Natural Product Chemistry. Part 160 [1]. Synthesis of 8-, 9-, 10- and 11-Methylacronycines to Improve the Cytostatic Activity of Acronycine

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With the help of drug design, 8-, 9-, 10- and 11-methylacronycines **24**, **25**, **26** and **27** have been selected and synthesised to improve the cytostatic potency of acronycine (**31**). The condensation of phloroglucinol with 6-methylanthranilic acid gave 7-hydroxy-1,9-dimethyldibenzo[*b*,*j*][1,7]phenanthroline-8,14(5*H*,13*H*)-dione (**32**) as the main product.

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The structure-activity-relationship (SAR) studies of the acridinone alkaloid, acronycine (**31**) through molecular modifications have been carried out by our research group for several years. Some of the modifications led to an increase in the cytotoxic activity [4] but the desired cytostatic potency was not obtained. Having this in mind, theoretical studies were taken up using the Molecular Modelling Software MOBY [5]. As a direct relationship between the isoelectrostatic potential and the biological activity has been established [6], the isoelectrostatic potential of the various analogs have been studied taking acronycine as the lead. These studies revealed that a methyl group on ring A could not significantly modify the isoelectrostatic potential of **31**. It could be expected that, though this modification might not alter the cytostatic potency, an improvement is possible.

The different methylated 1,3-dihydroxy-9(10*H*)-acridinones **2**, **3**, **4** and **5** have been synthesised following an unambiguous method as described by Smolders [7,8]. Further methylation using methyl iodide in the presence of anhydrous potassium carbonate in absolute acetone led to the following: 1,3-dihydroxy-6-methyl-9(10*H*)-acridinone (**4**) at room temperature gave 1,3-dimethoxy-6,10-dimethyl-9(10*H*)-acridinone (**6**) as the major product and 1-hydroxy-3-methoxy-4,6,10-trimethyl-9(10*H*)-acridinone (**8**) as a side product. But 1,3-dihydroxy-7-methyl-9(10*H*)-acridinone (**3**) and 1,3-dihydroxy-8-methyl-9(10*H*)-acridinone (**2**) gave 1,3-dimethoxy-7,10-dimethyl-9(10*H*)-acridinone (**7**) and 1-hydroxy-3-methoxy-8,10-dimethyl-9(10*H*)-acridinone (**9**) respectively as the only products. Interestingly 1,3-dihydroxy-5-methyl-9(10*H*)-acridinone (**5**) yielded 1-hydroxy-3-methoxy-5-methyl-9(10*H*)-acridinone (**10**) as the only product even when the reaction mixture was heated under reflux. Methylation of **5** using potassium hydroxide as the base gave 1,3-dimethoxy-5,10-dimethyl-9(10*H*)-acridinone (**11**).

Further steps leading to the respective methylnoracronycine analogs (Scheme) were carried out as recently reported by us [9]. Along with the methylnoracronycines **16-19**, two methylisonoracronycines **20** and **21** and one corresponding ether derivative **23** were also isolated.

Methylation of **16-19** was successfully carried out by sodium hydride and methyl iodide in anhydrous tetrahydrofurane to yield **24-27** as major products. The respective 5-methylated derivatives **28-30** appeared as side products.

Compounds **6-30** are being screened for antitumor activity [10] and the results will be published elsewhere.

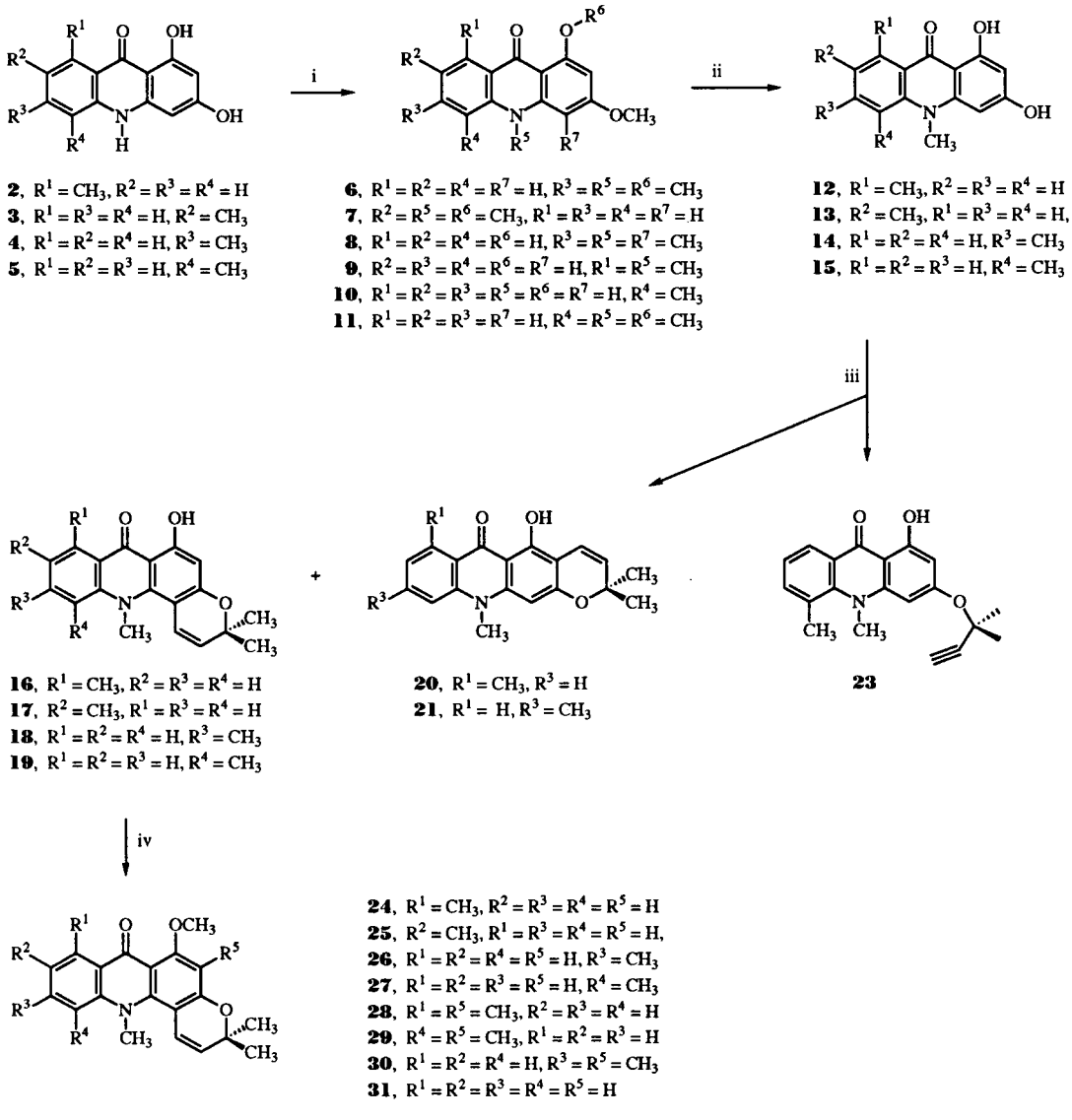
On prolongation of reaction from 2 hours to 6 hours, 1,3-dihydroxy-8-methyl-9(10*H*)-acridinone (**2**) gave a dimeric product as the major product. It has been identified as the angular dimer, 7-hydroxy-1,9-dimethyldibenzo[*b*,*j*]-[1,7]phenanthroline-8,14(5*H*,13*H*)-dione (**32**). Although a linear dimerisation could be expected, the angular isomer **32** appeared as the only product. Perhaps this could be due to the stabilization resulting from the hydrogen bonding between the carbonyl oxygen at C-14 and NH-13 of **32**.

The ^{1}H nmr spectrum of **32** showed seven aromatic protons. The confirmation of the structure of **32** was possible with ms and elemental analysis data. Ambiguity in the assignment of the interchangeable aromatic protons by virtue of similar chemical environment could be clarified by methylating **32**. The methylation of **32**, which was successfully carried out following a well documented procedure from our group [11], gave **33**. The six different methyl signals in the ^{1}H and ^{13}C nmr spectrum of **33** unequivocally confirmed the structures of **32** and **33**.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The ir spectra were recorded as potassium bromide disks on a Shimadzu IR-470 spectrophotometer.

Scheme



2, $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$
3, $R^1 = R^3 = R^4 = H$, $R^2 = CH_3$
4, $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$
5, $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$

6, $R^1 = R^2 = R^4 = R^7 = H$, $R^3 = R^5 = R^6 = CH_3$
7, $R^2 = R^5 = R^6 = CH_3$, $R^1 = R^3 = R^4 = R^7 = H$
8, $R^1 = R^2 = R^4 = R^6 = H$, $R^3 = R^5 = R^7 = CH_3$
9, $R^2 = R^3 = R^4 = R^6 = R^7 = H$, $R^1 = R^5 = CH_3$
10, $R^1 = R^2 = R^3 = R^5 = R^6 = R^7 = H$, $R^4 = CH_3$
11, $R^1 = R^2 = R^3 = R^7 = H$, $R^4 = R^5 = R^6 = CH_3$

12, $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$
13, $R^2 = CH_3$, $R^1 = R^3 = R^4 = H$,
14, $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$
15, $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$

16, $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$
17, $R^2 = CH_3$, $R^1 = R^3 = R^4 = H$
18, $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$
19, $R^1 = R^2 = R^3 = H$, $R^4 = CH_3$

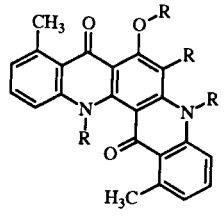
20, $R^1 = CH_3$, $R^3 = H$
21, $R^1 = H$, $R^3 = CH_3$

23

24, $R^1 = CH_3$, $R^2 = R^3 = R^4 = R^5 = H$
25, $R^2 = CH_3$, $R^1 = R^3 = R^4 = R^5 = H$,
26, $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = CH_3$
27, $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = CH_3$
28, $R^1 = R^5 = CH_3$, $R^2 = R^3 = R^4 = H$
29, $R^4 = R^5 = CH_3$, $R^1 = R^2 = R^3 = H$
30, $R^1 = R^2 = R^4 = H$, $R^3 = R^5 = CH_3$
31, $R^1 = R^2 = R^3 = R^4 = R^5 = H$

i: abs. acetone, K_2CO_3, MeI, 6 hours, reflux; ii: 47% HBr, 5 hours, reflux; iii: a) 0,1 *N* ethanolic KOH, 30 min, 60°; b) abs. DMF, K_2CO_3, KI, 2-chloro-2-methyl-3-butyne, 80°, N_2; c) abs. DMF, 130°, N_2; iv: abs. THF, NaH, MeI, reflux.

Diagram



32 R = H
33 R = CH_3

The uv spectra (methanol) were obtained on a Shimadzu photospectrometer UV-160A. The ^1H nmr and ^{13}C nmr were obtained on a Varian Gemini 200 spectrometer in dimethyl sulfoxide-d_6 and deuteriochloroform respectively, with tetramethylsilane as an internal standard. Mass spectra (70 eV) were recorded with a Varian MAT 44 S spectrometer. Merck silica gel 60 F_{254} and Merck silica gel 60 (70-230 mesh) were used for preparative thin layer chromatography and column chromatography respectively. Solvent Systems (SS): SS I: dichloromethane/methanol 95:5; SS II: dichloromethane/methanol 98:2; SS III: toluene/ethyl acetate/-formic acid 40:32:1; SS IV: toluene/ethyl formate/acetone 5:5:1; SS V: toluene/dichloromethane 1:1; SS VI: *n*-hexane/acetone 3:1.

Synthesis of 8-Methylacronycine (**24**).

1,3-Dihydroxy-8-methyl-9(10*H*)-acridinone (**2**).

Method A.

A mixture of 2-amino-6-methylbenzoic acid (10 g, 65 mmoles), phloroglucinol (8.2 g, 65 mmoles) and *p*-toluenesulfonic acid (650 mg, 3.8 mmoles) was dissolved in 40 ml of *n*-heptanol and heated to reflux with a Dean-Stark-apparatus. After 2 hours, dichloromethane was added to the cooled heptanol solution. The crude precipitate was filtered and washed successively with dichloromethane and heptane and purified by column chromatography using SS III to give 1.9 g (12%) of **2**, Rf 0.4 (SS III), mp > 320° dec; ir: ν 3335 (NH), 1647 (C=O), 1603, 1539, 1490 (C=C), 1466 (CH_3), 1255 (OH), 1180 (C-O) cm^{-1}; uv: λ max (log ϵ) 384 nm (3.645), 319 (3.626) sh, 294 (4.075), 269 (4.475), 259 (4.484), 223 (3.983); ^1H nmr: δ 2.84 (s, 3H, CH_3), 5.96 (d, J = 2.1 Hz, 1H, 4-H), 6.23 (d, J = 2.1 Hz, 1H, 2-H), 6.95 (d, J = 7.1 Hz, 1H, 7-H), 7.28 (d, J = 8.1 Hz, 1H, 5-H), 7.52 (dd, J = 7.1 and 8.1 Hz, 6-H), 10.44 (s, 1H, 3-OH), 11.60 (s, 1H, NH), 14.62 (s, 1H, 1-OH); ^{13}C nmr: δ 23.51 (CH_3), 90.08 (C-4), 95.35 (C-2), 103.96 (C-9a), 114.90 (C-5), 117.24 (C-8a), 123.78 (C-7), 132.74 (C-6), 139.69 (C-8), 142.26 (C-5a), 142.64 (C-4a), 163.79 (C-3), 163.94 (C-1), 182.74 (C-9); ms: m/z 241 (100, M^+), 212 (13, M^+ -CHO), 184 (5, 212 -CO).

Anal. Calcd. for $C_{14}H_{11}NO_3 \cdot H_2O$ (241.25): C, 64.85; H, 5.05; N, 5.40. Found: C, 64.98; H, 5.12; N, 5.63.

1-Hydroxy-3-methoxy-8,10-dimethyl-9(10*H*)-acridinone (**9**).

Method B.

A mixture of 1,3-dihydroxy-8-methyl-9(10*H*)-acridinone (**2**) (1.7 g, 7 mmoles) and methyl iodide (5.2 g, 37 mmoles) in acetone (75 ml) in the presence of potassium carbonate (8 g) was heated under reflux for 6 hours. After removing the solvent and the excess of methyl iodide, the reaction mixture was washed with water. Recrystallization from methanol/water gave yellow needles (1.7 g, yield 89%), mp 165-167°, Rf 0.58 (SS III); ir: ν 3400 (br, OH), 2960 (C-H), 1636 (C=O), 1593, 1556, 1503 (C=C), 1466 (CH_3), 1258 (O-CH_3), 1227, 1162 (C-O) cm^{-1}; ^1H nmr: δ 2.86 (s, 3H, CH_3), 3.79 (s, 3H, NCH_3), 3.90 (s, 3H, OCH_3), 6.21 (d, J = 2.1 Hz, 1H, 4-H), 6.48 (d, J = 2.1 Hz, 1H, 2-H), 7.08 (m, 1H, 6-H), 7.63 (m, 2H, 5-H and 7-H), 15.19 (s, 1H, OH); ^{13}C nmr: δ 24.37 (CH_3), 35.28 (NCH_3), 55.61 (OCH_3), 89.5 (C-4), 94.25 (C-2), 105.22 (C-9a), 114.12 (C-5), 118.65 (C-8a), 124.81 (C-7), 133.39 (C-6), 140.73 (C-8), 143.84 (C-10a), 144.15 (C-4a), 164.87 (C-3), 165.35 (C-1), 182.60 (C-9); ms: m/z 269 (100, M^+), 240 (54, M^+ -CHO), 225 (9, 240 -CH_3).

Anal. Calcd. for $C_{16}H_{15}NO_3 \cdot 1/2H_2O$ (269.30): C, 69.05; H, 5.79; N, 5.03. Found: C, 68.71; H, 5.48; N, 4.88.

1,3-Dihydroxy-8,10-dimethyl-9(10*H*)-acridinone (**12**).

Method C.

1-Hydroxy-3-methoxy-8,10-dimethyl-9(10*H*)-acridinone (**9**) (1.4 g, 5 mmoles) was dissolved in 46% hydrobromic acid (100 ml) and heated under reflux for 5 hours. After cooling overnight at 0°, the hydrobromide was filtered and hydrolyzed by stirring for 2 hours in distilled water. Recrystallization from ethanol/water gave brown needles (950 mg, yield 75%), Rf 0.44 (SS III), mp 270-272°; ir: ν 3375 (br, OH), 2940 (C-H), 1629 (C=O), 1599, 1556, 1506 (C=C), 1250, 1153 (C-OH) cm^{-1}; ^1H nmr: δ 2.85 (s, 3H, CH_3), 3.72 (s, 3H, NCH_3), 6.07 (s, 1H, 4-H), 6.38 (s, 1H, 2-H), 7.03 (d, J = 9 Hz, 1H, 7-H), 7.59 (m, 2H, 5-H and 6-H), 10.56 (s, 1H, 3-OH), 15.17 (s, 1H, 1-OH); ^{13}C nmr: δ 24.27 (CH_3), 34.97 (NCH_3), 90.50 (C-4), 95.64 (C-2), 104.53 (C-9a), 113.86 (C-5), 118.57 (C-8a), 124.58 (C-7), 133.09 (C-6), 140.61 (C-8), 143.68 (C-5a), 144.39 (C-4a), 164.25 (C-3), 164.95 (C-1), 182.27 (C-9); ms: m/z 255 (100, M^+), 240 (7, M^+ -CH_3), 226 (11, M^+ -CHO), 198 (7, 226 -CO).

Anal. Calcd. for $C_{15}H_{13}NO_3 \cdot H_2O$ (255.28): C, 65.93; H, 5.53; N, 5.13. Found: C, 65.75; H, 5.46; N, 4.97.

Potassium Salt of 1,3-Dihydroxy-8,10-dimethyl-9(10*H*)-acridinone.

Method D.

A solution of **12** (640 mg, 2.5 mmoles) in 0.1 *N* ethanolic potassium hydroxide (25 ml) was heated 30 minutes at 60°. After removing ethanol, the dark brown powder was dried overnight *in vacuo*. The crude potassium salt was used directly in the following step.

Synthesis of 8-Methylnoracronycine (**16**) and 7-Methylisonoracronycine (**20**).

Method E.

A solution of the potassium salt of **12** (733 mg, 2.5 mmoles) and 2-chloro-2-methyl-3-butyne (455 mg, 4.5 mmoles) in the presence of dried potassium carbonate (500 mg) and potassium iodide (725 mg) in absolute DMF (15 ml) was heated at 80° for 6 hours under a nitrogen atmosphere. After the removal of the solvent under reduced pressure, the thick reaction mixture was treated with chloroform and washed with 2% sodium hydroxide solution and water. The crude product was dried overnight and purified by column chromatography to give **16** and **20**.

8-Methylnoracronycine (**16**).

This compound was obtained in 14% (109 mg) yield, mp 182-184°, Rf 0.41 (SS V); ir: ν 2955 (CH), 1613 (C=O), 1580, 1530, 1489 (C=C, arom), 1460 (CH_3), 1256 (C-O-C), 1178, 1140 (C-OH) cm^{-1}; uv: λ max (log ϵ) 406 nm (3.847), 315 (4.412), 274 (4.533), 294 (4.514); ^1H nmr: δ 1.51 (s, 6H, 2 x CH_3), 2.91 (s, 3H, CH_3), 3.84 (s, 3H, NCH_3), 5.84 (d, J = 7.6 Hz, 1H, 2-H), 6.22 (s, 1H, 5-H), 6.51 (d, J = 7.6 Hz, 1H, 1-H), 7.02 (d, J = 7.3 Hz, 1H, 9-H), 7.26 (d, J = 8.4 Hz, 1H, 11-H), 7.52 (dd, J = 7.3 and 8.4 Hz, 1H, 10-H), 14.96 (s, 1H, OH); ^{13}C nmr: δ 24.06 (CH_3), 26.95 (2 x CH_3), 44.49 (NCH_3), 76.23 (C-3), 92.61 (C-5), 97.76 (C-12b), 113.21 (C-6a), 114.35 (C-11), 120.89 (C-9), 121.45 (C-7a), 122.94 (C-2), 125.32 (C-1), 125.43 (C-10), 132.82 (C-8), 141.81 (C-11a), 146.65 (C-12a), 160.99 (C-6), 165.21 (C-4a), 183.83 (C-7); ms: m/z 321 (27, M^+), 306 (80, M^+ -CH_3), 291 (25, 306 -CH_3), 262 (7, 291 -CHO), 234 (5, 262 -CO); hrms: Calcd. for $C_{20}H_{19}NO_3$: 321.136494. Found: 321.137056.

7-Methylisonoracronycine (**12**).

This compound was obtained in 2.6% (21 mg) yield, mp 141-143°, Rf 0.54 (SS V); ir: ν 3500 (OH), 2925 (CH), 1637 (C=O), 1592, 1551, 1496 (C=C), 1456 (CH_3), 1253 (OH), 1146, 1108 (C-OH) cm^{-1}; uv: λ max (log ϵ) 400 (3.823), 324 (4.109) sh, 302 (4.674), 264 (3.859); ^1H nmr: δ 1.40 (s, 6H, 2 x CH_3), 2.87 (s, 3H, CH_3), 3.64 (s, 3H, NCH_3), 5.48 (d, J = 10 Hz, 1H, 3-H), 6.14 (s, 1H, 12-H), 6.71 (d, J = 10 Hz, 1H, 4-H), 6.92 (d, J = 7.4 Hz, 1H, 10-H), 7.19 (d, J = 8.6 Hz, 1H, 8-H), 7.42 (dd, J = 7.4 and 8.6 Hz, 1H, 9-H), 15.45 (s, 1H, OH); ^{13}C nmr: δ 24.77 (CH_3), 28.50 (2 x CH_3), 35.08 (NCH_3), 77.83 (C-2), 90.92 (C-12), 93.15 (C-4a), 102.48 (C-5a), 106.14 (C-10), 112.82 (C-8), 116.24 (C-6a), 125.08 (C-3), 125.51 (C-4), 126.39 (C-9), 132.84 (C-7), 142.45 (C-11a), 144.07 (C-10a), 159.66 (C-5), 160.33 (C-12a), 183.52 (C-6); ms:

m/z 321 (28, M$^+$), 306 (100, M$^+$ -CH_3), 291 (20, 306 -CH_3), 262 (5, 291 -CHO), 234 (4, 262 -CO); hrms: Calcd. for $C_{20}H_{19}NO_3$: 321.136494. Found: 321.137065.

Synthesis of 8-Methylacronycine (**24**) and 5,8-Dimethylacronycine (**28**).

Method F.

A solution of **16** (90 mg, 0.3 mmole) in absolute THF (15 ml) in the presence of sodium hydride (110 mg, 4.5 mmoles) and methyl iodide (410 mg, 4 mmoles) was heated for 2 hours under reflux. After cooling the excess sodium hydride was destroyed with methanol, the solvent was removed and product mixture dried *in vacuo*. The residue was separated by column and preparative thin layer chromatography (SS III).

8-Methylacronycine (**24**).

This compound was obtained in 57% (53 mg) yield, mp 198-200°, Rf 0.39 (SS I); ir: ν 2970 (CH), 1638 (C=O), 1616, 1589, 1488 (C=C), 1463 (CH_3), 1391 (CH_3), 1233, 1063 (C-O-C) cm^{-1}; uv: λ max (log ϵ) 407 nm (3.809), 315 (4.398), 294 (4.529); ^{1}H nmr: δ 1.53 (s, 6H, 2 x CH_3), 2.89 (s, 3H, CH_3), 3.78 (NCH_3), 3.97 (s, 3H, OCH_3), 5.50 (d, J = 9.6 Hz, 1H, 2-H), 6.30 (s, 1H, 5-H), 6.54 (d, J = 9.6 Hz, 1H, 1-H), 6.99 (d, J = 7.3 Hz, 1H, 9-H), 7.21 (d, J = 8.4 Hz, 1H, 11-H), 7.44 (dd, J = 7.3 and 8.4 Hz, 1H, 10-H); ^{13}C nmr: δ 23.39 (CH_3), 26.90 (2 x CH_3), 44.82 (NCH_3), 56.27 (OCH_3), 76.21 (C-3), 94.31 (C-5), 102.84 (C-12b), 114.12 (C-6a), 115.04 (C-11), 121.65 (C-2), 123.21 (C-9), 124.72 (C-7a), 125.25 (C-1), 131.37 (C-10), 141.19 (C-8), 146.01 (C-11a), 146.12 (C-12a), 158.64 (C-6), 162.37 (C-4a), 179.92 (C-7); ms: m/z 335 (63, M$^+$), 320 (100, M$^+$ -CH_3), 306 (16, M$^+$ -CHO), 305 (12, 320 -CH_3), 290 (19, 305 -CH_3), 276 (33, 305 -CHO), 275 (13, 290 -CH_3), 262 (12, 290 -CO); hrms: Calcd. for $C_{21}H_{21}NO_3$: 335.152144. Found: 335.151258.

5,8-Dimethylacronycine (**28**).

This compound was obtained in 17% (16 mg) yield, mp 75-77° (yellow resinous substance), Rf 0.59 (SS III); ir: ν 2965 (CH), 1621 (C=O), 1602, 1581, 1491 (C=C), 1259, 1021 (C-O-C) cm^{-1}; uv: λ max (log ϵ) 405 nm (3.322), 269 (3.971), 210 (3.924); ^{1}H nmr: δ 1.46 (s, 6H, 2 x CH_3), 2.11 (s, 3H, 5-CH_3), 2.80 (s, 3H, 8-CH_3), 3.69 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 5.48 (d, J = 9.6 Hz, 1H, 2-H), 6.49 (d, J = 9.6 Hz, 1H, 1-H), 6.91 (d, J = 7.3 Hz, 1H, 9-H), 7.13 (d, J = 8.4 Hz, 1H, 11-H), 7.36 (dd, J = 7.3 and 8.4 Hz, 1H, 10-H); ^{13}C nmr: δ 22.00 (8-CH_3), 26.03 (2 x CH_3), 28.71 (5-CH_3), 43.67 (N-CH_3), 60.25 (O-CH_3), 74.88 (C-3), 100.15 (C-5), 104.96 (C-12b), 113.10 (C-6a), 120.76 (C-11), 123.37 (C-9), 123.54 (C-7a), 123.70 (C-2), 123.85 (C-1), 130.78 (C-10), 139.78 (C-8), 142.45 (C-12a), 145.32 (C-11a), 155.91 (C-6), 158.40 (C-4a), 178.85 (C-7); ms: m/z 349 (48, M$^+$), 334 (100, M$^+$ -CH_3), 320 (16, M$^+$ -CHO), 304 (25, 334 -CH_2O), 290 (24, 320 -CH_2O), 276 (10, 304 -CO); hrms: Calcd. for $C_{22}H_{23}NO_3$: 349.167794. Found: 349.168325.

7-Hydroxy-1,9-dimethyldibenzo[*b,j*][1,7]phenanthroline-8,14-(5*H*,13*H*)-dione (**32**).

This compound was obtained in 18% (2.7 g) yield, mp >330° (subl); ir: ν 3300 (NH), 2960 (CH), 1596, 1530, 1493 (C=C), 1456, 1367 (CH_3), 1297 (OH), 1206, 1166 (C-O) cm^{-1}; uv: λ max (log ϵ) 391 nm (4.125), 372 (4.039), 327 (4.443), 311.5 (4.011), 302 (4.091); ^{1}H nmr: δ 2.93 (s, 3H, 9-CH_3), 3.03 (s, 3H, 1-CH_3), 7.30 (m, 7H, 2-H, 3-H, 4-H, 6-H, 10-H, 11-H and 12-H); ^{13}C nmr: δ 25.55 (9-CH_3), 26.31 (1-CH_3), 114.95 (C-6), 118.88 (C-7a), 119.81 (C-13b), 120.28 (C-4, C-12), 131.81 (C-2, C-10), 133.02 (C-14a), 137.75 (C-8a), 143.47 (C-3, C-11), 143.99 (C-1, C-9), 144.8 (C-4a, C-12a), 164.52 (C-13a), 165.35 (C-5a), 165.72 (C-7), 174.44 (C-14), 185.18 (C-8); ms: m/z 356 (100, M$^+$), 327 (6, M$^+$ -CHO), 299 (5, 327 -CO).

Anal. Calcd. for $C_{22}H_{16}N_2O_3 \cdot 1/3H_2O$ (356.38): C, 73.05; H, 4.64; N, 7.74. Found: C, 73.25; H, 4.60; N, 7.54.

7-Methoxy-1,5,6,9,13-pentamethyldibenzo[*b,j*][1,7]phenanthroline-8,14(5*H*,13*H*)-dione (**33**).

To a solution of **32** (0.5 g, 1.4 mmoles) in absolute dimethylformamide (50 ml) methyl iodide (2.5 ml) and dried silver oxide (3 g) was added and the mixture was stirred at room temperature for 24 hours. The excess methyl iodide was destroyed by adding methanol to the reaction mixture. The solvent was removed *in vacuo* and the product mixture was separated by column chromatography to afford **33** (55 mg, 9.5%), Rf 0.5 (SS IV), mp 247-259°; ir: ν 2955 (CH), 1617 (C=O), 1591, 1539, 1476 (C=C), 1392 (CH_3), 1250 (C-O-C), 1184, 1149 (C-O), 1080 (C-O-C) cm^{-1}; uv: λ max (log ϵ) 413 nm (4.177), 330 (4.478), 289 sh (4.321), 248 (4.670), 215 (4.386); ^{1}H nmr: δ 2.44 (s, 3H, 6-CH_3), 2.92 (s, 3H, 9-CH_3), 2.94 (s, 3H, 1-CH_3), 3.70 (s, 3H, 5-NCH_3), 3.79 (s, 3H, 13-NCH_3), 4.00 (s, 3H, OCH_3), 7.22 (m, 6H, 2-H, 3-H, 4-H, 10-H, 11-H and 12-H); ^{13}C nmr: δ 15.41 (6-CH_3), 22.74 (9-CH_3), 23.28 (1-CH_3), 43.96 (5-NCH_3), 44.33 (13-NCH_3), 61.23 (OCH_3), 111.97 (C-7a), 112.15 (C-6), 114.26 (C-4), 114.44 (C-13b), 115.21 (C-12), 115.59 (C-2), 116.08 (C-10), 125.53 (C-14a), 126.49 (C-8a), 131.64 (C-11), 131.86 (C-3), 139.89 (C-8), 140.54 (C-2), 144.98 (C-12a), 145.19 (C-13a), 146.03 (C-4a), 151.93 (C-5a), 163.14 (C-7), 178.90 (C-14), 179.79 (C-8); ms: m/z 412 (31, M$^+$), 397 (100, M$^+$ -CH_3), 383 (20, M$^+$ -CHO), 365 (26), 351 (21), 206 (16), 190 (44), 169 (30).

Anal. Calcd. for $C_{26}H_{24}N_2O_3$ (412.49): C, 75.70; H, 5.86; N, 6.79. Found: C, 75.36; H, 5.77; N, 6.57.

Synthesis to 9-Methylacronycine (**25**).

1,3-Dihydroxy-7-methyl-9(10*H*)-acridinone (**3**).

To 10 g (65 mmoles) of 2-amino-5-methylbenzoic acid 8.2 g (18.4 mmoles) of phloroglucinol was added under the same conditions as in method A. The reaction product was separated by column chromatography. Recrystallization from methanol gave yellow needles (7.4 g, 47%), Rf 0.3, mp 326-328°; ir: ν 3395 (N-H), 1646 (C=O), 1593, 1528 (C=C), 1480 (CH_3), 1240 (OH), 1155 (C-O) cm^{-1}; uv: λ max (log ϵ) 215 nm (4.404), 271 (4.549), 297 (3.884), 327 (3.883), 399 (3.846); ^{1}H nmr: δ 2.41 (s, 3H, CH_3), 6.03 (d, J = 2 Hz, 1H, 4-H), 6.31 (d, J = 2 Hz, 1H, 2-H), 7.39 (d, J = 8.5 Hz, 1H, 5-H), 7.54 (dd, J = 8.5 and 2 Hz, 1H, 6-H), 7.95 (br s, 1H, 8-H), 10.53 (br s, 1H, N-H), 11.73 (br s, 1H, 3-OH), 14.38 (s, 1H, 1-OH); ^{13}C nmr: δ 20.51 (CH_3), 90.63 (C-4), 95.39 (C-2), 103.28 (C-9a), 116.73 (C-5), 118.69 (C-8a), 124.05 (C-7), 130.24 (C-8), 135.08 (C-6), 138.85 (C-4a), 143.21 (C-5a), 163.69 (C-1), 164.03 (C-3), 179.77 (C-9); ms: m/z 241 (100, M$^+$), 212 (14, M$^+$ -CHO), 184 (10, 212 -CO); hrms: Calcd. for $C_{14}H_{11}NO_3$: 241.073894. Found: 241.074405.

1,3-Dimethoxy-7,10-dimethyl-9(10*H*)-acridinone (**7**).

Under the conditions of method B compound **3** (3.7 g, 15 mmoles) were methylated. The recrystallization from methanol gave yellow needles (3.4 g, 78%), Rf 0.41 (SS II), mp 160-162°; ir:

ν 2950 (CH), 1625 (C=O), 1583, 1506 (C=C), 1235, 1070 (C-O-C) cm^{-1}; uv: λ max (log ϵ) 272 nm (3.700), 316 (3.221) sh, 325 (3.374), 399 (3.403); ^1H nmr: δ 2.42 (s, 3H, CH_3), 3.45 (s, 3H, 3-OCH_3), 3.83 (s, 3H, N-CH_3), 3.89 (s, 3H, 1-OCH_3), 6.23 (d, J = 1.9 Hz, 1H, 4-H), 6.54 (d, J = 1.9 Hz, 1H, 2-H), 7.70 (dd, J = 8.8 and 2.0 Hz, 1H, 6-H), 7.76 (d, J = 8.8 Hz, 1H, 5-H), 8.06 (br s, 1H, 8-H); ^{13}C nmr: δ 20.08 (CH_3), 34.19 (NCH_3), 55.61 (3-OCH_3), 55.98 (1-OCH_3), 89.55 (C-4), 94.18 (C-2), 104.30 (C-9a), 115.92 (C-5), 119.77 (C-8a), 124.65 (C-8), 130.78 (C-7), 135.74 (C-6), 140.25 (C-4a), 144.32 (C-5a), 164.54 (C-1), 165.50 (C-3), 179.47 (C-9); ms: m/z 283 (100, M^+), 268 (64, $M^+ - CH_3$), 254 (21, 268 $-CH_3$), 240 (62, 268 -CO), 225 (18, 240 $-CH_3$), 197 (15, 225 -CO), 168 (10, 197 -CHO); hrms: Calcd. for $C_{17}H_{17}NO_3$: 283.120844. Found: 283.119150.

1,3-Dihydroxy-7,10-dimethyl-9(10*H*)-acridinone (**13**).

Compound **7** (2.5 g, 9 mmoles) was treated with 47% hydrobromic acid under the conditions of method C. Recrystallization from methanol/water gave pale yellow needles (1.8 g, 79%), Rf 0.65 (SS II), mp 294-296°; ir: ν 3150 (br, OH), 1623 (C=O), 1588, 1539, 1508 (C=C), 1275, 1159 (C-O-C) cm^{-1}; uv: λ max (log ϵ) 215 nm (4.404), 271 (4.549), 297 (4.883), 327 (3.883), 399 (3.846); ^1H nmr: δ 2.40 (s, 3H, CH_3), 3.73 (s, 3H, N-CH_3), 6.08 (d, J = 2 Hz, 1H, 4-H), 6.35 (d, J = 2 Hz, 1H, 2-H), 7.54 (dd, J = 8.8 and 1.9 Hz, 1H, 6-H), 7.62 (d, J = 8.8 Hz, H, 5-H), 8.01 (s, 1H, 8-H); ^{13}C nmr: δ 20.16 (CH_3), 33.87 (NCH_3), 90.62 (C-4), 95.60 (C-2), 103.70 (C-9a), 115.44 (C-5), 119.83 (C-8a), 124.75 (C-8), 130.33 (C-7), 135.12 (C-6), 140.06 (C-4a), 144.58 (C-5a), 164.57 (C-1), 164.73 (C-3), 179.17 (C-9); ms: m/z 255 (100, M^+), 240 (12, $M^+ - CH_3$), 227 (13, M^+ -CO), 212 (18, 240 -CO), 198 (10, 227 -CHO); hrms: Calcd. for $C_{15}H_{13}NO_3$: 255.089544. Found: 255.089975.

9-Methylnoracronycine (**17**).

Under the conditions of method E the potassium salt of **13** (150 mg) was treated. The separation by preparative thin layer chromatography gave the pure product **17** (50 mg, 31%), Rf 0.66 (SS II), mp 226-228°; ir: ν 3340 (br, OH), 2930 (CH), 1624 (C=O), 1592, 1542, 1450 (C=C), 1175, 1040 (C-O-C) cm^{-1}; uv: λ max (log ϵ) 296 nm (4.515), 313 (4.126), 415 (3.658); ^1H nmr: δ 1.52 (s, 6H, 2 x CH_3), 2.43 (s, 3H, CH_3), 3.86 (3H, N-CH_3), 5.47 (d, J = 9.6 Hz, 1H, 2-H), 6.22 (s, 1H, 5-H), 6.53 (d, J = 9.6 Hz, 1H, 1-H), 7.30 (d, J = 8.7 Hz, 1H, 11-H), 7.49 (dd, J = 8.7 and 2.0 Hz, 1H, 10-H), 8.10 (br s, 1H, 8-H), 14.79 (s, 1H, 6-OH); ^{13}C nmr: δ 20.96 (CH_3), 26.89 (3-$(CH_3)_2$), 43.55 (NCH_3), 76.32 (C-3), 97.61 (C-5), 100.74 (C-12b), 106.93 (C-6a), 116.08 (C-11), 121.65 (C-8), 121.74 (C-7a), 122.66 (C-2), 125.55 (C-1), 131.82 (C-9), 135.30 (C-10), 142.99 (C-12a), 144.34 (C-11a), 161.48 (C-6), 165.32 (C-4a), 180.99 (C-7); ms: m/z 321 (36, M^+), 306 (100, $M^+ - CH_3$), 291 (12, $M^+ - CH_2O$); hrms: Calcd. for $C_{20}H_{19}NO_3$: 321.136494. Found: 321.136122.

9-Methylacronycine (**25**).

Using the same conditions of method F 50 mg (0.16 mmole) of **17** was treated. The crude product was separated by preparative thin layer chromatography (SS III) to give **25** (20 mg, 33%), Rf 0.76 (SS II), mp 211-213°; ir: ν 3055 (CH), 1639 (C=O), 1581, 1518, 1498 (C=C), 1180, 1045 (C-O-C) cm^{-1}; uv: λ max (log ϵ) 280 nm (4.045), 295 (4.423), 329 (4.111), 399 (3.827); ^1H nmr: δ 1.53 (s, 6H, 2 x CH_3), 2.43 (s, 3H, CH_3), 3.80 (s, 3H, N-CH_3), 3.97 (s, 3H, O-CH_3), 5.47 (d, J = 9.5 Hz, 1H, 2-H), 6.30 (s, 1H, 5-H), 6.53 (d, J = 9.5 Hz, 1H, 1-H), 7.25 (d, J = 8.5 Hz, 1H, 11-H), 7.43 (dd, J = 8.5 and 2.1 Hz, 1H, 10-H), 8.17 (br s, 1H, 8-H); ^{13}C nmr: δ 20.78 (CH_3), 26.84 (2 x CH_3), 44.22 (NCH_3), 56.29 (OCH_3), 76.29 (C-3), 94.11 (C-5), 102.88 (C-12b), 110.53 (C-6a), 115.85 (C-11), 121.96 (C-8), 122.76 (C-2), 125.34 (C-7a), 126.67 (C-1), 131.44 (C-9), 133.86 (C-10), 142.61 (C-12a), 146.78 (C-11a), 159.15 (C-6), 163.08 (C-4a), 177.30 (C-7); ms: m/z 335 (45, M^+), 320 (100, $M^+ - CH_3$), 306 (40, M^+ -CHO), 290 (21, 320 $-CH_2O$), 262 (11, 290 -CO); hrms: Calcd. for $C_{21}H_{21}NO_3$: 335.15214. Found: 335.15125.

Synthesis to 10-Methylacronycine (**26**).

The preparation of 2-amino-4-methylbenzoic acid followed the Sandmeyer reaction described in [12,13].

1,3-Dihydroxy-6-methyl-9(10*H*)-acridinone (**4**).

2-Amino-4-methylbenzoic acid (700 mg, 4.6 mmoles) was treated with 580 mg (4.6 mmoles) of phloroglucinol under the conditions of method A. The crude product was purified by column chromatography to yield **4** (380 mg, 34%), mp >310° dec; Rf 0.38 (SS IV); ir: ν 3280 (NH), 3170 (OH), 3060 (CH), 1647 (C=O), 1601, 1539, 1495 (C=C), 1461 (CH_3), 1249 (O-H), 1159 (C-O) cm^{-1}; uv: λ max (log ϵ) 375 nm (3.081), 323 (3.416), 263 (3.811); ^1H nmr: δ 2.45 (s, 3H, CH_3), 5.99 (d, J = 2.1 Hz, 1H, 4-H), 6.28 (d, J = 2.1 Hz, 1H, 2-H), 7.07 (dd, J = 8.2 and 1 Hz, 1H, 7-H), 7.23 (s, 1H, 5-H), 8.04 (d, J = 8.2 Hz, 1H, 8-H), 10.5 (s, 1H, 3-OH), 11.65 (s, 1H, NH), 14.31 (s, 1H, 1-OH); ^{13}C nmr: δ 21.51 (CH_3), 90.80 (C-4), 95.41 (C-2), 103.07 (C-9a), 115.90 (C-5), 116.78 (C-8a), 122.88 (C-7), 124.93 (C-8), 140.88 (C-6), 143.23 (C-10a), 144.12 (C-4a), 163.64 (C-3), 163.98 (C-1), 179.73 (C-9); ms: m/z 241 (100, M^+), 212 (15, M^+ -CHO), 184 (20, 212 -CO).

Anal. Calcd. for $C_{14}H_{11}NO_3$ (241.25): C, 69.70; H, 4.60; N, 5.81. Found: C, 69.70; H, 4.72; N, 6.11.

1,3-Dimethoxy-6,10-dimethyl-9(10*H*)-acridinone (**6**).

1,3-Dihydroxy-6-methyl-9(10*H*)-acridinone (**4**) (370 mg, 1.5 mmoles) was methylated under the conditions of method B. Separation of the mixture gave 1-hydroxy-3-methoxy-4,6,10-trimethyl-9(10*H*)-acridinone (**8**) and 1,3-dimethoxy-6,10-dimethyl-9(10*H*)-acridinone (**6**) (310 mg, 72%), mp 88-89° (dichloromethane/petroleum ether), Rf 0.29 (SS IV); ir: ν 2960 (CH), 1602 (C=O), 1550, 1506 (C=C), 1466 (CH_3), 1247, 1099 (C-O-C) cm^{-1}; uv: λ max (log ϵ) 377 nm (3.845), 318 (3.815) sh, 289 (4.079), 266 (4.715), 223 (4.234) sh, 211 (4.284); ^1H nmr: δ 2.43 (s, 3H, CH_3), 3.70 (s, 3H, 3-OCH_3), 3.84 (s, 3H, NCH_3), 3.91 (s, 3H, 1-OCH_3), 6.33 (d, J = 1.8 Hz, 1H, 2-H), 6.52 (d, J = 1.8 Hz, 1H, 4-H), 7.03 (d, J = 8 Hz, 1H, 7-H), 7.39 (s, 1H, 5-H), 8.07 (d, J = 8 Hz, 1H, 8-H); ^{13}C nmr: δ 21.63 (CH_3), 34.52 (NCH_3), 55.37 (3-OCH_3), 55.69 (1-OCH_3), 90.73 (C-2), 92.33 (C-4), 107.32 (C-9a), 114.95 (C-5), 121.69 (C-7), 122.21 (C-8a), 126.24 (C-8), 141.53 (C-6), 142.90 (C-10a), 146.28 (C-4a), 162.34 (C-1), 163.39 (C-3), 174.54 (C-9); ms: m/z 283 (100, M^+), 268 (24, $M^+ - CH_3$), 240 (10, 268 -CO), 225 (10, 240 $-CH_3$), 210 (4, 225 $-CH_3$), 197 (5, 225 -CO), 182 (3, 210 -CO), 168 (5, 197 -CHO), 154 (10, 182 -CO).

Anal. Calcd. for $C_{17}H_{17}NO_3$ (283.33): C, 72.07; H, 6.05; N, 4.94. Found: C, 72.23; H, 6.33; N, 4.94.

1-Hydroxy-3-methoxy-4,6,10-trimethyl-9(10*H*)-acridinone (**8**).

This compound was obtained in 2.5% yield (10 mg), mp 153-156°, Rf 0.29 (SS VI); ir: ν 3425 (br, OH), 2915 (CH), 1623 (C=O), 1585, 1546 (C=C), 1449 (CH_3), 1382 (OH), 1297 (C-O-C), 1140 (C-OH) cm^{-1}; uv: λ max (log ϵ) 406 nm (3.901), 330 (4.089), 297

(4.168) sh, 272 (4.805), 252 (4.619), 211 (4.492); ^{1}H nmr: δ 2.24 (s, 3H, 4-CH_3), 2.47 (s, 3H, 6-CH_3), 3.78 (s, 3H, NCH_3), 3.88 (s, 3H, OCH_3), 6.42 (s, 1H, 2-H), 7.12 (d, J = 8 Hz, 1H, 7-H), 7.44 (s, 1H, 5-H), 8.04 (d, J = 8 Hz, 1H, 8-H), 14.69 (s, 1H, OH); ^{13}C nmr: δ 14.38 (4-CH_3), 21.85 (6-CH_3), 43.76 (NCH_3), 56.12 (OCH_3), 92.94 (C-2), 102.27 (C-4), 107.30 (C-9a), 116.97 (C-5), 118.50 (C-7), 123.10 (C-8a), 125.00 (C-8), 145.10 (C-6), 146.12 (C-10a), 146.60 (C-4a), 162.48 (C-1), 164.45 (C-3), 180.69 (C-9); ms: m/z 283 (100, M^+), 266 (30, M^+ -OH), 254 (100, M^+ -CHO), 237 (24, 266 -CHO), 224 (13), 210 (25, 237 -HCN), 197 (11), 182 (42, 210 -CO), 167 (24, 182 -CH_2), 154 (11, 182 -CO).

Anal. Calcd. for $C_{17}H_{17}NO_3 \cdot 1/2H_2O$ (292.33): C, 69.84; H, 6.21; N, 4.79. Found: C, 69.80; H, 6.09; N, 4.68.

1,3-Dihydroxy-6,10-dimethyl-9(10*H*)-acridinone (**14**).

1,3-Dimethoxy-6,10-dimethyl-9(10*H*)-acridinone (**6**) (250 mg, 0.9 mmole) was treated with 47% hydrobromic acid under the conditions of method C. The crystallization of the crude product from dimethyl sulfoxide/water gave 150 mg (67%) of **14**, mp 265-267° dec, Rf 0.42 (SS IV); ir: ν 3325 (br, OH), 1623 (C=O), 1595, 1520, 1495 (C=C), 1454 (CH_3), 1313 (OH), 1272 (C-O), 1162 (C-OH) cm^{-1}; uv: λ max (log ε) 392 nm (3.846), 326 (3.955), 268 (4.748), 234 (4.553), 212 (4.307); ^{1}H nmr: δ 2.47 (s, 3H, CH_3), 3.72 (s, 3H, NCH_3), 6.09 (d, J = 1.6 Hz, 1H, 2-H), 6.37 (d, J = 1.6 Hz, 1H, 4-H), 7.06 (d, J = 8.1 Hz, 1H, 7-H), 7.53 (s, 1H, 5-H), 8.10 (d, J = 8.1 Hz, 1H, 8-H), 10.63 (s, 1H, 3-OH), 14.93 (s, 1H, 1-OH); ^{13}C nmr: δ 21.87 (CH_3), 33.85 (NCH_3), 90.95 (C-2), 95.67 (C-4), 103.45 (C-9a), 115.25 (C-5), 117.81 (C-7), 122.79 (C-8a), 125.37 (C-8), 142.01 (C-6), 144.70 (C-10a), 144.80 (C-4a), 164.51 (C-1), 164.72 (C-3), 179.10 (C-9); ms: m/z 255 (100, M^+), 240 (5, M^+ -CH_3), 227 (9, M^+ -CO), 212 (12, 240 -CO), 198 (8, 227 -CHO), 184 (3, 212 -CO).

Anal. Calcd. for $C_{15}H_{13}NO_3 \cdot 1/2H_2O$ (255.27): C, 68.17; H, 5.34; N, 5.32. Found: C, 68.40; H, 5.55; N, 5.68.

10-Methylnoracronycine (**18**).

The potassium salt of **14** (150 mg, 0.5 mmole), formed under the conditions of method D, came to reaction following the conditions of method E. The isomer mixture was separated by preparative thin layer chromatography (5 x chloroform) to give 70 mg (43%) of **18**, mp 171-172°, Rf 0.73 (SS IV); ir: ν 3480 (br, OH), 2960 (CH), 1619 (C=O), 1587, 1542, 1478 (C=C), 1454 (CH_3), 1265 (OH), 1170, 1138 (C-O) cm^{-1}; uv: λ max (log ε) 414 nm (3.572), 291 (4.421) sh, 284 (4.555), 211 (4.734); ^{1}H nmr: δ 1.52 (s, 6H, 2 x CH_3), 2.51 (s, 3H, CH_3), 3.86 (s, 3H, NCH_3), 5.49 (d, J = 9.6 Hz, 1H, 2-H), 6.23 (s, 1H, 5-H), 6.53 (d, J = 9.6 Hz, 1H, 1-H), 7.07 (dd, J = 8.2 and 1 Hz, 1H, 9-H), 7.26 (s, 1H, 11-H), 8.19 (d, J = 8.2 Hz, 1H, 8-H), 14.79 (s, 1H, OH); ^{13}C nmr: δ 22.45 (CH_3), 26.90 (2 x CH_3), 43.65 (NCH_3), 76.27 (C-3), 92.71 (C-5), 97.76 (C-12b), 100.94 (C-6a), 114.81 (C-11), 116.04 (C-9), 119.83 (C-7a), 121.63 (C-2), 122.80 (C-8), 123.65 (C-1), 126.07 (C-10), 145.02 (C-11a), 161.39 (C-6), 165.28 (C-4a), 180.92 (C-7); ms: m/z 321 (43, M^+), 306 (100, M^+ -CH_3), 291 (32, M^+ -CH_2O), 278 (4, 306 -CO), 262 (4, 291 -CHO); hrms: Calcd. for $C_{20}H_{19}NO_3$: 321.136494. Found: 321.137368.

9-Methylisonoracronycine (**21**).

This compound was obtained in a yield of 28 mg (17%), mp sublimation >200°, Rf 0.73 (SS IV); ir: ν 3435 (br, OH), 2960 (CH), 1625 (C=O), 1595, 1545, 1490 (C=C), 1265 (OH), 1140 (C-O) cm^{-1}; uv: λ max (log ε) 404 nm (3.724), 302 (4.721), 293 (4.662) sh, 254 (4.371), 217 (4.243), 207 (4.245); ^{1}H nmr: δ 1.48 (s, 6H, 2 x CH_3), 2.50 (s, 3H, CH_3), 3.72 (s, 3H, NCH_3), 5.57 (d, J = 10 Hz, 1H, 3-H), 6.25 (s, 1H, 12-H), 6.77 (d, J = 10 Hz, 1H, 4-H), 7.05 (dd, J = 8.2 and 0.8 Hz, 1H, 8-H), 7.20 (s, 1H, 10-H), 8.26 (d, J = 8.2 Hz, 1H, 7-H), 15.20 (s, 1H, OH); ^{13}C nmr: δ 22.56 (CH_3), 28.47 (2 x CH_3), 33.92 (NCH_3), 77.88 (C-2), 91.33 (C-12), 93.25 (C-4a), 102.48 (C-5a), 114.42 (C-10), 115.97 (C-8), 118.94 (C-6a), 123.14 (C-3), 126.51 (C-4), 126.59 (C-7), 142.22 (C-9), 144.26 (C-11a), 144.95 (C-10a), 159.92 (C-5), 165.83 (C-12a), 180.42 (C-6); ms: m/z 321 (39, M^+), 306 (100, M^+ -CH_3), 291 (15, 306 -CH_3), 262 (4, 291 -CHO), 234 (3, 262 -CO); hrms: Calcd. for $C_{20}H_{19}NO_3$: 321.136494. Found: 321.137368.

10-Methylacronycine (**26**).

To a solution of **18** (70 mg, 0.2 mmole) in 10 ml of absolute tetrahydrofuran 85 mg of sodium hydride and 0.2 ml of methyl iodide were added (method F). The products were separated by preparative thin layer chromatography (SS III). Compound **26** (35 mg, 49%) had mp 165-167°, Rf 0.30 (SS IV); ir: ν 2955 (CH), 2855 (OCH_3), 1606 (C=O), 1584, 1562, 1475 (C=C), 1453 (CH_3), 1393 (CH_3), 1198, 1133, 1035 (C-O) cm^{-1}; uv: λ max (log ε) 390 nm (4.113), 306 (4.485) sh, 292 (4.760), 273 (4.899), 224 (4.522), 208 (4.630); ^{1}H nmr: δ 1.54 (s, 6H, 2 x CH_3), 2.48 (s, 3H, CH_3), 3.81 (s, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 5.50 (d, J = 9.6 Hz, 1H, 2-H), 6.30 (s, 1H, 5-H), 6.52 (d, J = 9.6 Hz, 1H, 1-H), 7.06 (dd, J = 8.0 and 1.0 Hz, 1H, 9-H), 7.14 (s, 1H, 11-H), 8.26 (d, J = 8.0 Hz, 1H, 8-H); ^{13}C nmr: δ 21.00 (CH_3), 26.86 (2 x CH_3), 44.27 (NCH_3), 56.15 (OCH_3), 76.39 (C-3), 94.27 (C-5), 101.34 (C-12b), 110.30 (C-6a), 114.61 (C-11), 115.86 (C-7a), 121.87 (C-9), 122.92 (C-2), 123.55 (C-8), 127.18 (C-1), 143.65 (C-10), 144.67 (C-12a), 146.85 (C-11a), 159.39 (C-6), 163.06 (C-4a), 177.29 (C-7); ms: m/z 335 (85, M^+), 320 (100, M^+ -CH_3), 306 (54, M^+ -CHO), 290 (23, 320 -CH_2O), 276 (51, 306 -CH_2O), 262 (11, 290 -CO); hrms: Calcd. for $C_{21}H_{21}NO_3$: 335.15214. Found: 335.15125.

5,10-Dimethylacronycine (**30**).

This compound (8 mg, 11%) had mp 136-138°, Rf 0.57 (SS II); ir: ν 2960 (CH), 2850 (OCH_3), 1601 (C=O), 1571, 1495 (C=C), 1398 (CH_3), 1196, 1129, 1100 (C-O) cm^{-1}; uv: λ max (log ε) 398 nm (3.869), 279 (4.662), 206 (4.419); ^{1}H nmr: δ 1.55 (s, 6H, 2 x CH_3), 2.19 (s, 3H, 5-CH_3), 2.51 (s, 3H, 10-CH_3), 3.81 (s, 3H, NCH_3), 3.91 (s, 3H, OCH_3), 5.56 (d, J = 9.6 Hz, 1H, 2-H), 6.56 (d, J = 9.6 Hz, 1H, 1-H), 7.07 (dd, J = 8.2 and 0.8 Hz, 1H, 9-H), 7.15 (s, 1H, 11-H), 8.29 (d, J = 8.2 Hz, 1H, 8-H); ^{13}C nmr: δ 22.31 (10-CH_3), 26.99 (2 x CH_3), 29.71 (5-CH_3), 44.26 (NCH_3), 61.26 (OCH_3), 76.01 (C-3), 97.30 (C-5), 106.26 (C-12b), 115.04 (C-6a), 115.90 (C-11), 122.11 (C-9), 122.91 (C-7a), 123.16 (C-2), 123.97 (C-1), 127.22 (C-8), 143.48 (C-10), 144.56 (C-12a), 144.98 (C-11a), 157.40 (C-6), 160.03 (C-4a), 176.68 (C-7); ms: m/z 349 (100, M^+), 334 (69, M^+ -CH_3), 320 (45, M^+ -CHO), 304 (22, 334 -CH_2O), 290 (25, 320 -CH_2O), 276 (8, 304 -CO); hrms: Calcd. for $C_{22}H_{23}NO_3$: 349.167794. Found: 349.168325.

Synthesis of 11-Methylacronycine (**27**).

1,3-Dihydroxy-5-methyl-9(10*H*)-acridinone (**5**).

2-Amino-3-methylbenzoic acid (5.0 g, 33 mmoles) was treated with 4.2 g (33 mmoles) of phloroglucinol (method A) to give 1.25 g (15%) of **5**, mp >320° dec; Rf 0.33 (SS III); ir: ν 3230 (NH), 3080 (CH), 1650 (C=O), 1600, 1530 (C=C), 1460 (CH_3), 1270 (OH), 1160 (C-O) cm^{-1}; uv: λ max (log ε) 389 nm (3.882), 322 (3.865) sh, 291 (4.291) sh, 260 (4.752), 226 (4.217); ^{1}H nmr: δ 2.55 (s, 3H, CH_3), 6.04 (d, J = 2.1 Hz, 1H, 4-H), 6.7 (d, J = 2.1 Hz, 1H, 2-H),

7.18 (dd, J = 7.0 and 8.0 Hz, 1H, 7-H), 7.56 (d, J = 7 Hz, 1H, 6-H), 8.05 (d, J = 8 Hz, 1H, 8-H), 10.54 (s, 1H, 3-OH), 10.62 (s, 1H, NH), 14.32 (s, 1H, 1-OH); ^{13}C nmr: δ 17.66 (CH_3), 91.89 (C-4), 95.75 (C-2), 103.09 (C-9a), 118.95 (C-8a), 120.75 (C-7), 122.85 (C-8), 124.80 (C-6), 134.34 (C-5), 139.32 (C-10a), 143.49 (C-4a), 163.40 (C-3), 164.02 (C-1), 180.19 (C-9); ms: m/z 241 (100, M^+), 213 (9, M^+ -CO), 185 (7, 213 -CO).

Anal. Calcd. for $C_{14}H_{11}NO_3$ (241.25): C, 69.70; H, 4.60; N, 5.81. Found: C, 69.59; H, 4.61; N, 5.61.

1-Hydroxy-3-methoxy-5-methyl-9(10*H*)-acridinone (**10**).

To a mixture of 1,3-dihydroxy-5-methyl-9(10*H*)-acridinone (**5**) (770 mg, 3.2 mmoles) and potassium carbonate (1.5 g) in absolute acetone (30 ml) methyl iodide (1 ml) was added (method B). The reaction mixture was stirred at room temperature for 24 hours. After removing the solvent reaction mixture was washed with water. Recrystallization of the crude product from methanol/-

water yielded 770 mg (95%) of **10**, mp 235-237°, Rf 0.42 (SS III); ir: ν 3345 (NH), 1638 (C=O), 1605, 1581, 1492 (C=C), 1458 (CH_3), 1210 (O-CH_3), 1288, 1161 (C-OH) cm^{-1}; uv: λ max (log ε) 385 nm (3.537), 292 (3.899), 260 (4.424), 226 (3.630) sh, 214 (3.650); ^{1}H nmr: δ 2.55 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.15 (d, J = 2.3 Hz, 1H, 4-H), 6.84 (d, J = 2.2 Hz, 1H, 2-H), 7.18 (t, J = 7.8 Hz, 1H, 7-H), 7.58 (d, J = 6.6 Hz, 1H, 6-H), 8.05 (d, J = 8.1 Hz, 1H, 8-H), 10.73 (s, 1H, 10-H), 14.26 (s, 1H, OH); ^{13}C nmr: δ 17.51 (CH_3), 55.38 (OCH_3), 89.92 (C-4), 94.75 (C-2), 103.79 (C-9a), 119.07 (C-8a), 121.01 (C-7), 122.85 (C-8), 124.92 (C-6), 134.48 (C-5), 139.28 (C-10a), 143.30 (C-4a), 163.05 (C-3), 165.04 (C-1), 80.44 (C-9); ms: m/z 255 (100, M^+), 240 (6, M^+ -CH_3), 226 (61, M^+ -CHO), 212 (8, 240 -CO), 197 (17, 226 -CHO), 184 (7, 212 -CO), 168 (9, 197 -CHO), 154 (11, 184 -CH_2O).

Anal. Calcd. for $C_{15}H_{13}NO_3$ (255.28): C, 70.58; H, 5.13; N, 5.49. Found: C, 70.48; H, 5.02; N, 5.60.

1,3-Dimethoxy-5,10-dimethyl-9(10*H*)-acridinone (**11**).

For the synthesis of **11** a mixture of 700 mg (2.75 mmoles) of **10**, methyl iodide (0.6 ml) and potassium carbonate (1 g) in absolute acetone (25 ml) was heated under reflux for 5 hours. As thin layer chromatography indicated no reaction, potassium hydroxide (0.5 g) was added to the cooled reaction mixture. After 2 hours, the solvent was removed *in vacuo* and the bases were extracted with water. Separation of the product mixture by column chromatography afforded 650 mg (84%) of **11**, mp 143-145° (methanol/water), Rf 0.18 (SS III); ir: ν 3510 (br, OH), 2930 (CH), 2850 (OCH_3), 1625 (C=O), 1604, 1587, 1498 (C=C), 1470 (CH_3), 1298, 1084 (C-O-C) cm^{-1}; uv: λ max (log ε) 380 nm (3.896), 315 (3.925) sh, 293 (4.131), 262 (4.689), 226 (4.136), 214 (4.138); ^{1}H nmr: δ 2.60 (s, 3H, CH_3), 3.78 (s, 3H, 3-OCH_3), 3.83 (s, 3H, NCH_3), 3.94 (s, 3H, 1-OCH_3), 6.37 (d, J = 2 Hz, 1H, 2-H), 6.57 (d, J = 2 Hz, 1H, 4-H), 7.17 (t, J = 7 Hz, 1H, 7-H), 7.49 (dd, J = 7 and 2 Hz, 1H, 6-H), 7.94 (dd, J = 7 and 2 Hz, 1H, 8-H); ^{13}C nmr: δ 21.96 (CH_3), 43.34 (N-CH_3), 55.58 (3-OCH_3), 55.78 (1-OCH_3), 92.23 (C-2), 92.89 (C-4), 108.07 (C-9a), 121.80 (C-8a), 123.60 (C-7), 126.56 (C-8), 126.89 (C-6), 135.98 (C-5), 143.99 (C-10a), 149.98 (C-4a), 161.64 (C-1), 163.72 (C-3), 175.73 (C-9); ms: m/z 283 (100, M^+), 254 (18, M^+ -CHO).

Anal. Calcd. for $C_{17}H_{17}NO_3$ (283.33): C, 72.07; H, 6.05; N, 4.94. Found: C, 71.96; H, 5.99; N, 4.87.

1,3-Dihydroxy-5,10-dimethyl-9(10*H*)-acridinone (**15**).

A mixture of **11** (600 mg, 2.1 mmoles) and 50 ml of concentrated hydrobromic acid was allowed to react under the conditions of method C. Recrystallization from dimethyl sulfoxide/water gave brown needles, 440 mg (81%), mp >220° subl, Rf 0.44 (SS III); ir: ν 3450 (br, OH), 3110 (CH), 2925 (CH), 1633 (C=O), 1607, 1543, 1505 (C=C), 1468 (CH_3), 1273 (OH), 1162 (C-OH) cm^{-1}; uv: λ max (log ε) 397 nm (3.347), 327 (3.550), 264 (4.139), 226 (3.706); ^{1}H nmr: δ 2.67 (s, 3H, CH_3), 3.81 (s, 3H, NCH_3), 6.10 (d, J = 2 Hz, 1H, 2-H), 6.34 (d, J = 2 Hz, 1H, 4-H), 7.26 (t, J = 7.6 Hz, 1H, 7-H), 7.62 (d, J = 7.1 Hz, 1H, 6-H), 8.11 (dd, J = 7.8 and 1.3 Hz, 1H, 8-H), 10.73 (s, 1H, 3-OH), 14.44 (s, 1H, 1-OH); ^{13}C nmr: δ 22.61 (CH_3), 42.71 (N-CH_3), 92.28 (C-4), 95.84 (C-2), 103.81 (C-9a), 121.93 (C-8a), 123.12 (C-7), 126.63 (C-6), 137.73 (C-5), 144.52 (C-10a), 148.1 (C-4a), 164.07 (C-3), 164.82 (C-1), 180.01 (C-9); ms: m/z 255 (100, M^+), 240 (51, M^+ -CH_3), 226 (8, M^+ -CHO), 212 (9, 240 -CO), 198 (5, 226 -CO), 184 (6, 212 -CO).

Anal. Calcd. for $C_{15}H_{13}NO_3 \cdot 1/4H_2O$ (255.28): C, 69.35; H, 5.24; N, 5.39. Found: C, 69.52; H, 5.42; N, 5.29.

3-[(1,1-Dimethyl-2-propinyl)oxy]-1-hydroxy-5,10-dimethyl-9-(10*H*)-acridinone (**23**).

Under the conditions of method E the potassium salt of **15** (360 mg, 1.4 mmoles) was obtained. The synthesis of 11-methylnoracronycine (**19**) would follow by the reaction of the potassium salt with potassium iodide (410 mg), potassium carbonate (280 mg) and 2-chloro-2-methyl-3-butyne (260 mg) in absolute DMF (10 ml) at 80°. After heating for 7 hours, tlc indicated the total disappearance of the starting material. Removal of the solvent *in vacuo* followed by extracting the salts with water and separation of the reaction mixture by column chromatography gave 150 mg (29%) of **23**, mp 159-161°, Rf 0.27 (SS VI); ir: ν 3300 (≡C-H), 2960, 2940 (CH), 1629 (C=O), 1586, 1557, 1507 (C=C), 1449 (CH_3), 1304 (OH), 1265 (C-O-C), 1240, 1136 (C-OH) cm^{-1}; uv: λ max (log ε) 399 nm (3.932), 320 (4.019) sh, 306 (4.108), 266 (4.594); ^{1}H nmr: δ 1.76 (s, 6H, 2 x CH_3), 2.66 (s, 3H, CH_3), 2.71 (s, 1H, ≡CH), 3.82 (s, 3H, NCH_3), 6.59 (d, J = 2.1 Hz, 1H, 4-H), 6.70 (d, J = 2.1 Hz, 1H, 2-H), 7.20 (t, J = 7.6 Hz, 1H, 7-H), 7.50 (dd, J = 7.2 and 0.8 Hz, 1H, 6-H), 8.26 (dd, J = 8.0 and 1.3 Hz, 1H, 8-H), 14.26 (s, 1H, OH); ^{13}C nmr: δ 23.12 (CH_3), 29.77 ($(CH_3)_2$), 43.12 (N-CH_3), 75.52 (*C*≡CH), 74.90 (*C*-$(CH_3)_2$), 85.30 (C≡*C*H), 95.99 (C-2), 99.44 (C-4), 103.00 (C-9a), 122.18 (C-8a), 123.51 (C-7), 124.34 (C-8), 125.93 (C-6), 137.83 (C-5), 145.30 (C-10a), 147.89 (C-4a), 162.63 (C-3), 164.38 (C-1), 181.64 (C-9); ms: m/z 321 (59, M^+), 306 (100, M^+ -CH_3), 292 (39, M^+ -CHO), 278 (34, 306 -CO), 264 (12, 292 -CO), 255 (39, M^+ -C_5H_6), 250 (9, 278 -CO), 240 (51, 255 -CH_3), 226 (21, 255 -CHO), 212 (11, 240 -CO).

Anal. Calcd. for $C_{20}H_{19}NO_3 \cdot H_2O$ (339.35): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.66; H, 5.96; N, 4.36.

11-Methylnoracronycine (**19**).

Heating **23** in DMF (100 ml) at 120° for 8 hours resulted in the cyclization to give 127 mg (96%) of **19**, mp 130-133°, Rf 0.38 (SS V); ir: ν 3420 (br, OH), 2965 (CH), 1630 (C=C), 1581, 1549, 1488 (C=C), 1448 (CH_3), 1297 (OH), 1264 (C-O-C), 1137, 1109 (C-O) cm^{-1}; uv: λ max (log ε) 298 nm (3.797), 299 (4.095), 265 (4.665), 224 (4.058); ^{1}H nmr: δ 1.50 (s, 6H, 2 x CH_3), 2.60 (s, 3H, CH_3), 3.57 (s, 3H, NCH_3), 5.57 (d, J = 9.8 Hz, 1H, 2-H), 6.24 (d, J = 0.6 Hz, 1H, 5-H), 6.57 (d, J = 9.8 Hz, 1H, 1-H), 7.25 (t, J = 3.8 Hz, 1H, 9-H), 7.50 (ddd, J = 1.2, 2.4 and 7.9 Hz, 1H, 10-H), 8.16 (dd, J = 1.2 and 7.9 Hz, 1H, 8-H), 14.05 (s, 1H, OH); ^{13}C nmr: δ 21.69 (CH_3), 27.39 (2 x CH_3), 49.18 (NCH_3), 76.85 (C-3), 92.83 (C-5), 98.71 (C-12b), 103.25 (C-6a), 116.02 (C-9), 120.59 (C-7a), 123.35

(C-11), 124.10 (C-2), 124.91 (C-8), 128.68 (C-1), 137.08 (C-10), 148.34 (C-12a), 148.71 (C-11a), 161.42 (C-6), 164.59 (C-4a), 182.88 (C-7); ms: m/z 321 (56, M^+), 306 (100, $M^+ -CH_3$), 291 (61, 306 $-CH_3$), 277 (5, 306 -CHO), 262 (6, 291 -CHO), 248 (5, 277 -CHO), 233 (5, 262 -CHO), 220 (4, 248 -CO), 206 (4, 233 -HCN), 191 (3, 206 $-CH_3$); hrms: Calcd. for $C_{20}H_{19}NO_3$: 321.136494. Found: 321.135884.

11-Methylacronycine (**27**).

The methylation of **19** (105 mg, 0.33 mmole) followed method F by heating for 3 hours in 17.5 ml of absolute THF with 130 mg of sodium hydride and 475 mg of methyl iodide. The product mixture was separated by preparative tlc (SS III) to give 55 mg (51%) of **27**, mp 158-160°, Rf 0.39 (SS III); ir: ν 3060 (CH), 2930 (CH), 1626 (C=O), 1586, 1552, 1494 (C=C), 1376 (CH_3), 1265, 1137 (C-O-C) cm^{-1}; uv: λ max (log ϵ) 383 nm (3.406), 331 (3.586), 303 (3.781) sh, 277 (4.151), 208 (4.140); ^1H nmr: δ 1.52 (s, 6H, 2 x CH_3), 2.58 (s, 3H, CH_3), 3.45 (s, 3H, NCH_3), 3.96 (s, 3H, OCH_3), 5.60 (d, J = 9.8 Hz, 1H, 2-H), 6.32 (s, 1H, 5-H), 6.65 (d, J = 9.8 Hz, 1H, 1-H), 7.20 (t, J = 7.6 Hz, 1H, 9-H), 7.41 (dd, J = 7.3 and 0.9 Hz, 1H, 10-H), 8.12 (dd, J = 7.8 and 1.1 Hz, 1H, 8-H); ^{13}C nmr: δ 20.65 (2 x CH_3), 27.33 (CH_3), 48.30 (NCH_3), 56.27 (OCH_3), 76.76 (C-3), 95.47 (C-5), 105.31 (C-12b), 111.82 (C-6a), 120.61 (C-9), 123.38 (C-2), 124.72 (C-11), 125.31 (C-7a), 128.65 (C-1), 129.34 (C-8), 135.22 (C-10), 147.27 (C-12a), 150.61 (C-11a), 159.12 (C-6), 162.12 (C-4a), 179.48 (C-7); ms: m/z 335 (63, M^+), 320 (100, $M^+ -CH_3$), 305 (23, 320 $-CH_3$), 290 (8, 305 $-CH_3$), 276 (39, 305 -CHO), 262 (7, 290 -CO); hrms: Calcd. for $C_{21}H_{21}NO_3$: 335.15214. Found: 335.15125.

5,11-Dimethylacronycine (**29**).

This compound was obtained in 11% yield (12 mg), mp 121-123°, Rf 0.62 (SS III); ir: ν 2965, 2850 (CH), 1622 (C=O), 1584 (C=C), 1454 (CH_3), 1281, 1131 (C-O-C) cm^{-1}; uv: λ max (log ϵ) 391 nm (3.730), 325 (3.841) sh, 279 (4.519), 204 (4.360); ^1H nmr: δ 1.53 (s, 3H, 11-CH_3), 2.18 (s, 6H, 2 x CH_3), 2.59 (s, 3H, 5-CH_3), 3.42 (s, 3H, NCH_3), 3.89 (s, 3H, OCH_3), 5.66 (d, J = 9.6 Hz, 1H, 2-H), 6.71 (d, J = 9.6 Hz, 1H, 1-H), 7.21 (t, J = 7.4 Hz, 1H, 9-H), 7.43 (dd, J = 7.4 and 1.0 Hz, 1H, 10-H), 8.13 (dd, J = 7.4 and 1.1 Hz, 1H, 8-H); ^{13}C nmr: δ 20.61 (2 x CH_3), 27.44 (11-CH_3), 30.90 (5-CH_3), 48.31 (NCH_3), 61.22 (OCH_3), 77.28 (C-3), 98.45 (C-5), 108.72 (C-12b), 116.19 (C-6a), 117.03 (C-9), 120.79 (C-2), 123.27 (C-11), 124.63 (C-7a), 126.44 (C-8), 128.91 (C-1), 135.28 (C-10), 147.74 (C-12a), 148.10 (C-11a), 157.35 (C-6), 159.43 (C-4a), 180.43 (C-7); ms: m/z 349 (48, M^+), 333 (100), 334 (67, $M^+ -CH_3$), 320 (16, M^+ -CHO), 304 (25, 334 $-CH_2O$), 290 (24, 320 $-CH_2O$), 276 (10, 304 -CO), 262 (9, 290 -CO); hrms: Calcd. for $C_{22}H_{23}NO_3$: 349.167794. Found: 349.167296.

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