Pergamon

Tetrahedron 58 (2002) 6373–6380

TETRAHEDRON

Efficient relay syntheses and assessment of the DNA-cleaving properties of the pyrrole alkaloid derivatives permethyl storniamide A, lycogalic acid A dimethyl ester, and the halitulin core

Alois Fürstner,* Helga Krause and Oliver R. Thiel

Max-Planck-Institut für Kohlenforschung, Kaiser Wilhelm-Platz 1, D-45470 Mülheim/Ruhr, Germany

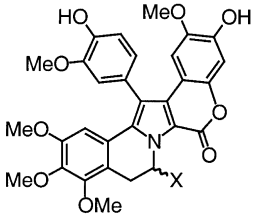
This paper is dedicated to Professor Yoshito Kishi in recognition of his outstanding contributions to modern organic chemistry and natural product synthesis

Received 11 April 2002; accepted 9 May 2002

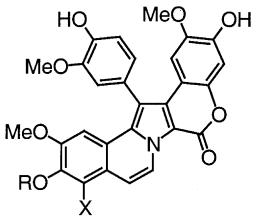
Abstract—Palladium catalyzed Suzuki- and Negishi cross coupling reactions are used to convert the now readily available 3,4-dibromopyrrole derivatives **13** and **26** into the core structures of different pyrrole alkaloids. Several compounds of this series exhibit respectable cytotoxicity and resensitize multidrug resistant (MDR) cancer cell lines at non-toxic concentrations. Cytotoxicity and MDR reversal can be efficiently uncoupled by per-*O*-methylation of the peripheral hydroxyl groups. For the storniamide core structure **9** it is demonstrated that this chemical modification goes hand in hand with a complete loss of the DNA-cleaving capacity of the alkaloid.

1. Introduction

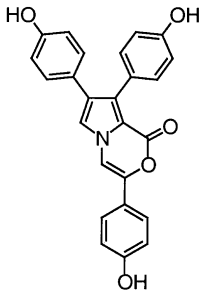
The ability of malignant cell lines to develop resistance against approved anticancer agents constitutes a major problem for efficient chemotherapy. This phenotype of multidrug resistance (MDR) is frequently caused by the overexpression of the plasma membrane glycoprotein P-gp which functions as an ATP-dependent pump able to export a wide variety of drugs out of mammalian cells, thus lowering their intramolecular concentration below the cytotoxic threshold.[1] Agents that either retain activity on MDR cells or resensitize them by specifically interfering with the P-gp mediated efflux are needed to improve prognosis for patients failing to respond to conventional chemotherapy.



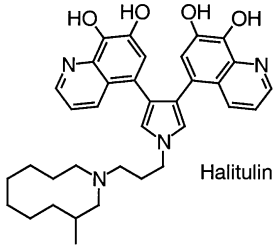
Lamellarin A (**1**, X = OH)
Lamellarin C (**3**, X = H)



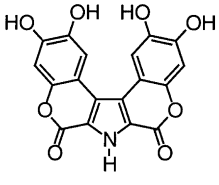
Lamellarin B (**2**, R = Me, X = OMe)
Lamellarin D (**4**, R = H, X = H)



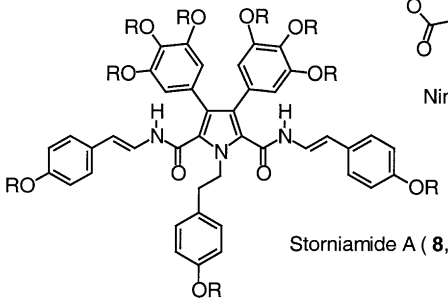
Lukianol A (**5**)



Halitulin (**6**)



Ningalin A (**7**)



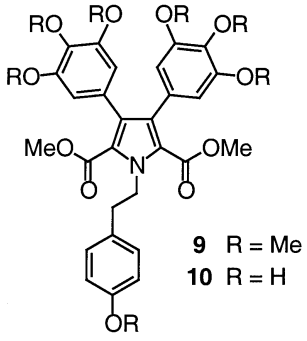
Storniamide A (**8**, R = H)

In this context, a series of marine alkaloids consisting of a pyrrole core surrounded by a periphery of polyoxygenated phenyl rings such as **1**–**8** (and many congeners) has recently attracted considerable attention.[2,3] They have been isolated from widely varying locations and organisms (ascidians, molluscs, sponges) and apparently derive from tyrosine or

Keywords: cross coupling; DNA; natural products; palladium; pyrrole.
* Corresponding author. Fax: +49-208-306-2994;
e-mail: fuerstner@mpi-muelheim.mpg.de

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00637-3

DOPA metabolism. Interestingly, exhaustive O-methylation of the lateral hydroxyl groups significantly reduces the cytotoxicity of these compounds but leaves the capacity for MDR reversal virtually unchanged.[3] Thus, permethyl storniamide **8** (R=Me) as a prototype example exhibits essentially no cytotoxic activity against four different cancer cell lines (IC_{50}>100 μM) but completely reverses MDR at 1 μM concentration, thus being more potent than the reference compound verapamil. Even more strikingly, the resistant human colon cancer cell line HTC116/VM46 becomes *hypersensitive* to doxorubicin and vincristine on treatment with 7.5 μM solutions of compound **9** representing the permethylated storniamide core region.[3]

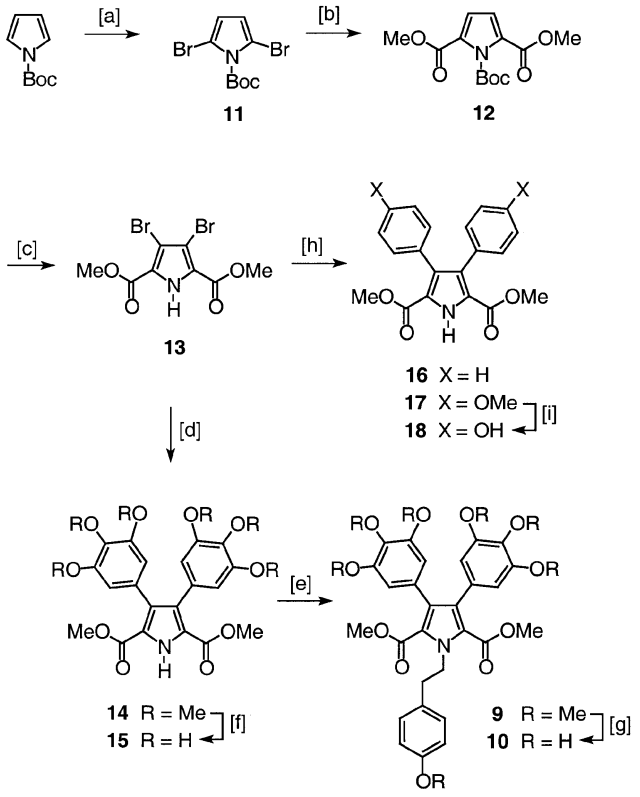


Insights into the molecular mechanism of action of such pyrrole alkaloids, however, are still missing and no explanation as to why simple ether formation uncouples their cytotoxicity and MDR reversing capacity has been reported to date. Described below is a preliminary study showing that the nature of the peripheral –OR groups determines the ability of such alkaloids to interact with double stranded DNA. Whereas the storniamide core **10** containing free –OH groups at the rim constitutes a very potent strand cleaving agent, its –OMe congener **9** causes no damage under otherwise identical conditions.

2. Results and discussion

2.1. Syntheses

Following the first total syntheses of lukianol A and lamellarin O dimethyl ether based on a titanium-mediated oxo-amide coupling reaction,[4,5] various imaginative approaches to alkaloids belonging to the lukianol-,[6] lamellarin-,[7] storniamide-,[8] ningalin-[9] and related families[10] have been reported in the literature.[11] Herein we describe a streamlined synthesis of the particularly promising compound **9** which is flexible enough to provide analogues as well. In view of its symmetrical core structure, we elaborated on established cross coupling methodology[12,13] which allows to use dimethyl 3,4-dibromopyrrole-2,5-dicarboxylate **13** as the starting material (Scheme 1). Compound **13** is readily prepared from *N*-Boc pyrrole by reaction with NBS in THF at low temperature to give dibromide **11**[14] followed by metal–halogen exchange with *tert*-BuLi and quenching of the resulting dilithio species with methyl chloroformate;[15] thereby, it is essential to add the cold solution of the organometallic reagent to an excess of the electrophile to ensure good results. Reaction of diester **12** with Br_2 provides product **13** in excellent overall yield.



Scheme 1. (a) NBS, THF, −78→0°C, 70%; (b) (i) *tert*-BuLi, THF, −78°C; (ii) ClC(O)OMe, −78°C, 83%; (c) Br_2, H_2O, 0°C, 91%; (d) 3,4,5-trimethoxybenzeneboronic acid, $Pd(PPh_3)_4$ cat., K_2CO_3, DME/H_2O, 110°C, 88%; (e) 2-(4-methoxyphenyl)ethyl bromide, K_2CO_3, DMF, 110°C, 90%; (f) BBr_3, CH_2Cl_2, −78°C, 57%; (g) BBr_3, CH_2Cl_2, −78°C, 39%; (h) phenylboronic acid, $Pd(PPh_3)_4$ cat., K_2CO_3, DME/H_2O, 110°C, 60% (**16**), or 4-methoxyphenylboronic acid, $Pd(PPh_3)_4$ cat., K_2CO_3, DME/H_2O, 100°C, 99% (**17**); (i) BBr_3, CH_2Cl_2, −78°C, 54%.

A Suzuki cross coupling reaction[12,16] of **13** with commercial 3,4,5-trimethoxybenzene boronic acid delivers diarylpyrrole **14** in 88% yield. An X-ray structure of this compound shows the orthogonal array of its benzene rings in the solid state (Fig. 1). Subsequent *N*-alkylation under

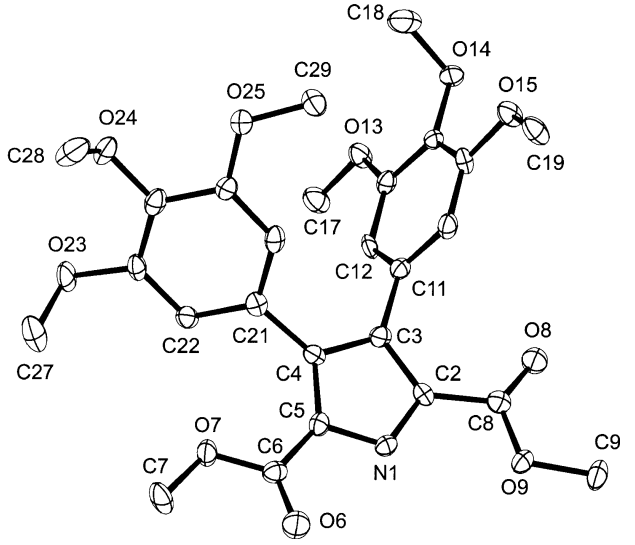
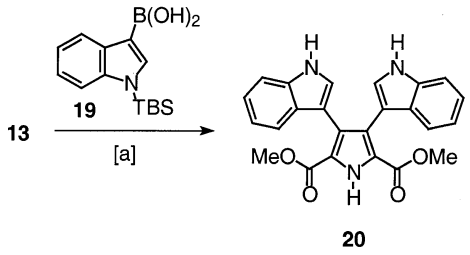
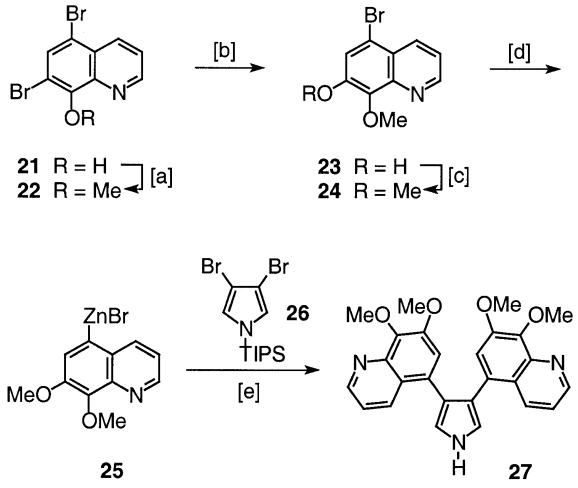


Figure 1. Molecular structure of **14**. Anisotropic displacement parameters are shown at 50% probability level.



Scheme 2. (i) Boronic acid **19**, $Pd(PPh_3)_4$ cat., Na_2CO_3, DMF, 150°C; (ii) TBAF·$3H_2O$, 81%.



Scheme 3. (a) MeI, $(n\text{-}Bu)_4NI$, NaOH, THF/H_2O, 40°C, 78%; (b) (i) PhLi, Et_2O, −78°C; (ii) $B(OMe)_3$, −78°C; (iii) peracetic acid, 0°C, 77%; (c) MeI, K_2CO_3, acetone, r.t., 83%; (d) Rieke-Zn, THF, 80°C; (e) (i) dibromide **26**, $Pd(dppf)Cl_2$ cat., THF, 80°C; (ii) TBAF·$3H_2O$, THF, room temperature, 44% (over both steps).

standard conditions leads to the desired target **9** which can be converted into permethyl storniamide A **8** (R=Me) according to literature procedures.[3a,17] Demethylation of compounds **14** or **9** on treatment with BBr_3 furnishes the corresponding phenol derivatives **15** and **10**, respectively.

As expected, the Suzuki cross coupling step is rather general and can be used to prepare related 3,4-diarylated pyrrole derivatives as well. In addition to products **16**–**18**, this refers to lycogalic acid dimethyl ester **20** (Scheme 2), an alkaloid isolated from the mycomycete *Lycogala epidendrum* exhibiting some anti-HIV I activity.[18]

This methodology can be extended to provide 3,4-diarylpyrrole alkaloids devoid of the carboxylic acid esters at C-2 and C-5. A particularly interesting member of this series is halitulin **6**, a strongly cytotoxic bisquinolinyl pyrrole derivative isolated from the Indo-Pacific sponge *Haliclona tulearensis*.[19] Our synthesis of its core segment is depicted in Scheme 3. Starting from commercial bromoxine **21**, a sequence of *O*-methylation (→**22**), directed metal–bromine exchange followed by borylation/oxidation furnished phenol **23**, which is treated with MeI in the presence of K_2CO_3 to give product **24** in good overall yield.[20] While several attempts to effect metal–bromine exchange at the 5-position with *tert*-BuLi, PhLi, *i*-PrMgBr, or *i*-$PrBu_2MgLi$ met with failure, it was found that highly activated zinc[21] oxidatively inserts into the C–Br bond leading to the formation of the corresponding organozinc reagent **25** which reacts with the known dibromide **26**[22] in the presence of $Pd(dppf)Cl_2$ in THF.[23] Under these conditions, the Negishi reaction[12] gave access to the halitulin core **27** in reasonable yield. Interestingly, the use of either $Pd(PPh_3)_4$ or $Pd_2(dba)_3$/dppf as the catalyst led to no productive C–C-bond formation.

2.2. Investigation of the DNA-cleaving properties

Various ascidians and related marine organisms are known to accumulate large quantities of transition metals from sea water. DOPA derived metabolites are likely responsible for this phenomenon because their polyhydroxylated phenyl rings confer potent chelating properties towards metal cations if the pH of the medium is greater than 4.[24]

Previous studies from this and other laboratories[25,26] suggest that the specific ability to sequester metal cations might also be relevant with regard to the cytotoxicity of such compounds. It is well precedented in the literature that certain metal–catechol or metal–pyrogallol complexes, particularly those incorporating Cu^{II}, are immediately further oxidized to the corresponding *o*-quinones with concomitant release of H_2O_2. Its subsequent cleavage by the metal cation then produces diffusible oxygen radicals[27] and thereby triggers massive DNA-damage.

To study whether this mechanism accounts—at least in part—for the cytotoxicity exerted by the polyarylated pyrrole alkaloids described above, representative compounds have been assayed for their capacity to induce DNA strand

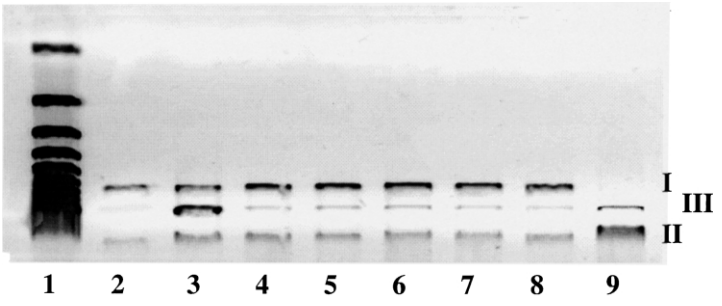


Figure 2. Result of an agarose gel electrophoresis showing the extent of DNA cleavage produced by different pyrrole alkaloids (50 μM) in the presence of $Cu(OAc)_2$ after an incubation time of 1.5 h at 37°C. Lane 1: DNA marker (500 base pairs molecular weight difference); lane 2: DNA alone; lane 3: DNA enriched in linear form (partial cleavage of parent DNA by restriction endonuclease *Xho* I); lane 4: DNA+compound **16**+Cu^{II}; lane 5: DNA+compound **20**+Cu^{II}; lane 6: DNA+compound **17**+Cu^{II}; lane 7: DNA+compound **18**+Cu^{II}; lane 8: DNA+compound **14**+Cu^{II}; lane 9: DNA+compound **15**+Cu^{II}.

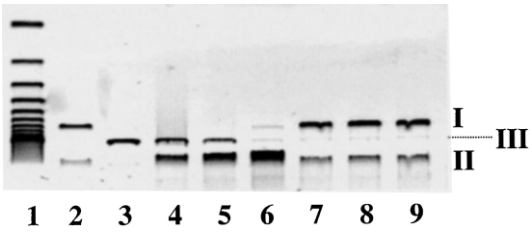


Figure 3. Agarose gel electrophoresis showing a comparison of the extent of DNA cleavage produced by different concentrations of compound **10** and the parent trimethyl ether derivative **9**, respectively, in the presence of $Cu(OAc)_2$ after an incubation time of 1.5 h at 37°C. Lane 1: DNA marker (500 base pairs molecular weight difference); lane 2: DNA alone; lane 3: linear DNA produced by cleavage of parent DNA with restriction endonuclease *Xho* I; lane 4: DNA+compound **10** (50 μM)+Cu^{II}; lane 5: DNA+compound **10** (30 μM)+Cu^{II}; lane 6: DNA+compound **10** (10 μM)+Cu^{II}; lane 7: DNA+compound **9** (100 μM)+Cu^{II}; lane 8: DNA+compound **9** (50 μM)+Cu^{II}; lane 9: DNA+compound **9** (10 μM)+Cu^{II}.

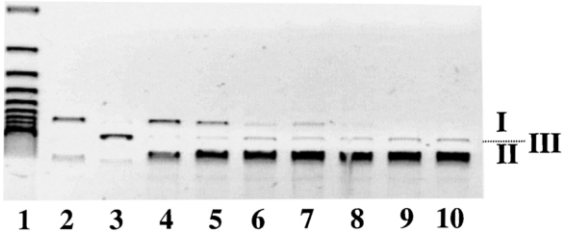


Figure 4. Result of an agarose gel electrophoresis showing the extent of DNA cleavage produced by compound **10** (10 μM) in the presence of $Cu(OAc)_2$ with increasing incubation time at 37°C. Lane 1: DNA marker (500 base pairs molecular weight difference); lane 2: DNA alone; lane 3: linear DNA produced by cleavage of parent DNA with restriction endonuclease *Xho* I; lane 4: 5 min; lane 5: 15 min; lane 6: 30 min; lane 7: 45 min; lane 8: 60 min; lane 9: 90 min; lane 10: 120 min.

cleavage in the presence of $Cu(OAc)_2$. As can be seen from the agarose gel depicted in Fig. 2, only compound **15** containing two pyrrolgallol rings relaxes the supercoiled plasmid DNA of the bacteriophage ΦX174 (form **I**) to the nicked form **II** and even to the linear form **III** under these conditions (lane 9), whereas all other derivatives have no appreciable effect.[28] This includes the corresponding permethyl ether **14** (lane 8), as well as compounds **16**, **17**, **18** and **20** (lanes 4–7) in which the electron rich pyrogallol units of **15** are replaced by either phenyl-, methoxyphenyl-, phenol- or indole moieties, respectively.

Fig. 3 illustrates the exceptional potency of the intact storniamide core **10** and shows that strand cleavage is clearly concentration dependent. After incubation with this compound (50 μM) in the presence of $Cu(OAc)_2$ for 1.5 h at 37°C, the double stranded plasmid DNA **I** has completely disappeared and only the nicked form **II** and substantial amounts of the linear DNA **III** formed by double strand cleavage are observed (lane 4, compare with lane 3 showing linear DNA obtained with the restriction endonuclease *Xho* I). Reducing the concentration of **10** to 30 μM (lane 5) or 10 μM (lane 6) under otherwise identical conditions diminishes the amount of the linear form **III**, whereas single strand cleavage to the nicked form **II** remains essentially complete. This effect is in striking contrast to the inability of the permethylated analogue **9** to induce any strand cleavage even at 10-times higher concentration (lane 7) as evident by comparison with the native DNA sample (lane 2).

As expected, DNA cleavage induced by **10**/$Cu(OAc)_2$ is a function of the incubation time (Fig. 4). The progress can be nicely followed by comparing lanes 4–10, showing that single strand cleavage is complete after ~60 min even if the concentration of **10** is only 10 μM (lane 8). After that time, only band **III** representing the linear form of the DNA slowly gains intensity. A virtually identical concentration- and time-dependent behavior was observed for compound **15** (gels not shown). Hence, we conclude that the presence of at least two unprotected hydroxyl groups within one arene ring constitutes a minimum structural requirement for efficient DNA cleavage under oxidative conditions. This structure/activity profile in the DNA assay is strongly reminiscent of previous observations in various cytotoxicity experiments on a panel of tumor cell lines which have shown that (i) an increase in the number of peripheral methylations of such pyrrole alkaloids causes a sharp decrease in their antitumoral activity, whereas (ii) no distinct correlation between the structure and the cytotoxic activity of diverse members of the lamellarin family with similar oxygenation patterns could be established.[2,3] Although further experiments are necessary to confirm the possible link between the observed DNA damage and the cell culture assays, the results summarized above provide a tentative explanation why similarly hydroxylated derivatives of this series exert virtually identical cytotoxicity that is lost on *O*-alkylation while MDR reversal activity persists. Further studies on this and related aspects are currently underway.[29]

3. Experimental

3.1. General

All reactions were carried out under Ar. The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O, DME (Mg–anthracene), CH_2Cl_2 (P_4O_{10}), MeCN, Et_3N, pyridine, DMF (CaH_2), MeOH (Mg), hexane, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: spectra were recorded on a Bruker DPX 300 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. IR: Nicolet FT-7199 spectrometer, wavenumbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), HRMS: Finnigan MAT 95. Melting points: Büchi melting point apparatus (uncorrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Lancaster, Fluka, Aldrich) were used as received.

3.1.1. 2,5-Dibromo-pyrrole-1-carboxylic acid *tert*-butyl ester (11). Freshly recrystallized NBS (10.6 g, 60.0 mmol) is added in portions to a solution of 1-*tert*-butoxycarbonylpyrrole (5.0 g, 29.9 mmol)[14] in THF (200 mL) at −78°C. After stirring for 1 h at −78°C, the resulting mixture is allowed to warm to 0°C and stirring is continued for 18 h at that temperature. For work-up, Na_2SO_3 (3.9 g, 31.0 mmol) is added to the stirred solution, the solvent is evaporated, the residue is dispersed in CCl_4 (170 mL) and the resulting suspension is filtered with suction. Evaporation

of the filtrate followed by flash chromatography (hexanes/EtOAc, 40:1) provides dibromide **11** as a colorless syrup which solidifies on standing at room temperature (6.82 g, 70%). The analytical and spectroscopic data are in full agreement with those reported in the literature.[14]

3.1.2. Pyrrole-1,2,5-tricarboxylic acid 1-*tert*-butyl ester 2,5-dimethyl ester (12). A solution of *tert*-BuLi (1.7 M in pentane, 15 mL, 25.5 mmol) is added over a period of 1 h to a solution of dibromide **11** (2.20 g, 6.77 mmol) in THF (35 mL) at −78°C and stirring is continued for 70 min once the addition is complete. The chilled solution of the resulting dilithium species is slowly added over 1 h to a solution of methyl chloroformate (6.70 g, 71 mmol) in THF (40 mL) at −78°C and the resulting mixture is stirred at that temperature for 16 h. For work-up, aq. sat. NH_4Cl is introduced into the cold mixture, the aqueous phase is extracted with CH_2Cl_2, the combined organic phases dried over Na_2SO_4 and evaporated, and the residue is purified by flash chromatography (hexanes/EtOAc, 20:1) to afford compound **12** as a colorless solid (1.60 g, 83%). Mp 124–125°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.81 (2H, s), 3.84 (6H, s), 1.64 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 159.8, 126.7, 115.8, 86.3, 52.0, 27.3; IR (KBr) 2999, 2957, 2936, 1777, 1733, 1707, 1536, 1475, 1457, 1439, 1419, 1377, 1262, 1212, 1199, 1168, 1100, 1024, 947, 847, 809, 771, 746 cm^{-1}; MS (EI) *m/z* (rel. intensity) 283 ([M$^+$], >1), 210 (23), 183 (100), 152 (42), 125 (3), 120 (31), 93 (9), 57 (90), 41 (19); HR-MS (CI) ($C_{13}H_{17}NO_6$+H) calcd 284.1134, found 284.1136; $C_{13}H_{17}NO_6$ (283.28) calcd C 55.12, H 6.06, N 4.94, found C 54.97, H 5.93, N 5.02.

3.1.3. 3,4-Dibromo-1*H*-pyrrole-2,5-dicarboxylic acid dimethyl ester (13). Bromine (0.5 mL, 9.7 mmol) is added at 0°C to a suspension of compound **12** (251 mg, 0.886 mmol) in water (10 mL). The reaction mixture is stirred for 5 min. Sat. aq. Na_2SO_3 is then introduced and stirring is continued until complete reduction of excess bromine is achieved. Extraction with CH_2Cl_2, drying of the combined organic phases over Na_2SO_4, evaporation of the solvent and flash chromatography (hexanes/EtOAc, 2:1→1:1) affords dibromide **13** as a colorless solid (274 mg, 91%). Mp 220–222°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.83 (6H, s), 9.95 (1H, br s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 159.3, 123.5, 107.8, 52.7; IR (KBr) 3266, 2957, 1716, 1699, 1530, 1440, 1273, 1050, 954, 738 cm^{-1}; MS (EI) *m/z* (rel. intensity) 343 ([M$^+$], 50), 341 ([M$^+$], 100), 339 ([M$^+$], 50), 309 (28), 278 (48), 251 (31), 222 (3), 198 (5), 172 (8), 115 (3), 91 (10); HR-MS (EI) ($C_8H_7Br_2NO_4$) calcd 338.8742, found 338.8743; $C_8H_7Br_2NO_4$ (340.96) calcd C 28.18, H 2.07, N 4.11, found C 28.28, H 2.15, N 4.06.

3.1.4. 3,4-Bis-(3,4,5-trimethoxy-phenyl)-1*H*-pyrrole-2,5-dicarboxylic acid dimethyl ester (14). A solution of compound **13** (51.9 mg, 0.15 mmol), 3,4,5-trimethoxyphenylboronic acid (96.0 mg, 0.45 mmol), $Pd(PPh_3)_4$ (8.7 mg, 0.0075 mmol) and K_2CO_3 (83 mg, 0.6 mmol) in DME (6 mL) and water (0.5 mL) is stirred at 110°C for 2.5 h. A standard extractive work-up followed by flash chromatography (hexanes/EtOAc, 1:1→1:2) affords product **14** as a colorless solid (68.0 mg, 88%). Mp 172–174°C; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 10.10–9.90 (1H, br s), 6.38 (4H, s), 3.80 (6H, s), 3.75 (6H, s), 3.63 (12H, s); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 160.9, 153.0, 137.7, 131.3, 128.8, 121.5, 109.0, 66.5, 56.4, 52.1; IR (KBr) 3445, 3385, 3273, 2999, 2942, 2836, 1729, 1717, 1701, 1603, 1586, 1558, 1506, 1482, 1461, 1435, 1411, 1342, 1282, 1262, 1239, 1193, 1126, 1074, 1054, 1006, 878, 839, 783 cm^{-1}; MS (EI) *m/z* (rel. intensity) 515 ([M$^+$], 100), 483 (47), 468 (36), 452 (2), 378 (2), 350 (2), 292 (1), 218 (5); HR-MS (EI) ($C_{26}H_{29}NO_{10}$) calcd 515.1791, found 515.1793.

3.1.5. 3,4-Diphenyl-1*H*-pyrrole-2,5-dicarboxylic acid dimethyl ester (16). A solution of compound **13** (60.0 mg, 0.175 mmol), phenylboronic acid (64.3 mg, 0.527 mmol), $Pd(PPh_3)_4$ (10.1 mg, 0.0087 mmol) and K_2CO_3 (97.3 mg, 0.7 mmol) in DME (6 mL) and water (0.5 mL) is stirred at 110°C for 2.5 h. A standard extractive work-up followed by flash chromatography (hexanes/EtOAc, 1:1) affords product **16** as a colorless solid (35.0 mg, 60%). ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 10.10–9.90 (1H, br s), 7.25–7.18 (6H, m), 7.16–7.10 (4H, m), 3.75 (6H, s); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 160.9, 133.5, 131.6, 131.2, 127.6, 127.3, 121.7, 52.0; IR (KBr) 3309, 3064, 3027, 2957, 2927, 2854, 1709, 1664, 1607, 1556, 1518, 1496, 1463, 1444, 1429, 1296, 1242, 1194, 1156, 1072, 1040, 1017, 1008, 952, 919, 842, 799, 787, 774, 702 cm^{-1}; MS (EI) *m/z* (rel. intensity) 335 ([M$^+$], 100), 303 (63), 272 (16), 244 (26), 216 (27), 189 (17), 136 (3), 107 (5); HR-MS (EI) ($C_{20}H_{17}NO_4$) calcd 335.1158, found 335.1161.

3.1.6. 3,4-Bis-(4-methoxy-phenyl)-1*H*-pyrrole-2,5-dicarboxylic acid dimethyl ester (17). A solution of compound **13** (47.0 mg, 0.137 mmol), 4-methoxyphenylboronic acid (63.0 mg, 0.42 mmol), $Pd(PPh_3)_4$ (8.0 mg, 0.007 mmol) and K_2CO_3 (80 mg, 0.58 mmol) in DME (6 mL) and water (0.5 mL) is stirred at 100°C for 2.5 h. A standard extractive work-up followed by flash chromatography (hexanes/EtOAc, 10:1→2:1) affords product **17** as a colorless solid (57.0 mg, 99%). Mp 192–193°C; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 9.82 (br s, 1H), 7.05 (d, 4H), 6.74 (d, 4H), 3.76 (s, 6H), 3.73 (s, 6H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 160.9, 159.2, 132.3, 131.3, 125.7, 121.5, 113.1, 55.4, 51.9; IR (KBr) 3350, 3008, 2953, 2838, 1707, 1613, 1535, 1469, 1437, 1308, 1248, 1181, 1036, 854, 826, 785 cm^{-1}; MS (EI) *m/z* (rel. intensity) 396 (18), 395 (76, [M$^+$]), 364 (24), 363 (100), 305 (7), 276 (7), 233 (4), 190 (5), 166 (10).

3.1.7. Lycogalic acid A dimethyl ether (20). A suspension of dibromopyrrole **13** (68.2 mg, 0.2 mmol), indole-3-boronic acid **19** (330 mg, 1.20 mmol),[30] $Pd(PPh_3)_4$ (11.4 mg, 0.01 mmol) and Na_2CO_3 (127.2 mg, 1.2 mmol, dissolved in minimum amount of water) in DMF (5 mL) is heated to 150°C for 1 h. The reaction mixture is then allowed to cool to ambient temperature before TBAF·3H_2O (157 mg, 0.5 mmol) is added and the solution is stirred for 10 min. Addition of brine, extraction with Et_2O, drying of the combined organic phases over Na_2SO_4, evaporation of the solvent and flash chromatography (hexanes/EtOAc, 1:1) affords product **20** as a colorless solid (66.9 mg, 81%). Mp 122–125°C. ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 10.10–9.90 (1H, br s), 8.11 (2H, br s), 7.25 (2H, d, J=8.1 Hz), 7.20 (2H, d, J=7.9 Hz), 7.10–7.04 (2H, m), 6.95–6.87 (4H, m), 3.70 (6H, m); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 161.0,

135.8, 128.0, 125.3, 124.9, 122.9, 121.8, 120.3, 119.6, 111.3, 109.2, 51.9; IR (KBr) 3403, 3051, 2949, 1701, 1619, 1519, 1478, 1455, 1434, 1408, 1346, 1313, 1267, 1241, 1194, 1130, 1097, 1060, 1008, 971, 926, 783, 741 cm^{-1}; MS (EI) *m/z* (rel. intensity) 413 ([M^+], 100), 381 (67), 349 (34), 320 (9), 294 (14), 266 (8), 240 (3), 175 (6), 133 (7); HR-MS (EI) ($C_{24}H_{19}N_3O_4$) calcd 413.1376, found 413.1374.

3.1.8. 3-Bis-(3,4,5-trimethoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]pyrrole-2,5-dicarboxylic acid dimethyl ester (9). A solution of pyrrole **14** (179 mg, 0.347 mmol), 2-(4-methoxyphenyl)ethyl bromide (413 mg, 1.91 mmol) and K_2CO_3 (265 mg, 1.91 mmol) in DMF (3 mL) is stirred for 2 h at 110°C. Evaporation of the solvent followed by flash chromatography of the crude product (CH_2Cl_2/acetone, 98:2) affords product **9** as a yellow syrup which solidifies upon standing (204 mg, 90%). Mp 118–119°C (lit.[3a] 118–119°C); ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 7.18 (d, 2H), 6.87 (d, 2H), 6.27 (s, 4H), 4.85 (t, 2H, J=6.2 Hz), 3.79 (s, 3H), 3.75 (s, 6H), 3.64 (s, 18H), 3.09 (t, 2H, J=6.2 Hz); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 162.5, 158.8, 152.7, 137.3, 130.7, 130.6, 130.3, 130.1, 124.2, 114.1, 108.5, 60.8, 56.3, 55.5, 51.7, 49.0, 37.6, 29.4; IR (KBr) 3438, 2995, 2935, 2835, 1712, 1693, 1584, 1512, 1463, 1436, 1407, 1339, 1237, 1125, 825, 702 cm^{-1}; MS (EI) *m/z* (rel. intensity) 650 (43), 649 (100, [M^+]), 528 (16), 483 (5), 135 (18).

3.2. Representative procedure for the exhaustive demethylation

3.2.1. 3,4-Bis-(4-hydroxy-phenyl)-1*H*-pyrrole-2,5-dicarboxylic acid dimethyl ester (18). BBr_3 (1 M in CH_2Cl_2, 1.3 mL, 1.3 mmol) is added to a solution of compound **17** (50 mg, 0.126 mmol) in CH_2Cl_2 (2.5 mL) at −78°C and stirring is continued for 4 h at that temperature. The reaction is quenched with MeOH (2.5 mL), all volatiles are evaporated in vacuo, the residue is suspended twice in MeOH (2.5 mL) which is subsequently stripped off. The remaining solid is then purified by flash chromatography (CH_2Cl_2/MeOH, 7:1) to afford compound **18** as a colorless air-sensitive solid (25.0 mg, 54%). Mp 247–249°C. ^{1}H NMR (CD_3OD, 300 MHz) δ 6.86 (d, 4H), 6.59 (d, 4H), 3.71 (s, 6H), 3.33 (s, 2H); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 163.0, 157.6, 133.5, 133.1, 126.5, 123.1, 115.5, 52.3; IR (KBr) 3536, 3459, 3390, 3037, 2952, 2508, 1701, 1614, 1554, 1482, 1437, 1259, 1243, 1122, 999, 838, 783, 535. MS (ESI): 406 ([M+K]$^+$), 390 ([M+Na]$^+$), 368 ([M+H]$^+$).

3.2.2. 3,4-Bis-(3,4,5-trihydroxy-phenyl)-1*H*-pyrrole-2,5-dicarboxylic acid dimethyl ester (15). Prepared as described above from compound **14** (51.5 mg, 0.1 mmol) and BBr_3 (1 mL, 1 M in CH_2Cl_2, 1 mmol) as a colorless air-sensitive solid (24.8 mg, 57%). ^{1}H NMR (CD_3OD, 300 MHz) δ 6.08 (4H, s), 3.67 (6H, s); ^{13}C NMR (CD_3OD, 75.5 MHz) δ 162.8, 145.9, 133.3, 132.9, 126.0, 122.6, 111.3, 51.9; IR (KBr) 3423, 2954, 2925, 2852, 2517, 1699, 1616, 1559, 1489, 1436, 1325, 1267, 1235, 1192, 1105, 1079, 1025, 974, 888, 845, 782 cm^{-1}.

3.2.3. 3,4-Dibromo-1-triisopropylsilanyl-1*H*-pyrrole (26). Freshly recrystallized NBS (5.60 g, 31.5 mmol) is added in portions to a solution of 1-triisopropylsilanyl-1*H*-pyrrole (3.35 g, 15.0 mmol)[22] in THF (50 mL) at −78°C. After stirring for 15 min, the reaction is quenched with aq. sat. $NaHCO_3$, the organic layer is extracted with Et_2O, the combined organic phases are dried over Na_2SO_4 and evaporated, and the residue is purified by recrystallization from pentane affording the title compound as a colorless solid (3.61 g, 63%). Mp 78–80°C (lit.[22b] 78–80°C). In contrast to the published procedure, we noticed that any warming of the reaction mixture to temperatures >-78°C results in significantly reduced yields. ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 6.68 (s, 2H), 1.33 (m, 3H), 1.04 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 124.3, 101.0, 17.8, 11.8.

3.2.4. Halitulin core (27). A suspension of lithium powder (83 mg, 12.0 mmol) and naphthalene (1.589 g, 12.4 mmol) in THF (10 mL) is stirred for 2 h at ambient temperature. A solution of $ZnCl_2$ (818 mg, 6.0 mmol) in THF (5 mL) is added to the resulting dark green mixture and stirring is continued for 15 min. To the suspension of the activated Zn thus formed is added 5-bromo-7,8-dimethoxy-quinoline **24** (536 mg, 2.0 mmol)[20] and the resulting mixture is stirred for 2 h at 80°C to complete the oxidative insertion process. Excess Zn is allowed to settle before the supernatant liquid is transferred via canula into a second flask containing a solution of dibromopyrrole **26** (229 mg, 0.6 mmol) and Pd(dppf)Cl_2 (44 mg, 0.06 mmol). The resulting mixture is stirred at 80°C for 2 h. After cooling to ambient temperature, the reaction is quenched with brine, the aqueous layer is extracted with CH_2Cl_2, the combined organic phases are dried over Na_2SO_4, concentrated and rapidly passed through a plug of silica gel. The product containing fractions are combined and evaporated, the crude product is dissolved in THF (20 mL) and treated with a TBAF (1 M in THF, 0.6 mL) to complete the cleavage of the TIPS group. A standard extractive work-up followed by flash chromatography (CH_2Cl_2/MeOH, 20:1) affords the title compound as a colorless air-sensitive solid (117 mg, 44%). ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 10.20–10.00 (1H, br s), 8.74 (2H, dd, J=4.1, 1.7 Hz), 8.28 (2H, dd, J=8.5, 1.7 Hz), 7.16 (2H, d, J=2.7 Hz), 7.11 (2H, s), 7.04 (2H, dd, J=8.5, 4.1 Hz), 3.95 (6H, s), 3.66 (6H, s); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 151.3, 150.0, 143.8, 141.9, 135.2, 130.4, 123.7, 121.5, 119.4, 119.0, 117.6, 61.7, 56.9; IR (KBr) 3416, 3076, 2995, 2933, 2847, 1715, 1600, 1496, 1474, 1431, 1399, 1385, 1344, 1333, 1281, 1251, 1212, 1193, 1155, 1126, 1109, 1078, 1037, 992, 925, 876, 790, 720 cm^{-1}; MS (EI) *m/z* (rel. intensity) 441 ([M^+], 100), 426 (61), 408 (51), 394 (26), 364 (8), 309 (6), 242 (4), 213 (5), 154 (5); HR-MS (EI) ($C_{26}H_{23}N_3O_4$) calcd 441.1689, found 441.1687; $C_{26}H_{23}N_3O_4$ (441.49) calcd C 70.74, H 5.25, N 9.52, found C 70.66, H 5.35, N 9.44.

3.3. DNA cleavage assay. Representative procedure

A solution of purified scDNA (2 μL of a stock solution containing ca. 400 μg mL^{-1}) [ΦX174 RF1 DNA, purchased from MBI Fermentas GmbH, St. Leon-Rot, Germany; the EDTA contained in the commercial sample was removed according to the Qiaex II protocol for desalting and concentrating DNA by using a Qiaex II Gel Extraction Kit] was incubated at 37°C for the time given in the figures with the respective pyrrole alkaloid derivative (for the

concentrations see Figs. 2–4), $Cu(OAc)_2$ (2 μL of a 1 mM stock solution) and aq. NaCl (3 μL of a 0.5 mM stock solution) in water (complemented to give a total volume of 20 μL). The mixture was quenched with loading buffer (BioRad laboratories) and the DNA resolved by electrophoresis (Powerpac 300, BioRad) (85 V, 1 h) on a 0.8% agarose gel (containing ethidium bromide) in tris/boronic acid buffer (BioRad). The bands detected by UV were analyzed and processed using the Bio Doc II software (Biometra).

3.4. X-Ray crystallographic study

Suitable crystals of compound **14** were obtained by recrystallization from dichloromethane. Data were recorded using an Enraf–Nonius Kappa CCD diffractometer with graphite-monochromated Mo K_α-radiation (λ=0.71073 Å). The crystal was mounted in a stream of cold nitrogen gas. The structures were solved by direct methods (SHELXS-97)[31] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97).[32] Hydrogen atoms were inserted from geometry consideration using the HFIX option of the program. Crystal and intensity data for **14**: $C_{26}H_{29}NO_{10}$, M_r=515.50 g mol^{-1}, colorless, crystal size 0.20×0.08×0.06 mm, monoclinic, $P2_1/n$ [No. 14], a=6.8512 (3), b=17.8082 (8), c=20.3371 (10) Å, β=94.530 (2)°, V=2473.5 (2) Å^3, Z=4, D_{calc}=1.384 mg m^{-3}, μ=0.107 mm^{-1}, T=100 K, 12,220 reflections collected, 5239 independent reflections, 2364 reflections with $I > 2\sigma(I)$, θ_{max}=27.10°, 342 refined parameters, R=0.092, R_w=0.186, S=1.025, largest diff. peak and hole=0.3/−0.3 e Å^{-3}. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 182533. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

Generous financial support by the Deutsche Forschungsgemeinschaft (Leibniz award to A. F.) and by the Fonds der Chemischen Industrie is gratefully acknowledged. We thank Dr C. W. Lehmann for solving the X-ray structure of compound **14**.

References

1. (a) Gottesman, M. M.; Pastan, I. *Annu. Rev. Biochem.* **1993**, *62*, 385–427. (b) Patel, N. H.; Rothenberg, M. L. *Invest. New Drugs* **1994**, *12*, 1–13.
2. (a) Quesada, A. R.; Cravalos, M. D. G.; Puentes, J. L. F. *Br. J. Cancer* **1996**, *74*, 677–682. (b) Puentes, J. L. F.; Cravalos, M. D. G.; Rodriguez, A. US Patent 5,852,033, 1995.
3. (a) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54–62. (b) Boger, D. L.; Soenen, D. R.; Boyce, C. W.; Hedrick, M. P.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 2479–2483.
4. Fürstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637–6641.
5. Fürstner, A.; Bogdanovic, B. *Angew. Chem.* **1996**, *108*, 2583–2609 *Angew. Chem., Int. Ed. Engl.* **1996**, *35* 2442–2469.
6. Yoshida, W. Y.; Lee, K. K.; Carroll, A. R.; Scheuer, P. J. *Helv. Chim. Acta* **1992**, *75*, 1721–1725.
7. (a) Andersen, R. J.; Faulkner, D. J.; Cun-heng, H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 5492–5495. (b) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 4570–4574. (c) Reddy, M. V. R.; Faulkner, D. J.; Venkateswarlu, Y.; Rao, M. R. *Tetrahedron* **1997**, *53*, 3457–3466. (d) Urban, S.; Capon, R. J. *Aust. J. Chem.* **1996**, *49*, 711–713. (e) Carroll, A. R.; Bowden, B. F.; Coll, J. C. *Aust. J. Chem.* **1993**, *46*, 489–501. (f) Urban, S.; Hobbs, L.; Hooper, J. N. A.; Capon, R. J. *Aust. J. Chem.* **1995**, *48*, 1491–1494. (g) Urban, S.; Butler, M. S.; Capon, R. J. *Aust. J. Chem.* **1994**, *47*, 1919–1924. (h) Reddy, M. V. R.; Rao, M. R.; Rhodes, D.; Hansen, M. S. T.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901–1907.
(i) Davis, R. A.; Carroll, A. R.; Pierens, G. K.; Quinn, R. J. *J. Nat. Prod.* **1999**, *62*, 419–424.
8. Palermo, J. A.; Brasco, M. F. R.; Seldes, A. M. *Tetrahedron* **1996**, *52*, 2727–2734.
9. Kang, H.; Fenical, W. *J. Org. Chem.* **1997**, *62*, 3254–3262.
10. (a) Polycitone: Rudi, A.; Goldberg, I.; Stein, Z.; Frolow, F.; Benayahu, Y.; Schleyer, M.; Kashman, Y. *J. Org. Chem.* **1994**, *59*, 999–1003. (b) Rudi, A.; Evan, T.; Aknin, M.; Kashman, Y. *J. Nat. Prod.* **2000**, *63*, 832–833. (c) Purpurone: Chan, G. W.; Francis, T.; Thureen, D. R.; Offen, P. H.; Pierce, N. J.; Westley J. W.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1993**, *58*, 2544–2546.
11. See the following for leading references concerning the synthesis of these and related alkaloids: (a) Banwell, M. G.; Flynn, B. L.; Hamel, E.; Hockless, D. C. R. *Chem. Commun. (Cambridge)* **1997**, 207–208. (b) Banwell, M.; Flynn, B.; Hockless, D. *Chem. Commun. (Cambridge)* **1997**, 2259–2260. (c) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem.* **1997**, *109*, 158–159 *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 155–156. (d) Peschko, C.; Winklhofer, C.; Steglich, W. *Chem.-Eur. J.* **2000**, *6*, 1147–1152. (e) Gupton, J. T.; Krumpe, K. E.; Burnham, B. S.; Webb, T. M.; Shuford, J. S.; Sikorski, J. A. *Tetrahedron* **1999**, *55*, 14515–14522. (f) Ishibashi, F.; Miyazaki, Y.; Iwao, M. *Tetrahedron* **1997**, *53*, 5951–5962. (g) Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587–3595. (h) Diaz, M.; Guitian, E.; Castedo, L. *Synlett* **2001**, 1164–1166. (i) Ruchirawat, S.; Mutarapat, T. *Tetrahedron Lett.* **2001**, *42*, 1205–1208. (j) Terpin, A.; Polborn, K.; Steglich, W. *Tetrahedron* **1995**, *51*, 9941–9946. (k) Peschko, C.; Steglich, W. *Tetrahedron Lett.* **2000**, *41*, 9477–9481.
12. *Metal-catalyzed Cross-coupling Reactions*, Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.
13. Related cross coupling reactions have previously been used for the synthesis of some members of the lamellarin and lukianol series, cf. Ref. 11a,g. For previous applications of Suzuki and Negishi cross coupling reactions to the synthesis of cytotoxic natural products from our laboratory see: (a) Fürstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275–8280. (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817–2825. (c) Fürstner, A.; Grabowski, J.; Lehmann, C. W.; Kataoka, T.; Nagai, K. *ChemBioChem* **2001**, *2*, 60–68. (d) Fürstner, A.; Nikolakis, K. *Liebigs Ann.* **1996**, 2107–2113

14. Martina, S.; Enkelmann, V.; Wegner, G.; Schlüter, A. D. *Synthesis* **1991**, 613–615.
15. (a) Chen, W.; Cava, M. P. *Tetrahedron Lett.* **1987**, *28*, 6025–6026. (b) Donohoe, T. J.; Harji, R. R.; Cousins, R. P. C. *Tetrahedron Lett.* **2000**, *41*, 1327–1330.
16. (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168. (b) Miyaura, N.; Suzuki, A. *Chem. Rev. (Washington, DC)* **1995**, *95*, 2457–2483.
17. (a) Ebel, H.; Terpin, A.; Steglich, W. *Tetrahedon Lett.* **1998**, *39*, 9165–9166. (b) For an alternative enamide synthesis see: Fürstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett.* **2001**, *3*, 3955–3957.
18. (a) Fröde, R.; Hinze, C.; Josten, I.; Schmidt, B.; Steffan, B.; Steglich, W. *Tetrahedron Lett.* **1994**, *35*, 1689–1690. (b) Hashimoto, T.; Yasuda, A.; Akazawa, K.; Takaoka, S.; Tori, M.; Asakawa, Y. *Tetrahedron Lett.* **1994**, *35*, 2559–2560. (c) Hoshino, T.; Kojima, Y.; Hayashi, T.; Uchiyama, T.; Kaneko, K. *Biosci. Biotechnol. Biochem.* **1993**, *57*, 775–781.
19. Kashman, Y.; Koren-Goldshlager, G.; Gravalos, M. D. G.; Schleyer, M. *Tetrahedron Lett.* **1999**, *40*, 997–1000.
20. Trécourt, F.; Mallet, M.; Mogin, F.; Quéguiner, G. *Synthesis* **1995**, 1159–1162.
21. (a) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445–1453. (b) Fürstner, A. *Angew. Chem.* **1993**, *105*, 171–197 *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 164–189.
22. (a) Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317–6328. (b) Shum, P. W.; Kozikowski, A. P. *Tetrahedron Lett.* **1990**, *31*, 6785–6788.
23. Attempted formation of the corresponding Grignard reagent by insertion of magnesium into the C–Br bond was unsuccessful.
24. Review: Kustin, K.; McLeod, G. C. *Top. Curr. Chem.* **1977**, *69*, 1–37.
25. (a) Fürstner, A.; Grabowski, E. J. *ChemBioChem* **2001**, *2*, 706–709. (b) Fürstner, A.; Stelzer, F.; Rumbo, A.; Krause, H. *Chem.-Eur. J.* **2002**, *8*, 1856–1871.
26. (a) Borah, S.; Melvin, M. S.; Lindquist, N.; Manderville, R. A. *J. Am. Chem. Soc.* **1998**, *120*, 4557–4562. (b) Melvin, M. S.; Tomlinson, J. T.; Saluta, G. R.; Kucera, G. L.; Lindquist, N.; Manderville, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 6333–6334.
27. (a) Brackman, W.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 937–956. (b) Brackman, W.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 1100–1106. (c) Brackman, W.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 1107–1118.
28. Control experiments have been carried out which confirm that only a combination of compound **15** and $Cu(OAc)_2$ is effective, while incubation of the plasmid DNA with either **15** or $Cu(OAc)_2$ alone under otherwise identical conditions induces no strand cleavage.
29. For recent studies on other anticancer agents from this laboratory see: (a) Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem.-Eur. J.* **2001**, *7*, 5286–5298. (b) Fürstner, A.; Mathes, C.; Grela, K. *Chem. Commun. (Cambridge)* **2001**, 1057–1059. (c) Fürstner, A.; Guth, O.; Düffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem.-Eur. J.* **2001**, *7*, 4811–4820. (d) Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem.-Eur. J.* **2001**, *7*, 5299–5317. (e) Fürstner, A.; Rumbo, A. *J. Org. Chem.* **2000**, *65*, 2608–2611.
30. (a) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887–1901. (b) See also: Amat, M.; Hadida, S.; Sathyanarayana, S.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 10–11.
31. Sheldrick, G. M. *SHELXS-97: Program for the Determination of Crystal Structures*; University of Göttingen: Germany, 1997.
32. Sheldrick, G. M. *SHELXL-97: Program for Least-squares Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.