, NH), 15.39 (s, 1H, C_6-O*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.0 (2 × CH_3), 77.6 (C-3), 97.8 (C-5), 98.6 (C-14b), 106.7 (C-6a), 111.2 (C-7a), 116.7 (C-1), 118.7 (C-13), 125.7 (C-10), 126.4 (C-2), 126.6 (C-8), 129.2 (C-11), 129.4 (C-9), 129.7 (C-11a), 131.2 (C-8a), 136.2 (C-12), 136.5 (C-14a), 143.1 (C-13a), 158.8 (C-4a), 164.4 (C-6), 183.0 (C-7); DCI-MS *m*/*z* 344 $[MH]^+$; IR (KBr) ν 3340, 3048, 2971, 2924, 1639, 1588, 1550, 1499, 1359, 1173, 1142, 1126, 823, 746 cm^{-1}; UV λ (MeOH) (log ϵ) 245 (4.38), 295 (4.86), 331 (4.10), 398 nm (3.68). Anal. ($C_{22}H_{17}NO_3$) C, H, N.

6-Hydroxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*a*]pyrano-[3,2-*h*]acridin-7-one (20). Dry sodium carbonate (1.324 g, 9.6 mmol) was added to a solution of **19** (0.412 g, 1.2 mmol) in dry acetone (50 mL) and the mixture was stirred under argon at 0 °C for 30 min. Methyl iodide (0.852 g, 6 mmol) was added and the reaction mixture was refluxed for 2 h. Methanol (40 mL) and water (50 mL) were added to the cooled reaction mixture, and the solvents were removed under reduced pressure. After extraction with CH_2-

Cl_2 (4 × 50 mL), the combined organic layers were washed with 1 M NaOH aqueous solution (3 × 30 mL) and water (5 × 50 mL), dried over $NaSO_4$, and evaporated under reduced pressure. Silica gel column chromatography (solvent, cyclohexane and then cyclohexane/acetone, 99.5:0.5 to 95.5) gave **20** (0.412 g, 96%) as a yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 6H, 2 × CH_3), 4.03 (s, 3H, NCH_3), 5.53 (d, J = 10 Hz, 1H, H-2), 6.35 (s, 1H, H-5), 6.59 (d, J = 10 Hz, 1H, H-1), 7.56 (td, J = 8, 1 Hz, 1H, H-10), 7.60 (d, J = 9 Hz, 1H, H-13), 7.76 (td, J = 8, 1 Hz, 1H, H-9), 7.88 (dd, J = 8, 1 Hz, 1H, H-11), 8.11 (d, J = 9 Hz, 1H, H-12), 10.09 (dd, J = 8, 1 Hz, 1H, H-8), 15.37 (s, 1H, C_6-O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.9 (2 × CH_3), 44.7 (NCH_3), 76.2 (C-3), 90.5 (C-5), 100.7 (C-14b), 109.1 (C-6a), 114.6 (C-7a), 115.9 (C-13), 121.3 (C-1), 123.0 (C-2), 125.5 (C-10), 126.9 (C-8), 128.2 (C-11), 128.9 (C-11a), 129.2 (C-9), 131.1 (C-8a), 135.7 (C-12), 145.9 (C-13a + C-14a), 160.4 (C-4a), 164.8 (C-6), 182.7 (C-7); DCI-MS *m*/*z* 358 $[MH]^+$; IR (KBr) ν 3433, 3052, 2971, 2920, 1627, 1580, 1542, 1456, 1344, 1262, 1172, 1138, 819, 753 cm^{-1}; UV λ (MeOH) (log ϵ) 247 (4.23), 280 (sh), 303 (4.69), 411 nm (3.62). Anal. ($C_{23}H_{19}NO_3$) C, H, N.

Methylation of 19 with Dimethyl Sulfate. Sodium hydride (1.05 g of 80% oil dispersion, 35 mmol) was added to an iced-cooled solution of **19** (2 g, 5.83 mmol) in dry *N*,*N*-dimethylformamide (100 mL) and the mixture was stirred under argon for 30 min at 0 °C. After addition of dimethyl sulfate (3.3 mL, 35 mmol), the reaction mixture was stirred at room temperature for 4 h, poured carefully onto ice water, and extracted with ethyl acetate (5 × 100 mL). The combined organic layers were washed with 1 M NaOH aqueous solution (3 × 150 mL) and water (3 × 250 mL), dried over $NaSO_4$, and evaporated under reduced pressure. Flash chromatography (solvent, CH_2Cl_2 and then CH_2Cl_2/MeOH, 99.5:0.5 to 90:10) gave successively **21** as an amorphous orange solid (216.3 mg, 10%) and **4** (1.41 g, 65%) and **22** (416 mg, 20%) as yellow amorphous solids.

6-Methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*a*]pyrano-[3,2-*h*]acridin-7-one (4): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 6H, 2 × CH_3), 3.92 (s, 3H, NCH_3), 4.02 (s, 3H, OCH_3), 5.54 (d, J = 10 Hz, 1H, H-2), 6.39 (s, 1H, H-5), 6.60 (d, J = 10 Hz, 1H, H-1), 7.50 (td, J = 8, 1 Hz, 1H, H-10), 7.53 (d, J = 9 Hz, 1H, H-13), 7.66 (td, J = 8, 1 Hz, 1H, H-9), 7.82 (dd, J = 8, 1 Hz, 1H, H-11), 8.00 (d, J = 9 Hz, 1H, H-12), 9.90 (dd, J = 8, 1 Hz, 1H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0 (2 × CH_3), 45.1 (NCH_3), 56.5 (OCH_3), 76.4 (C-3), 95.2 (C-5), 103.0 (C-14b), 113.5 (C-6a), 116.2 (C-13), 119.1 (C-7a), 121.6 (C-1), 123.6 (C-2), 125.3 (C-10), 127.0 (C-8), 128.0 (C-11), 128.7 (C-9), 129.4 (C-11a), 131.2 (C-8a), 134.2 (C-12), 144.9 (C-13a + C-14a), 158.4 (C-4a), 162.2 (C-6), 179.4 (C-7); DCI-MS *m*/*z* 372 $[MH]^+$; IR (KBr) ν 3433, 3048, 2967, 2920, 2850, 1623, 1592, 1511, 1460, 1340, 1204, 1134, 819, 753 cm^{-1}; UV λ (MeOH) (log ϵ) 245 (4.38), 291 (sh), 298 (4.67), 390 nm (3.79). Anal. ($C_{24}H_{21}NO_3$) C, H, N.

6,7-Dimethoxy-3,3-dimethyl-3*H*-benzo[*a*]pyrano[3,2-*h*]acridin (21): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.49 (s, 6H, 2 × CH_3), 3.89 (s, 3H, C_7-OCH_3), 4.04 (s, 3H, C_6-OCH_3), 5.68 (d, J = 10 Hz, 1H, H-2), 6.69 (s, 1H, H-5), 7.45 (d, J = 10 Hz, 1H, H-1), 7.66 (td, J = 8, 1 Hz, 1H, H-10), 7.71 (td, J = 8, 1 Hz, 1H, H-9), 7.79 (d, J = 9 Hz, 1H, H-13), 7.98 (dd, J = 8, 1 Hz, 1H, H-11), 8.03 (d, J = 9 Hz, 1H, H-12), 9.45 (dd, J = 8, 1 Hz, 1H, H-8); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.4 (2 × CH_3), 57.1 (C_6-OCH_3), 62.2 (C_7-OCH_3), 78.2 (C-3), 99.0 (C-5), 107.5 (C-14b), 110.6 (C-6a), 115.3 (C-7a), 118.6 (C-1), 126.2 (C-2), 127.4 (C-10), 128.0 (C-8), 128.8 (C-9), 128.9 (C-13), 129.6 (C-11), 131.8 (C-8a + C-11a), 133.9 (C-12), 147.0 (C-14a), 151.5 (C-13a), 155.4 (C-4a), 157.4 (C-4a), 165.4 (C-6); DCI-MS *m*/z 372 $[MH]^+$; IR (NaCl) ν 2974, 2928, 2849, 1612, 1592, 1557, 1469, 1435, 1350, 1307, 1197, 1130, 1030, 856, 759 cm^{-1}; UV λ (MeOH) (log ϵ) 205 (4.40), 224 (4.48), 262 (4.37), 292 (4.58), 360 nm (3.77). Anal. ($C_{24}H_{21}NO_3$) C, H, N.

6-Methoxy-3,3-dimethyl-3,14-dihydro-7*H*-benzo[*a*]pyrano-[3,2-*h*]acridin-7-one (22): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 6H, 2 × CH_3), 4.03 (s, 3H, OCH_3), 5.75 (d, J = 10 Hz, 1H, H-2), 6.33 (s, 1H, H-5), 7.20 (d, J = 10 Hz, 1H, H-1), 7.49 (td, J = 8, 1 Hz, 1H, H-10), 7.63 (td, J = 8, 1 Hz, 1H, H-9), 7.88 (d, J = 9 Hz, 1H, H-13), 7.91 (dd, J = 8, 1 Hz, 1H, H-11), 8.08 (d, J = 9 Hz, 1H, H-12), 9.99 (dd, J = 8, 1 Hz, 1H, H-8), 10.75 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0 (2 × CH_3), 56.4 (OCH_3), 77.3 (C-3), 94.9 (C-5), 100.1 (C-14b), 109.6 (C-6a), 114.2 (C-7a), 116.9 (C-1), 118.6 (C-13), 125.1 (C-10), 126.3 (C-8), 126.8 (C-2), 128.7 (C-9), 128.9 (C-11), 129.6 (C-11a), 131.7 (C-8a), 134.5 (C-12), 138.1 (C-13a), 141.4 (C-14a), 156.9 (C-4a), 162.3 (C-6), 178.0 (C-7); ESI-MS m/z 358 $[MH]^+$, 380 $[MNa]^+$; IR (KBr) ν 3429, 2962, 2934, 1664, 1592, 1564, 1434, 1364, 1136, 1059, 820, 754 cm^{-1}; UV λ (MeOH) (log ϵ) 242 (4.39), 292 (4.82), 384 nm (3.77). Anal. ($C_{23}H_{19}NO_3$) C, H, N.

9,9-Dimethyl-12-methoxy-8-methylidene-8,9-dihydro-10-(1,1-dimethylpropyn-1-oxy)benzo[*a*]pyrrolo[1,2,3-*fg*]acridin-13-one (17) and 4-Methoxy-3,3,12-trimethyl-2-methylidene-2,3-dihydrobenzo[*a*]furo[3,2-*i*]acridin-5(13*H*)-one (18). Compounds **17** and **18** were synthesized from the unresolved mixture obtained in the course of the synthesis of **13**, according to the procedure described for the preparation of **4**. To a solution of the mixture (0.1 g) in dry *N*,*N*-dimethylformamide (15 mL) were added sodium hydride (50 mg of 80% oil dispersion, 1.65 mmol) and dimethyl sulfate (0.16 mL, 1.65 mmol). After the usual workup, the crude reaction mixture was purified by silica gel column chromatography (solvent, CH_2Cl_2 and then CH_2Cl_2/MeOH, 99.9:0.1 to 98:2) to give **17** (0.05 g) and **18** (0.025 g) as yellow amorphous products. Compound **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 6H, C_9-(CH_3)$_2$), 1.81 (s, 6H, $C_{1''}$-(CH_3)$_2$), 2.78 (s, 1H, H-3″), 4.04 (OCH_3), 4.92 (d, J = 3 Hz, 1H, H-1′a), 5.50 (d, J = 3 Hz, 1H, H-1′b), 7.27 (s, 1H, H-11), 7.54 (td, J = 8, 1 Hz, 1H, H-3), 7.71 (td, J = 8, 1 Hz, 1H, H-2), 7.85 (dd, J = 8, 1 Hz, 1H, H-4), 8.03 (d, J = 9 Hz, 1H, H-5), 8.25 (d, J = 9 Hz, 1H, H-6), 10.38 (dd, J = 8, 1 Hz, 1H, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.5 [C_9-(CH_3)$_2$], 29.9 [$C_{1''}$-(CH_3)$_2$], 45.2 (C-9), 56.5 (OCH_3), 72.2 (C-1″), 74.7 (C-3″), 86.1 (C-2″), 90.9 (C-1′), 96.4 (C-11), 107.6 (C-12a), 115.3 (C-9a), 115.6 (C-6), 118.2 (C-13a), 125.4 (C-3), 127.4 (C-1), 128.1 (C-4), 129.0 (C-2), 129.6 (C-4a), 132.6 (C-13b), 134.2 (C-5), 139.4 (C-9b), 144.6 (C-6a), 154.7 (C-10), 157.9 (C-8), 159.8 (C-12), 178.9 (C-13); ESI-MS *m*/*z* 424 $[MH]^+$, 446 $[MNa]^+$; IR (KBr) ν 3054, 2980, 2956, 2863, 1655, 1621, 1600, 1554, 1507, 1299, 1257, 1180, 1116, 1086, 1065, 825, 723 cm^{-1}; UV λ (MeOH) (log ϵ) 245 (4.51), 294 (4.71), 397 nm (3.86). Anal. ($C_{28}H_{25}NO_3$) C, H, N. Compound **18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (s, 6H, 2 × CH_3), 3.92 (s, 3H, NCH_3), 4.07 (s, 3H, OCH_3), 4.32 (d, J = 3 Hz, 1H, H-1′a), 4.73 (d, J = 3 Hz, 1H, H-1′b), 6.77 (s, 1H, H-14), 7.53 (td, J = 8, 1 Hz, 1H, H-9), 7.59 (d, J = 9 Hz, 1H, H-12), 7.73 (td, J = 8, 1 Hz, 1H, H-8), 7.85 (dd, J = 8, 1 Hz, 1H, H-10), 8.03 (d, J = 9 Hz, 1H, H-11), 10.07 (dd, J = 8, 1 Hz, 1H, H-7); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.3 (2 × CH_3), 36.7 (NCH_3), 44.2 (C-3), 62.8 (OCH_3), 83.3 (C-1′), 90.7 (C-14), 114.9 (C-12 + C-4a), 117.4 (C-5a), 120.3 (C-3a), 125.3 (C-9), 126.6 (C-1), 128.1 (C-10), 129.0 (C-10a), 129.2 (C-8), 131.6 (C-6a), 134.5 (C-11), 142.5 (C-12a), 145.2 (C-13a), 158.0 (C-14a), 160.3 (C-4), 172.3 (C-2), 179.0 (C-5); ESI-MS *m*/*z* 372 $[MH]^+$, 394 $[MNa]^+$; IR (KBr) ν 2957, 2920, 2848, 1694, 1622, 1594, 1520, 1482, 1436, 1206, 1094, 1025, 951, 923 cm^{-1}; UV λ (MeOH) (log ϵ) 203 (4.48), 245 (4.36), 295 (4.57), 342 (3.90), 399 nm (3.70). Anal. ($C_{24}H_{21}NO_3$) C, H, N.

Catalytic Osmium Tetroxide Oxidation of 4. Compound **4** (2.43 g, 6.55 mmol) was added to a solution of osmium tetroxide (2.5% in 2-methyl-2-propanol) (5.5 mL) and *N*-methylmorpholine *N*-oxide dihydrate (0.97 g, 10.32 mmol) in *t*-BuOH/THF/H_2O (10:3:1, v/v/v, 100 mL). The reaction mixture was stirred at room temperature for 4 days. After addition of saturated aqueous $NaHSO_3$, the mixture was stirred for 1 h and then extracted with CH_2Cl_2 (6 × 150 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography (solvent, CH_2Cl_2 then CH_2Cl_2/MeOH, 99.5:0.5 to 90:10) gave successively **24** (0.264 g, 10%) as bright yellow crystals and **23** (1.89 g, 71%) as a white amorphous solid.

(±)-*cis*-1,2-Dihydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (23): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 3.66

(t, $J = 4.5$ Hz, 1H, H-2), 3.83 (s, 3H, OCH_3), 3.94 (s, 3H, NCH_3), 4.63 (d, $J = 9$ Hz, 1H, C_1-O*H*), 5.05 (d, $J = 4.5$ Hz, 1H, C_2-O*H*), 5.09 (dd, $J = 9$, 4.5 Hz, 1H, H-1), 6.26 (s, 1H, H-5), 7.48 (td, $J = 8$, 1 Hz, 1H, H-10), 7.60 (td, $J = 8$, 1 Hz, 1H, H-9), 7.81 (d, $J = 9$ Hz, 1H, H-13), 8.01 (dd, $J = 8$, 1 Hz, 1H, H-11), 8.13 (d, $J = 9$ Hz, 1H, H-12), 9.78 (dd, $J = 8$, 1 Hz, 1H, H-8); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.4 (CH_3), 26.0 (CH_3), 42.9 (NCH_3), 56.9 (OCH_3), 64.7 (C-1), 71.2 (C-2), 78.4 (C-3), 95.9 (C-5), 104.2 (C-14b), 114.8 (C-6a), 118.3 (C-13), 118.5 (C-7a), 125.7 (C-10), 126.5 (C-8), 128.0 (C-11), 129.1 (C-9), 129.6 (C-11a), 131.3 (C-8a), 134.4 (C-12), 145.5 (C-13a), 147.7 (C-14a), 159.0 (C-4a), 161.0 (C-6), 178.6 (C-7); DCI-MS *m*/*z* 406 $[MH]^+$; IR (KBr) ν 3402, 3045, 2971, 2928, 1623, 1592, 1514, 1456, 1382, 1208, 1153, 819 cm^{-1}; UV λ (MeOH) (log ϵ) 249 (4.54), 294 (4.78), 310 (sh), 342 (sh), 378 (3.92), 398 nm (sh). Anal. ($C_{24}H_{23}NO_5$) C, H, N.

2-Hydroxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-1,7-dione (24): mp 150 °C (crystallized in CH_2Cl_2/acetone, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 3.80 (s, 3H, NCH_3), 4.04 (d, $J = 2$ Hz, 1H, C_2-O*H*), 4.11 (s, 3H, OCH_3), 4.39 (d, $J = 2$ Hz, 1H, H-2), 6.34 (s, 1H, H-5), 7.61 (td, $J = 8$, 1 Hz, 1H, H-10), 7.66 (d, $J = 9$ Hz, 1H, H-13), 7.69 (td, $J = 8$, 1 Hz, 1H, H-9), 7.86 (dd, $J = 8$, 1 Hz, 1H, H-11), 8.07 (d, $J = 9$ Hz, 1H, H-12), 9.91 (dd, $J = 8$, 1 Hz, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9 (CH_3), 27.1 (CH_3), 46.0 (NCH_3), 57.0 (OCH_3), 76.4 (C-3), 84.7 (C-2), 95.5 (C-5), 102.1 (C-14b), 113.6 (C-6a), 116.8 (C-13), 119.7 (C-7a), 125.9 (C-10), 127.0 (C-8), 128.1 (C-11), 129.0 (C-9), 129.8 (C-11a), 130.9 (C-8a), 134.7 (C-12), 144.3 (C-13a), 146.6 (C-14a), 166.2 (C-4a), 167.8 (C-6), 178.2 (C-7), 189.1 (C-1); ESI-MS *m*/*z* 404 $[MH]^+$, 426 $[MNa]^+$; IR (NaCl) ν 3434, 3057, 3022, 2974, 2920, 2844, 1669, 1628, 1602, 1580, 1564, 1517, 1406, 1209, 1108, 1070, 1029, 823, 750 cm^{-1}; UV λ (MeOH) (log ϵ) 214 (4.53), 241 (4.34), 296 (4.49), 330 (4.16), 391 nm (3.92). Anal. ($C_{24}H_{21}NO_5$) C, H, N.

General Procedure for the Preparation of (±)-*cis*-1,2-Diacyloxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-ones 25−28. An ice-cooled mixture of the appropriate acid anhydride (**25**, **26**) or acyl chloride (**27**, **28**) (52.5 mmol) and dry pyridine (20 mL) was added to **23** (610 mg, 1.5 mmol) and 4-(dimethylamino)pyridine (0.005 g). After stirring at room temperature for 2 days the mixture was evaporated under reduced pressure ($t < 40$ °C) or poured on cold water (20 mL) to give a precipitate, which was isolated by filtration. The crude product was purified by silica gel column chromatography (solvent, CH_2Cl_2/MeOH) (**26-28**) or by crystallization (**25**).

(±)-*cis*-1,2-Diacetoxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (25): white needles; mp 162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.98 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3-CO), 3.71 (s, 3H, NCH_3), 4.05 (s, 3H, OCH_3), 5.67 (d, $J = 5$ Hz, 1H, H-2), 6.38 (s, 1H, H-5), 6.55 (d, $J = 5$ Hz, 1H, H-1), 7.39 (d, $J = 9$ Hz, 1H, H-13), 7.50 (td, $J = 8$, 1 Hz, 1H, H-10), 7.67 (td, $J = 8$, 1 Hz, 1H, H-9), 7.82 (dd, $J = 8$, 1 Hz, 1H, H-11), 8.01 (d, $J = 9$ Hz, 1H, H-12), 9.78 (dd, $J = 8$, 1 Hz, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8 (*C*H_3CO), 21.0 (*C*H_3CO), 23.6 (CH_3), 24.5 (CH_3), 42.9 (NCH_3), 56.5 (OCH_3), 65.6 (C-1), 69.6 (C-2), 76.3 (C-3), 95.7 (C-5), 97.7 (C-14b), 115.1 (C-6a), 115.9 (C-13), 119.5 (C-7a), 125.4 (C-10), 126.7 (C-8), 128.0 (C-11), 128.8 (C-9), 129.4 (C-11a), 131.0 (C-8a), 134.5 (C-12), 145.3 (C-13a), 147.4 (C-14a), 158.9 (C-4a), 162.0 (C-6), 170.6 (CH_3*C*O), 171.1 (CH_3*C*O), 179.4 (C-7); ESI-MS *m*/*z* 490 $[MH]^+$, 512 $[MNa]^+$; IR (KBr) ν 3048, 2975, 2936, 1740, 1627, 1592, 1514, 1371, 1235, 1157, 1025, 904, 815, 753 cm^{-1}; UV λ (MeOH) (log ϵ) 247 (4.37), 292 (4.58), 311 (sh), 336 (sh), 374 (sh), 391 nm (3.78). Anal. ($C_{28}H_{27}NO_7$) C, H, N.

(±)-*cis*-1,2-Dipropanoyloxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (26): amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (m, 6H, 2 × CH_3), 1.47 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.18 (q, $J = 8$ Hz, 2H, CH_2), 2.31 (m, 2H, CH_2), 3.70 (s, 3H, NCH_3), 4.05 (s, 3H, OCH_3), 5.48 (d, $J = 5$ Hz, 1H, H-2), 6.38 (s, 1H, H-5), 6.58 (d, $J = 5$ Hz, 1H, H-1), 7.37 (d, $J = 9$ Hz, 1H, H-13), 7.50 (td, $J = 8$, 1 Hz, 1H, H-10), 7.67 (td, $J = 8$, 1 Hz, 1H, H-9), 7.82 (dd, $J = 8$, 1 Hz, 1H, H-11), 8.00 (d, $J = 9$ Hz, 1H, H-12), 9.78 (dd, $J = 8$, 1 Hz, 1H, H-8). Anal. ($C_{30}H_{31}NO_7$) C, H, N.

(±)-*cis*-1,2-Diisovaleroyloxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (27): amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88−0.93 (m, 12H, 2 × $(CH_3)_2$), 1.46 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.01−2.06 (m, 4H, 2 × CH, CH_2), 2.17 (d, $J = 7$ Hz, 2H, CH_2), 3.75 (s, 3H, NCH_3), 4.05 (s, 3H, OCH_3), 5.48 (d, $J = 5$ Hz, 1H, H-2), 6.38 (s, 1H, H-5), 6.62 (d, $J = 5$ Hz, 1H, H-1), 7.39 (d, $J = 9$ Hz, 1H, H-13), 7.52 (td, $J = 8$, 1 Hz, 1H, H-10), 7.65 (td, $J = 8$, 1 Hz, 1H, H-9), 7.82 (dd, $J = 8$, 1 Hz, 1H, H-11), 8.00 (d, $J = 9$ Hz, 1H, H-12), 9.79 (dd, $J = 8$, 1 Hz, 1H, H-8). Anal. ($C_{34}H_{39}NO_7$) C, H, N.

(±)-*cis*-1,2-Bis(4-pentenoyloxy)-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (28): Amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 3H, CH_3), 1.56 (CH_3), 2.27 (m, 4H, 2 × $OCOCH_2CH_2CHCH_2$), 2.38 (m, 4H, 2 × $OCOCH_2CH_2CHCH_2$), 3.70 (s, 3H, NCH_3), 4.05 (s, 3H, OCH_3), 4.96 (m, 4H, 2 × $OCOCH_2CH_2CHCH_2$), 5.49 (d, $J = 5$ Hz, 1H, H-2), 5.73 (m, 2H, 2 × $OCOCH_2CH_2CHCH_2$), 6.38 (s, 1H, H-5), 6.60 (d, $J = 5$ Hz, 1H, H-1), 7.39 (d, $J = 9$ Hz, 1H, H-13), 7.50 (td, $J = 8$, 1 Hz, 1H, H-10), 7.67 (td, $J = 8$, 1 Hz, 1H, H-9), 7.82 (dd, $J = 8$, 1 Hz, 1H, H-11), 8.00 (d, $J = 9$ Hz, 1H, H-12), 9.79 (dd, $J = 8$, 1 Hz, 1H, H-8). Anal. ($C_{34}H_{35}NO_7$) C, H, N.

General Procedure for the Preparation of (±)-*cis*-1-Hydroxy-2-acyloxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-ones 29−33. To an iced-cooled solution of **23** (0.05 g, 0.124 mmol) in dry pyridine (5 mL) was added the appropriate acid anhydride (**29**, **30**, **33**) or acyl chloride (**31**, **32**) (0.372 mmol). After stirring at room temperature for 2 days, the reaction mixture was evaporated under reduced pressure ($t < 40$ °C). The crude product was purified by flash chromatography (solvent, CH_2Cl_2, then CH_2Cl_2/MeOH).

(±)-*cis*-1-Hydroxy-2-acetoxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (29): amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.93 (d, $J = 9$ Hz, 1H, C_1-O*H*), 2.01 (s, 3H, CH_3CO), 3.95 (s, 3H, NCH_3), 4.01 (s, 3H, OCH_3), 5.35 (dd, $J = 9$, 5 Hz, 1H, H-1), 5.38 (d, $J = 5$ Hz, 1H, H-2), 6.34 (s, 1H, H-5), 7.49 (td, $J = 8$, 1 Hz, 1H, H-10), 7.52 (d, $J = 9$ Hz, 1H, H-13), 7.65 (td, $J = 8$, 1 Hz, 1H, H-9), 7.82 (dd, $J = 8$, 1 Hz, 1H, H-11), 8.00 (d, $J = 9$ Hz, 1H, H-12), 9.83 (dd, $J = 8$, 1 Hz, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (*C*H_3CO), 22.5 (CH_3), 25.4 (CH_3), 42.2 (NCH_3), 56.4 (OCH_3), 63.8 (C-1), 72.2 (C-2), 76.5 (C-3), 95.1 (C-5), 101.4 (C-14b), 114.8 (C-6a), 116.3 (C-13), 119.2 (C-7a), 125.3 (C-10), 126.8 (C-8), 128.0 (C-11), 128.7 (C-9), 129.3 (C-11a), 130.9 (C-8a), 134.3 (C-12), 145.0 (C-13a), 146.6 (C-14a), 157.9 (C-4a), 161.7 (C-6), 171.0 (C_2O*C*O), 179.4 (C-7); ESI-MS *m*/*z* 448 $[MH]^+$, 470 $[MNa]^+$; IR (KBr) ν 3430, 2975, 2925, 1741, 1662, 1591, 1153, 820 cm^{-1}; UV λ (MeOH) (log ϵ) 239 (4.51), 246 (4.51), 294 (4.70), 374 (3.87), 391 nm (3.89). Anal. ($C_{26}H_{25}NO_6$) C, H, N.

(±)-*cis*-1-Hydroxy-2-propioxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (30): amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, $J = 7.5$ Hz, 3H, CH_3CH_2CO), 1.44 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.92 (d, $J = 9$ Hz, 1H, C_1-O*H*), 2.32 (q, $J = 7.5$ Hz, 2H, CH_3CH_2CO), 3.95 (s, 3H, NCH_3), 4.04 (s, 3H, OCH_3), 5.35 (dd, $J = 9$, 5 Hz, 1H, H-1), 5.39 (d, $J = 5$ Hz, 1H, H-2), 6.34 (s, 1H, H-5), 7.49 (td, $J = 8$, 1 Hz, 1H, H-10), 7.52 (d, $J = 9$ Hz, 1H, H-13), 7.67 (td, $J = 8$, 1 Hz, 1H, H-9), 7.82 (dd, $J = 8$, 1 Hz, 1H, H-11), 8.00 (d, $J = 9$ Hz, 1H, H-12), 9.83 (dd, $J = 8$, 1 Hz, 1H, H-8). Anal. ($C_{27}H_{27}NO_6$) C, H, N.

(±)-*cis*-1-Hydroxy-2-isovaleroyloxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (31): amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87−0.90 (m, 6H, $(CH_3)_2CHCH_2CO$), 1.43 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.01−2.05 (m, 2H, C_1-O*H*, $(CH_3)_2CHCH_2CO$), 2.20 (d, $J = 7$ Hz, 2H, $(CH_3)_2CHCH_2CO$), 3.94 (s, 3H, NCH_3), 4.04 (s, 3H, OCH_3), 5.33

(d, J = 5 Hz, 1H, H-1), 5.39 (d, J = 5 Hz, 1H, H-1), 6.33 (s, 1H, H-5), 7.49 (td, J = 8, 1 Hz, 1H, H-10), 7.52 (d, J = 9 Hz, 1H, H-13), 7.66 (td, J = 8, 1 Hz, 1H, H-9), 7.82 (dd, J = 8, 1 Hz, 1H, H-11), 8.00 (d, J = 9 Hz, 1H, H-12), 9.83 (dd, J = 8, 1 Hz, 1H, H-8). Anal. ($C_{29}H_{31}NO_6$) C, H, N.

(±)-*cis*-1-Hydroxy-2-(4-pentenoyloxy)-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (32): amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.93 (d, J = 9 Hz, 1H, C_1-O*H*), 2.31 (m, 2H, OCOCH$_2$C*H*$_2$CHCH$_2$), 2.49 (m, 2H, OCOC*H*$_2$CH$_2$CHCH$_2$), 3.95 (s, 3H, NCH_3), 4.03 (s, 3H, OCH_3), 4.80 (m, 2H, OCOCH$_2$-CH$_2$CHC*H*$_2$), 5.32 (dd, J = 9, 5 Hz, 1H, H-1), 5.40 (d, J = 5 Hz, 1H, H-2), 5.66 (m, 1H, OCOCH$_2$CH$_2$C*H*CH$_2$), 6.34 (s, 1H, H-5), 7.48 (td, J = 8, 1 Hz, 1H, H-10), 7.52 (d, J = 9 Hz, 1H, H-13), 7.66 (td, J = 8, 1 Hz, 1H, H-9), 7.82 (dd, J = 8, 1 Hz, 1H, H-11), 8.01 (d, J = 9 Hz, 1H, H-12), 9.83 (dd, J = 8, 1 Hz, 1H, H-8). Anal. ($C_{29}H_{29}NO_6$) C, H, N.

(±)-*cis*-1-Hydroxy-2-benzoyloxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (33): amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 3.00 (br s, 1H, C_1-O*H*), 3.98 (s, 3H, NCH_3), 4.08 (s, 3H, OCH_3), 5.44 (d, J = 5 Hz, 1H, H-1), 5.64 (d, J = 5 Hz, 1H, H-2), 6.43 (s, 1H, H-5), 7.36 (m, 1H, H-5′), 7.46−7.52 (m, 3H, H-10, H-13, H-3′), 7.61−7.66 (m, 2H, H-9, H-4′), 7.80 (dd, J = 8, 1 Hz, 1H, H-11), 7.86 (td, J = 8, 1.5 Hz, 1H, H-6′), 7.98 (d, J = 9 Hz, 1H, H-12), 8.11 (td, J = 8, 1.5 Hz, 1H, H-2′), 9.85 (dd, J = 8, 1 Hz, 1H, H-8). Anal. ($C_{31}H_{27}NO_6$) C, H, N.

General Procedure for the Preparation of (±)-*cis*-1-Acetoxy-2-acyloxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-ones 34−36. Acetic anhydride (0.098 mL, 1.03 mmol) was added to an iced-cooled solution (0 °C) of the appropriate (±)-*cis*-1-hydroxy-2-acyloxy-6-methoxy-3,3,-14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*b*]pyrano[3,2-*h*]acridin-7-one (**31**, **32**, or **33**) (0.103 mmol) and 4-(dimethylamino)pyridine (0.005 g) in dry pyridine (3 mL). After stirring at room temperature during 15 h, the reaction mixture was evaporated under reduced pressure (t < 40 °C) and the crude product was purified by flash chromatography (solvent, CH_2Cl_2 and then CH_2Cl_2/MeOH).

(±)-*cis*-1-Acetoxy-2-isovaleroyloxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (34): Amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.88 (m, 6H, (C*H*$_3$)$_2$CHCH$_2$CO), 1.47 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.99 (s, 3H, CH_3CO), 2.01−2.03 (m, 1H, (CH$_3$)$_2$C*H*CH$_2$CO), 2.16 (d, J = 7 Hz, 2H, (CH$_3$)$_2$CHC*H*$_2$CO), 3.71 (s, 3H, NCH_3), 4.05 (s, 3H, OCH_3), 5.48 (d, J = 5 Hz, 1H, H-1), 6.38 (s, 1H, H-5), 6.55 (d, J = 5 Hz, 1H, H-1), 7.39 (d, J = 9 Hz, 1H, H-13), 7.50 (td, J = 8, 1 Hz, 1H, H-10), 7.66 (td, J = 8, 1 Hz, 1H, H-9), 7.82 (dd, J = 8, 1 Hz, 1H, H-11), 8.01 (d, J = 9 Hz, 1H, H-12), 9.80 (dd, J = 8, 1 Hz, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (*C*H$_3$-CO), 22.4 ((*C*H$_3$)$_2$CHCH$_2$CO), 23.6 (CH_3), 24.6 (CH_3), 25.5 ((CH$_3$)$_2$*C*HCH$_2$CO), 42.9 ((CH$_3$)$_2$CH*C*H$_2$O), 43.1 (NCH_3), 56.5 (OCH_3), 65.8 (C-1), 69.2 (C-2), 76.4 (C-3), 95.6 (C-5), 97.8 (C-14b), 115.0 (C-6a), 115.9 (C-13), 119.5 (C-7a), 125.4 (C-10), 126.7 (C-8), 128.0 (C-11), 128.8 (C-9), 129.4 (C-11a), 131.0 (C-8a), 134.5 (C-12), 145.3 (C-13a), 147.4 (C-14a), 159.0 (C-4a), 162.1 (C-6), 171.0 (C_1O*C*O), 172.6 (C_2O*C*O), 179.3 (C-7); ESI-MS m/z 532 [MH]$^+$, 554 [MNa]$^+$, 570 [MK]$^+$; IR (NaCl) ν 3053, 3016, 2983, 2963, 2920, 2868, 2851, 1744, 1738, 1635, 1592, 1573, 1513, 1490, 1460, 1430, 1368, 1219, 1150, 1090, 1070, 909, 823, 753 cm^{-1}; UV λ (MeOH) (log ϵ) 201 (4.77), 246 (4.41), 290 (4.63), 375 (3.70), 389 nm (3.73). Anal. ($C_{31}H_{33}NO_7$) C, H, N.

(±)-*cis*-1-Acetoxy-2-(4-pentenoyloxy)-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (35): amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.96 (s, 3H, CH_3CO), 2.30−2.41 (m, 4H, OCO(C*H*$_2$)$_2$CHCH$_2$), 3.71 (s, 3H, NCH_3), 4.05 (s, 3H, OCH_3), 4.93−4.98 (m, 2H, OCOCH$_2$CH$_2$CHC*H*$_2$), 5.48 (d, J = 5 Hz, 1H, H-2), 5.70−5.72 (m, 1H, OCOCH$_2$CH$_2$C*H*CH$_2$), 6.38 (s, 1H, H-5), 6.58 (d, J = 5 Hz, 1H, H-1), 7.39 (d, J = 9 Hz, 1H, H-13), 7.48 (td, J = 8, 1 Hz, 1H, H-10), 7.66 (td, J = 8, 1 Hz, 1H, H-9), 7.82 (dd, J = 8, 1 Hz, 1H, H-11), 8.01 (d, J = 9 Hz, 1H, H-12), 9.80 (dd, J = 8, 1 Hz, 1H, H-8). Anal. ($C_{31}H_{31}NO_7$) C, H, N.

(±)-*cis*-1-Acetoxy-2-benzoyloxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (36): amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.88 (s, 3H, CH_3CO), 3.73 (s, 3H, NCH_3), 4.09 (s, 3H, OCH_3), 5.74 (d, J = 5 Hz, 1H, H-2), 6.47 (s, 1H, H-5), 6.64 (d, J = 5 Hz, 1H, H-1), 7.37 (m, 3H, H-13, H-3′, H-5′), 7.46−7.50 (m, 2H, H-10, H-4′), 7.65 (td, J = 8, 1 Hz, 1H, H-9), 7.80 (dd, J = 8, 1 Hz, 1H, H-11), 7.85 (m, 2H, H-2′, H-6′), 7.98 (d, J = 9 Hz, 1H, H-12), 9.80 (dd, J = 8, 1 Hz, 1H, H-8). Anal. ($C_{33}H_{29}$-NO_7) C, H, N.

(±)-*cis*-7-Methoxy-4,4,15-trimethyl-15,15c-dihydro-4*H*-benzo-[*a*][1,3]dioxolo[4′,5′:4,5]pyrano[3,2-*h*]acridin-2,8[3a*H*]-dione (37). *N*,*N*′-Carbonyldiimidazole (0.231 g, 1.35 mmol) was added to a solution of **23** (0.109 g, 0.27 mmol) in 2-butanone (5 mL). The reaction mixture was refluxed for 2 h under argon and after cooling, 5% aqueous $NaHCO_3$ (7 mL) was added. The solution was extracted with ethyl acetate (3 × 15 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Flash chromatography (solvent, cyclohexane and then cyclohexane/acetone, 98:2 to 95:5) afforded **37** (0.066 g, 56%) as a white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 3.92 (s, 3H, NCH_3), 4.02 (s, 3H, OCH_3), 4.79 (d, J = 8 Hz, 1H, H-2), 6.27 (d, J = 8 Hz, 1H, H-1), 6.36 (s, 1H, H-5), 7.48 (d, J = 9 Hz, 1H, H-13), 7.51 (td, J = 8, 1 Hz, 1H, H-10), 7.67 (td, J = 8, 1 Hz, 1H, H-9), 7.83 (dd, J = 8, 1 Hz, 1H, H-11), 8.00 (d, J = 9 Hz, 1H, H-12), 9.70 (dd, J = 8, 1 Hz, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (CH_3), 24.3 (CH_3), 43.9 (NCH_3), 56.6 (OCH_3), 71.0 (C-1), 74.1 (C-2), 78.9 (C-3), 96.2 (C-5), 97.2 (C-14b), 115.1 (C-6a), 116.4 (C-13), 119.9 (C-7a), 125.7 (C-10), 126.5 (C-8), 128.1 (C-11), 128.9 (C-9), 129.5 (C-11a), 130.4 (C-8a), 134.4 (C-12), 145.4 (C-13a), 147.2 (C-14a), 153.7 (CO), 158.3 (C-4a), 162.8 (C-6), 179.5 (C-7); DCI-MS m/z 432 [MH]$^+$; IR (KBr) ν 3441, 3080, 2979, 2932, 1794, 1631, 1588, 1511, 1456, 1406, 1173, 1138, 1033, 815, 749 cm^{-1}; UV λ (MeOH) (log ϵ) 244 (4.54), 290 (4.78), 309 (sh), 332 (sh), 369 (sh), 388 nm (3.96). Anal. ($C_{25}H_{21}NO_6$) C, H, N.

(±)-*cis*-1,2-Bis(*N*,*N*-diethylcarbamoyloxy)-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (38). Potassium hydride (0.141 g of 35% oil dispersion, 1.24 mmol) was added to a solution of **23** (0.1 g, 0.25 mmol) in dry tetrahydrofuran (10 mL) at −10 °C. The mixture was stirred under argon for 15 min at −10 °C and the *N*,*N*-diethylcarbamoyl chloride (0.078 mL, 0.62 mmol) was added. After stirring at room temperature for 15 h, the reaction mixture was poured carefully onto ethyl acetate (50 mL) and saturated aqueous $NaHCO_3$ (10 mL) (pH 8). The organic layer was washed with water (3 × 10 mL), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure (t < 40 °C). Flash chromatography (solvent, CH_2Cl_2 and then CH_2Cl_2/MeOH, 99.5:0.5 to 98:2) gave **38** (0.045 g, 30%) as a white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (t, J = 7 Hz, 3H, C*H*$_3$CH$_2$), 0.79 (t, J = 7 Hz, 3H, C*H*$_3$CH$_2$), 1.03 (t, J = 7 Hz, 3H, C*H*$_3$CH$_2$), 1.20 (t, J = 7 Hz, 3H, C*H*$_3$CH$_2$), 1.47 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.77−2.82 (m, 2H, CH_2), 2.93−2.95 (m, 1H, CH), 3.00−3.04 (m, 1H, CH), 3.23−3.27 (m, 1H, CH), 3.32−3.36 (m, 2H, CH_2), 3.77 (s, 3H, NCH_3), 4.03 (s, 3H, OCH_3), 5.48 (d, J = 5 Hz, 1H, H-2), 6.37 (s, 1H, H-5), 6.48 (d, J = 5 Hz, 1H, H-1), 7.39 (d, J = 9 Hz, 1H, H-13), 7.48 (td, J = 8, 1 Hz, 1H, H-10), 7.51 (td, J = 8, 1 Hz, 1H, H-9), 7.81 (dd, J = 8, 1 Hz, 1H, H-11), 7.99 (d, J = 9 Hz, 1H, H-12), 9.91 (dd, J = 8, 1 Hz, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4 (2 × *C*H$_3$CH$_2$), 13.7 (*C*H$_3$CH$_2$), 13.8 (*C*H$_3$CH$_2$), 23.0 (CH_3), 24.9 (CH_3), 41.0 (CH_2), 41.5 (CH_2), 42.0 (CH_2), 42.1 (CH_2), 42.9 (NCH_3), 56.5 (OCH_3), 67.1 (C-1), 70.1 (C-2), 77.0 (C-3), 95.3 (C-5), 98.7 (C-14b), 114.7 (C-6a), 116.3 (C-13), 118.9 (C-7a), 125.3 (C-10), 127.0 (C-8), 128.0 (C-11), 128.7 (C-9), 129.3 (C-11a), 131.2 (C-8a), 134.1 (C-12), 145.1 (C-13a), 147.2 (C-14a), 154.8 (C-4a), 155.0 (C-6), 159.3 (C_1O*C*O), 161.9 (C_2O*C*O), 179.3 (C-7); ESI-MS m/z 604 [MH]$^+$, 626 [MNa]$^+$; 642 [MK]$^+$; IR (KBr) ν 2974, 2068, 2926, 2845, 1711, 1700, 1630, 1591, 1509, 1133, 1070, 817 cm^{-1}; UV λ (MeOH)

(log ϵ) 204 (4.71), 247 (4.47), 291 (4.69), 374 (3.80), 390 nm (3.82). Anal. ($C_{34}H_{41}N_3O_7$) C, H, N.

(±)-*cis*-1-Hydroxy-2-(*N*,*N*-dimethylcarbamoyloxy)-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]-acridin-7-one (39). Compound **39** was obtained from **23** (0.050 g, 0.124 mmol) according to the procedure described for the preparation of **38**, using *N*,*N*-dimethylcarbamoyl chloride (0.046 mL, 0.494 mmol), potassium hydride (0.085 g of 35% oil dispersion, 0.741 mmol), and dry tetrahydrofuran (8 mL). Flash chromatography (solvent, CH_2Cl_2 and then CH_2Cl_2/MeOH, 99.5:0.5 to 98:2) gave **39** (0.019 g, 32%) as a yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.65 (br.s, 1H, C_1-O*H*), 2.73 (s, 3H, CH_3N), 2.86 (s, 3H, CH_3N), 3.97 (s, 3H, NCH_3), 4.02 (s, 3H, OCH_3), 5.20 (d, J = 5 Hz, H-1), 5.36 (d, J = 5 Hz, 1H, H-2), 6.33 (s, 1H, H-5), 7.50 (td, J = 8, 1 Hz, 1H, H-10), 7.54 (d, J = 9 Hz, 1H, H-13), 7.66 (td, J = 8, 1 Hz, 1H, H-9), 7.81 (dd, J = 8, 1 Hz, 1H, H-11), 8.00 (d, J = 9 Hz, 1H, H-12), 9.86 (dd, J = 8, 1 Hz, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6 (CH_3), 25.3 (CH_3), 35.8 (CH_3N), 36.8 (CH_3N), 42.0 (NCH_3), 56.3 (OCH_3), 64.2 (C-1), 73.4 (C-2), 76.6 (C-3), 94.7 (C-5), 104.7 (C-14b), 114.7 (C-6a), 116.2 (C-13), 118.9 (C-7a), 125.1 (C-10), 126.7 (C-8), 127.8 (C-11), 128.5 (C-9), 129.2 (C-8a), 130.9 (C-11a), 134.1 (C-12), 144.9 (C-13a), 146.6 (C-14a), 156.5 (C-4a), 157.8 (C-6), 161.5 (C_2OCO), 179.1 (C-7); ESI-MS m/z 477 $[MH]^+$, 499 $[MNa]^+$; 515 $[MK]^+$; IR (KBr) ν 3429, 2935, 2880, 1701, 1633, 1623, 1598, 1520, 1399, 1145, 1056, 823 cm^{-1}; UV λ (MeOH) (log ϵ) 233 (4.28), 247 (4.42), 295 (4.62), 375 (3.75), 392 nm (3.77). Anal. ($C_{27}H_{28}N_2O_6$) C, H, N.

Catalytic Osmium Tetroxide Oxidation of 21. Compound **21** (0.243 g, 0.65 mmol) was added to a solution of osmium tetroxide (2.5% in 2-methyl-2-propanol) (0.53 mL) and *N*-methylmorpholine *N*-oxide dihydrate (0.097 g, 1.31 mmol) in *t*-BuOH/THF/H_2O (10:3:1, v/v/v, 10 mL). The reaction mixture was stirred at room temperature for 2 days. After addition of saturated aqueous $NaHSO_3$, the mixture was stirred for 1 h and extracted with CH_2Cl_2 (6 × 25 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography (solvent, CH_2Cl_2 and then CH_2Cl_2/MeOH, 99.5:0.5 to 90:10) gave successively **41** (0.04 g, 16%), **40** (0.04 g, 15%), and **42** (0.04 g, 16%) as amorphous solids.

(±)-*cis*-1,2-Dihydroxy-6,7-dimethoxy-3,3-dimethyl-3*H*-benzo[*a*]pyrano[3,2-*h*]acridine (40): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 3.97 (s, 3H, C_7-OC*H*$_3$), 4.01 (d, J = 4.5 Hz, 1H, H-2), 4.10 (s, 3H, C_6-OC*H*$_3$), 5.53 (d, J = 4.5 Hz, 1H, H-1), 6.56 (s, 1H, H-5), 7.63 (td, J = 8, 1 Hz, 1H, H-10), 7.72 (td, J = 8, 1 Hz, 1H, H-9), 7.82 (d, J = 9 Hz, 1H, H-13), 7.87 (dd, J = 8, 1 Hz, 1H, H-11), 7.93 (d, J = 9 Hz, 1H, H-12), 9.57 (dd, J = 8, 1 Hz, 1H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8 (CH_3), 29.3 (CH_3), 56.5 (C_6-OC*H*$_3$), 62.2 (C_7-OC*H*$_3$), 64.6 (C-1), 70.9 (C-2), 78.2 (C-3), 98.7 (C-5), 105.0 (C-14b), 111.3 (C-6a), 115.3 (C-7a), 126.9 (C-10), 127.6 (C-8), 128.1 (C-9), 128.3 (C-13), 129.0 (C-11), 129.6 (C-11a), 131.6 (C-8a), 134.0 (C-12), 147.3 (C-14a), 152.0 (C-13a), 155.1 (C-4a), 156.8 (C-7), 165.9 (C-6); ESI-MS m/z 406 $[MH]^+$, 428 $[MNa]^+$, IR (NaCl) ν 3390, 2920, 2854, 1610, 1581, 1555, 1448, 1435, 1407, 1363, 1302, 1201, 1137 cm^{-1}; UV λ (MeOH) (log ϵ) 225 (4.38), 289 (4.56), 332 (3.80), 347 (3.73), 367 nm (3.71). Anal. ($C_{24}H_{23}NO_5$) C, H, N.

2-Hydroxy-6-methoxy-3,3-dimethyl-1,2,3,14-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-1,7-dione (41): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.39 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 4.30 (d, J = 5 Hz, 1H, H-2), 6.24 (d, J = 5 Hz, 1H, C_2-O*H*), 6.40 (s, 1H, H-5), 7.56 (td, J = 8, 1 Hz, 1H, H-10), 7.67 (td, J = 8, 1 Hz, 1H, H-9), 7.69 (d, J = 9 Hz, 1H, H-13), 7.99 (dd, J = 8, 1 Hz, 1H, H-11), 8.18 (d, J = 9 Hz, 1H, H-12), 10.00 (dd, J = 8, 1 Hz, 1H, H-8), 12.80 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.5 (CH_3), 26.5 (CH_3), 57.5 (OCH_3), 76.4 (C-3), 83.6 (C-2), 95.5 (C-5), 104.7 (C-14b), 114.0 (C-6a), 116.9 (C-13), 119.6 (C-7a), 125.7 (C-10), 127.0 (C-8), 128.4 (C-11), 129.3 (C-9), 130.0 (C-11a), 131.1 (C-8a), 135.2 (C-12), 144.3 (C-13a), 147.1 (C-14a), 166.5 (C-4a), 169.0 (C-6), 177.4 (C-7), 195.1 (C-1); DCI-MS m/z 390 $[MH]^+$; IR (NaCl) ν 3380, 3059, 3025, 2919, 2845, 1654, 1633, 1617, 1600, 1496, 1450, 1436, 1380, 1213, 1133, 1103, 756 cm^{-1}; UV λ (MeOH) (log ϵ) 203 (4.34), 214 (4.38), 235 (4.21), 281 (4.32), 293 (4.34), 333 (3.86), 388 nm (3.85). Anal. ($C_{23}H_{19}NO_5$) C, H, N.

(±)-*cis*-1,2-Dihydroxy-6-methoxy-3,3-dimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-7-one (42): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.70 (dd, J = 6, 5 Hz, 1H, H-2), 3.82 (s, 3H, OCH_3), 5.11 (d, J = 7, 6, 1H, H-1), 5.34 (d, J = 7 Hz, 1H, C_1-O*H*), 5.47 (d, J = 5 Hz, 1H, C_2-O*H*), 6.20 (s, 1H, H-5), 7.49 (td, J = 8, 1 Hz, 1H, H-10), 7.66 (td, J = 8, 1 Hz, 1H, H-9), 7.70 (d, J = 9 Hz, 1H, H-13), 7.92 (dd, J = 8, 1 Hz, 1H, H-11), 8.09 (d, J = 9 Hz, 1H, H-12), 10.03 (dd, J = 8, 1 Hz, 1H, H-8), 10.57 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 23.2 (CH_3), 25.5 (CH_3), 56.2 (OCH_3), 62.8 (C-1), 71.1 (C-2), 79.2 (C-3), 94.7 (C-5), 100.3 (C-14b), 109.7 (C-6a), 114.0 (C-7a), 118.9 (C-13), 125.1 (C-10), 126.4 (C-8), 128.7 (C-11a), 128.9 (C-9), 129.6 (C-11), 131.8 (C-8a), 134.6 (C-12), 140.6 (C-13a), 142.4 (C-14a), 156.6 (C-4a), 161.5 (C-6), 177.9 (C-7); DCI-MS m/z 392 $[MH]^+$; IR (NaCl) ν 3400, 3056, 3025, 2921, 2847, 1633, 1623, 1451, 1154, 1030 cm^{-1}; UV λ (MeOH) (log ϵ) 203 (4.56), 213 (4.35), 243 (4.30), 288 (4.58), 348 (3.64), 367 (3.67), 386 nm (3.66). Anal. ($C_{23}H_{21}NO_5$) C, H, N.

(±)-*cis*-1,2-Diacetoxy-6,7-dimethoxy-3,3-dimethyl-3*H*-benzo[*a*]pyrano[3,2-*h*]acridine (43). Compound **43** was obtained from **40** (0.02 g, 0.049 mmol) according to the procedure described for the preparation of **25** from **23**, using excess acetic anhydride (0.1 mL, 1.04 mmol) and 4-(dimethylamino)pyridine (0.002 g). Flash chromatography (solvent, CH_2Cl_2 and then CH_2Cl_2/MeOH, 99.5:0.5 to 98:2) gave **43** (0.02 g, 83%) as a yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 2.07 (s, 3H, CH_3CO), 2.15 (s, 3H, CH_3CO), 3.96 (s, 3H, C_7-OC*H*$_3$), 4.10 (s, 3H, C_6-OC*H*$_3$), 5.42 (d, J = 5 Hz, 1H, H-2), 6.50 (s, 1H, H-5), 7.03 (d, J = 5 Hz, 1H, H-1), 7.61 (td, J = 8, 1 Hz, 1H, H-10), 7.66 (td, J = 8, 1 Hz, 1H, H-9), 7.76 (d, J = 9 Hz, 1H, H-13), 7.86 (dd, J = 8, 1 Hz, 1H, H-11), 7.88 (d, J = 9 Hz, 1H, H-12), 9.56 (dd, J = 8, 1 Hz, 1H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (CH_3CO), 20.8 (CH_3CO), 22.4 (CH_3), 25.9 (CH_3), 56.8 (C_6-OC*H*$_3$), 61.6 (C_7-OC*H*$_3$), 62.4 (C-1), 71.7 (C-2), 77.0 (C-3), 97.6 (C-5), 105.0 (C-14b), 111.3 (C-6a), 115.3 (C-7a), 126.7 (C-10), 127.4 (C-8), 127.8 (C-9), 128.6 (C-13), 128.9 (C-11), 129.6 (C-11a), 131.6 (C-8a), 133.0 (C-12), 147.3 (C-14a), 152.0 (C-13a), 154.7 (C-4a), 157.2 (C-7), 166.3 (C-6); 169.9 ($OCOCH_3$), 170.5 ($OCOCH_3$); DCI-MS m/z 490 $[MH]^+$; IR (NaCl) ν 2920, 2847, 1742, 1722, 1610, 1584, 1462, 1432, 1153 cm^{-1}; UV λ (MeOH) (log ϵ) 224 (4.28), 260 (4.06), 285 (4.46), 329 (3.42), 362 nm (3.43). Anal. ($C_{28}H_{27}NO_7$) C, H, N.

2-Acetoxy-6-methoxy-3,3,14-trimethyl-1,2,3,14-tetrahydro-7*H*-benzo[*a*]pyrano[3,2-*h*]acridin-1,7-dione (44). Compound **44** was synthesized from **41** (0.050 g, 0.124 mmol) according to the procedure described for the preparation of **25** from **23**, using excess acetic anhydride (0.2 mL, 2.08 mmol) and 4-(dimethylamino)-pyridine (0.002 g). Flash chromatography (solvent, CH_2Cl_2 and then CH_2Cl_2/MeOH, 99.5:0.5 to 98:2) gave **44** (0.054 g, 98%) as a yellow amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 2.26 (CH_3CO), 3.75 (s, 3H, NCH_3), 4.09 (s, 1H, H-2), 6.36 (s, 1H, H-5), 7.54 (td, J = 8, 1 Hz, 1H, H-10), 7.61 (d, J = 9 Hz, 1H, H-13), 7.68 (td, J = 8, 1 Hz, 1H, H-9), 7.83 (dd, J = 8, 1 Hz, 1H, H-11), 8.03 (d, J = 9 Hz, 1H, H-12), 9.91 (dd, J = 8, 1 Hz, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3 (CH_3), 20.8 (CH_3CO), 26.1 (CH_3), 45.9 (NCH_3), 57.0 (OCH_3), 76.3 (C-3), 82.0 (C-2), 95.0 (C-5), 103.2 (C-14b), 113.6 (C-6a), 116.7 (C-13), 119.5 (C-7a), 125.8 (C-10), 127.0 (C-8), 128.1 (C-11), 128.9 (C-9), 129.8 (C-11a), 130.8 (C-8a), 134.7 (C-12), 144.2 (C-13a), 146.4 (C-14a), 165.2 (C-4a), 167.4 (C-6), 170,0 (C_2OCO), 178.2 (C-7), 183.7 (C-1); ESI-MS m/z 446 $[MH]^+$, 468 $[MNa]^+$; IR (NaCl) ν 2927, 1747, 1654, 1630, 1581, 1404, 1206, 1067, 1026 cm^{-1}; UV λ (MeOH) (log ϵ) 224 (4.28), 260 (4.06), 285 (4.46), 329 (3.42), 362 nm (3.43). Anal. ($C_{26}H_{23}NO_6$) C, H, N.

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Supporting Information Available: Experimental procedures for the preparation of compounds **25**−**36**; ^{13}C NMR, MS, IR, and UV spectral data for compounds **26**−**28**, **30**−**33**, **35**, and **36**; elemental analysis data of compounds **4** and **8**−**44**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Hughes, G. K.; Lahey, F. N.; Price J. R. Alkaloids of the Australian Rutaceae. *Nature* **1948**, *162*, 223−224. (b) Macdonald, P. L.; Robertson, A. V. The structure of acronycine. *Aust. J. Chem*. **1966**, *19*, 275−281. (c) Govindachari, T. R.; Pai, B. R.; Subramaniam, P. S. Alkaloids of *Glycosmis pentaphylla* (Retz.) Correa. *Tetrahedron* **1966**, *22*, 3245−3252. (d) Gougoutas, J. Z.; Kaski, B. A. The crystal and molecular structure of bromodihydroacronycine. *Acta Crystallogr.* **1970**, *B26*, 853−859.

(2) Tillequin, F.; Michel, S.; Skaltsounis A.-L. Acronycine-type alkaloids: Chemistry and biology. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier: Amsterdam, 1998; Vol. 12, pp 1−102.

(3) (a) Svoboda, G. H. Alkaloids of *Acronychia baueri*. Extraction of the alkaloids and studies of structure−activity relationships. *Lloydia* **1966**, *29*, 206−224. (b) Svoboda, G. H.; Poore, G. A.; Simpson, P. J.; Boder, G. B. Alkaloids of *Acronychia baueri*. Isolation of the alkaloids and study of the antitumor and other biological properties of acronycine. *J. Pharm. Sci*. **1966**, *55*, 758−768. (c) Dorr, R. T.; Liddil, J. D.; Von Hoff, D. D.; Soble, M.; Osborne, C. K. Antitumor activity and murine pharmacokinetics of parenteral acronycine. *Cancer Res*. **1989**, *49*, 340−344.

(4) Scarffe, J. H.; Beaumont, A. R.; Crowther, D. Phase I−II evaluation of acronycine in patients with multiple myeloma. *Cancer Treat. Rep*. **1983**, *67*, 93−94.

(5) Brum-Bousquet, M.; Mitaku, S.; Skaltsounis A.-L.; Tillequin, F.; Koch, M. Acronycine epoxide: A new acridone alkaloid from several *Sarcomelicope* species. *Planta Med*. **1988**, *54*, 470−471.

(6) (a) Elomri, A.; Mitaku, S.; Michel, S.; Skaltsounis A.-L.; Tillequin, F.; Koch, M.; Pierré, A.; Guilbaud, N.; Léonce, S.; Kraus-Berthier, L.; Rolland, Y.; Atassi, Gh. Synthesis and cytotoxic and antitumor activity of esters in the 1,2-dihydroxy-1,2-dihydroacronycine series. *J. Med. Chem*. **1996**, *39*, 4762−4766. (b) Magiatis, P. Mitaku, S.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M.; Pierré, A.; Atassi, Gh. Synthesis and biological activity of esters in the *trans*-1,2-dihydroxy-1,2-dihydroacronycine series. *J. Nat. Prod*. **1998**, *61*, 198−201. (c) Costes, N.; Michel, S., Tillequin, F.; Koch, M.; Pierré, A.; Atassi, Gh. Chiral dihydroxylation of acronycine: Absolute configuration of natural *cis*-1,2-dihydroxy-1,2-dihydroacronycine and cytotoxicity of (1*R*,2*R*) and (1*S*,2*S*)-1,2-diacetoxy-1,2-dihydroacronycine. *J. Nat. Prod*. **1999**, *62*, 490−492.

(7) (a) Costes, N.; Le Deit, H.; Michel, S., Tillequin, F.; Koch, M.; Pfeiffer, B.; Renard, P.; Léonce, S.; Guilbaud, N.; Kraus-Berthier, L.; Pierré, A.; Atassi, Gh. Synthesis and cytotoxic and antitumor activity of benzo[*b*]pyrano[3,2-*h*]acridin-7-one analogues of acronycine. *J. Med. Chem.* **2000**, *43*, 2395−2402. (b) Doan Thi Mai, H.; Gaslonde, T.; Michel, S.; Koch, M.; Tillequin, F.; Pfeiffer, B.; Renard, P.; Kraus-Berthier, L.; Léonce, S.; Pierré, A. Synthesis and cytotoxic and antitumor activity of 1,2-dihydroxy-1,2-dihydrobenzo[*b*]acronycine diacid hemiesters and carbamates. *Chem. Pharm. Bull*. **2004**, *52*, 293−297.

(8) Doan Thi Mai, H.; Gaslonde, T.; Michel, S.; Tillequin, F.; Koch, M.; Bongui, J.-B.; Elomri, A.; Seguin, E.; Pfeiffer, B.; Renard, P.; David-Cordonnier, M.-H.; Laine, W.; Bailly, C.; Kraus-Berthier, L.; Léonce, S.; Hickman, J. A.; Pierré, A. Structure−activity relationships and mechanism of action of antitumor benzo[*b*]pyrano[3,2-*h*]acridin-7-one acronycine analogues. *J. Med. Chem.* **2003**, *46*, 3072−3082.

(9) (a) Guilbaud, N.; Kraus-Berthier, L.; Meyer-Losic, F.; Malivet, V.; Chacun, C.; Jan, J.; Tillequin, F.; Michel, S.; Koch, M.; Pfeiffer, B.; Atassi, Gh.; Hickman, J.; Pierré, A. Marked antitumor activity of a new potent acronycine derivative in orthotopic models of human solid tumors. *Clin.* Cancer Res. **2001**, *7*, 2573−2580. (b) Guilbaud, N.; Léonce, S.; Tillequin, F.; Koch, M.; Hickman, J.; Pierré, A. Acronycine derivatives as promising antitumor agents. *Anti-Cancer Drugs* **2002**, *13*, 445−449.

(10) (a) David-Cordonnier, M.-H.; Laine, W.; Lansiaux, A.; Kouach, M.; Briand, G.; Pierré, A.; Hickman, J. A.; Bailly, C. Alkylation of guanine by S-23906−1, a novel potent antitumor compound derived from the plant alkaloid acronycine. *Biochemistry* **2002**, *41*, 9911−9920. (b) David-Cordonnier, M.-H.; Laine, W.; Kouach, M.; Briand, G.; Vezin, H.; Gaslonde, T.; Michel, S.; Doan Thi Mai, H.; Tillequin, F.; Koch, M.; Léonce, S.; Pierré, A.; Bailly, C. A transesterification reaction is implicated in the covalent binding of benzo[*b*]acronycine anticancer agents with DNA and glutathion. *Bioorg. Med. Chem.* **2004**, *12*, 23−29. (c) David-Cordonnier, M.-H.; Laine, W.; Gaslonde, T.; Michel, S.; Tillequin, F.; Koch, M.; Léonce, S.; Pierré, A.; Bailly, C. Design of novel antitumor DNA alkylating agents: The benzacronycine series. *Curr. Med. Chem.*—*Anti-Cancer Agents* **2004**, *4*, 83−92. (d) Michel, S.; Gaslonde, T.; Tillequin, F. Benzo[*b*]-acronycine derivatives: A novel class of antitumor agents. *Eur. J. Med. Chem.* **2004**, *39*, 649−655.

(11) Michel, S.; Seguin, E.; Tillequin, F. Structure activity relationships in the acronycine series. *Curr. Med. Chem.* **2002**, *9*, 1689−1700.

(12) Zhang, W.; Liu, R.; Cook, J. M. The regiospecific synthesis of *ortho*-aminonaphthophenones via the addition of carbanions to naphthoxazin-4-ones. *Heterocycles* **1993**, *36*, 2229−2236.

(13) (a) Adams, J.; Gupta, P.; Lewis, J. R. A biomimetic synthesis of acronycine. *Chem. Ind.* (London) **1976**, 109−110. (b) Adams, J.; Brown, M.; Gupta, P.; Khan, M. S.; Lewis, J. R. Rutaceous constituents: A biomimetic synthesis of acronycine. *Tetrahedron* **1981**, *37*, 209−217.

(14) Koch, M.; Tillequin, F.; Michel, S.; Hickman, J.; Pierré, A.; Léonce, S.; Pfeiffer, B.; Renard, P. Benzo[*a*]pyrano[3,2-*h*]acridin-7-one derivatives structurally related to acronycine: Processes for their preparation and pharmaceutical compositions for treatment of cancer. Eur. Pat. Appl. 1,491,544, December 29, 2004. *Chem. Abstr*. **2005**, *142*, 94017*m*.

(15) (a) Traxler, P.; Green, J.; Mett, H.; Séquin, U.; Furet, P. Use of a pharmacophore model for the design of EGFR tyrosine kinase inhibitors: Isoflavones and 3-phenyl-4(1*H*)-quinolones. *J. Med*. Chem. **1999**, *42*, 1018−1026. (b) Hall, R. B.; Marchant, J.; Oliveira-Campos A. M. F.; Queiroz, M.-J. R. P.; Shannon, P. V. R. The synthesis of pyrido[4,3-*b*]carbazoles from diphenylamine derivatives: Alternative routes to and relay syntheses of ellipticines and olivacines. *J. Chem. Soc. Perkin Trans. 1* **1992**, 3439−3450.

(16) Cohen, J. B.; Dudley, H. W. The relation of position isomerism to optical activity. The rotation of the menthyl esters of the alkoxy- and alkylamino-derivatives of benzoic acid. *J. Chem. Soc*. **1910**, 1732−1751.

(17) Hlubucek, J.; Ritchie, E.; Taylor, W. C. A synthesis of acronycine. *Aust. J. Chem.* **1970**, *23*, 1881−1889.

(18) Hennion, G. F.; Boisselle, A. P. Preparation of *t*-acetylenic chlorides. *J. Org. Chem.* **1961**, *26*, 725−727.

(19) (a) Kirtany, J. K. Revised structure of a side-product obtained during synthesis of 11-hydroxynoracronycine. *Ind. J. Chem.* **1981**, *20B*, 614. (b) Evans, C. M.; Kirby, A. J. Intramolecular nucleophilic addition of phenolate to unactivated double and triple bonds. Relative reactivity, regiospecificity, stereochemistry and mechanism. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1269−1275.

(20) Rheenen, V. V.; Kelly, R. C.; Cha, D. Y. An improved catalytic OsO_4 oxidation of olefins to *cis*-1,2-glycols using tertiary amine oxides as the oxidant. *Tetrahedron Lett.* **1976**, *23*, 1973−1976.

(21) (a) Leonce, S.; Pierré, A.; Anstett, M.; Perez, V.; Genton, A.; Bizzari, J. P.; Atassi, Gh. Effects of a new triazinoaminopiperidine derivative on adriamycin accumulation and retention in cells displaying P-glycoprotein-mediated multidrug resistance. *Bio-Chem. Pharmacol*. **1992**, *44*, 1707. (b) Pierré, A.; Dunn, T. A.; Kraus-Berthier, L.; Léonce, S.; Saint-Dizier, D.; Regnier, G.; Dhainaut, A.; Berlion, M.; Bizarri, J. P.; Atassi, Gh. In vitro and in vivo circumvention of multidrug resistance by Servier 9788, a novel triazinoaminopiperidine derivative. *Invest. New Drugs* **1992**, *10*, 137.

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