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Total Synthesis of Mycenarubin A, Sanguinolentaquinone and Mycenaflavin B and Their Cytotoxic Activities

Jana Backenköhler,[a] Bernhard Reck,[a] Markus Plaumann[b] and Peter Spiteller*[a]

Dedicated to Professor Wolfgang Steglich on the occasion of his 85th birthday.

Abstract: Here we report the first total synthesis of the fungal alkaloids mycenarubin A, sanguinolentaquinone and mycenaflavin B. The pyrroloquinoline alkaloid mycenarubin A was obtained in ten steps (21 % total yield, 92 % ee) from the known key precursor 6,7-dibenzyloxyindole via an asymmetric alkylation and a biomimetic ring closure as the key steps. The indolo-6,7-quinone sanguinolentaquinone was obtained in eight steps (28 % total yield). Mycenaflavin B was obtained in eight steps starting from the same key precursor (total yield 15 %) with a biomimetic ring closure and an acid-catalysed decarboxylation reaction as the key steps. The cytotoxic activities of mycenarubin A and mycenaflavin B were evaluated against mouse fibroblasts (L929) and human malignant melanoma cells (RPMI-7951).

Introduction

Pyrroloquinoline alkaloids isolated from marine organisms like isobatzellines, damirones and makaluvamines are known for their numerous biological activities, for instance their potent anti-tumour activity.[1–5] In 1993 Steglich *et al.* isolated the first fungal pyrroloquinoline alkaloid haematopodin (**1**) from the fruiting bodies of *Mycena haematopus*.[6] Other pyrroloquinoline alkaloids were isolated from *Mycena rosea* (mycenarubin A (**2**)),[7] *Mycena sanguinolenta* (sanguinone A and B along with the indolo-6,7-quinone alkaloid sanguinolentaquinone (**3**))[8] and *Mycena pelianthina* (pelianthinarubin A and B).[9] Recently, the previously unknown pyrroloquinoline alkaloids mycenaflavin A (**4a**) and mycenaflavin B (**4b**) have been isolated from the fruiting bodies of *Mycena haematopus* (Figure 1).[10]

So far, the biological activities and the ecological role of the fungal alkaloids have not been studied in detail. But mycenarubin A (**2**) (1.7 µmol) and the pelianthinarubins A and B (1.1 µmol) did not show antimicrobial activities against selected bacteria (*Escherichia coli, Bacillus brevis* and *B. subtilis*) or fungi (*Cladosporium cucumerinum)*.[7,9] However, the anti-tumour activities of these compounds and the biological activities of mycenaflavin B (**4b**) have not been examined so far on account of the limited quantities of mushroom material available.
Hence, we developed total syntheses of mycenarubin A (**2**) and mycenaflavin B (**4b**) and investigated the cytotoxic activities of the synthesised compounds.

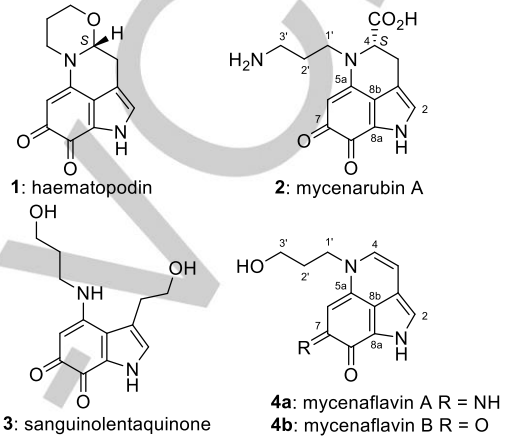

Figure 1. Pyrroloquinoline and indoloquinone alkaloids from mushrooms.

Results and Discussion

Two synthetic routes are known for the synthesis of pyrroloquinoline alkaloids.[11] In the first route the quinoline ring is constructed first and then the pyrrole ring is closed. This strategy was successfully used for the syntheses of the marine pyrroloquinoline alkaloids damirone A, B and C.[12,13] The second and most popular route starts with the formation of an indole scaffold followed by the closure of the piperidine ring. This synthetic strategy is similar to the proposed biosynthesis of pyrroloquinoline alkaloids.[11] Different methods for closing the piperidine ring have been described.[6,14–18] For instance, the piperidine ring can be constructed via a biomimetic Michael addition and reoxidation of the hydroquinone. This is an elegant cyclisation method reported by Steglich *et al.*,[6] Lown *et al.*,[16] Cava *et al.*[17] and our group.[18] The advantage of this method is that no functionalisation at the C-4 position of the indole is necessary. Thus, we intended to apply this strategy to synthesise mycenarubin A (**2**) (Scheme 1) and mycenaflavin B (**4b**).

In contrast to many marine pyrroloquinoline alkaloids[19] mycenarubin A (**2**) and mycenaflavin B (**4b**) possess side chains at N-5. These side chains should be introduced via reductive amination. The challenge of the synthesis of mycenarubin A (**2**) was the introduction of the stereocentre at the C-4 position.
We were able to synthesise an enantiopure tryptophan derivative **5** by using an enantioselective alkylation of *N*-(diphenylmethylene)glycine ethyl ester (**14**) in the presence of a cinchona alkaloid (Scheme 1). The required alkylation agent **6** could be obtained from the known aldehyde **7**.

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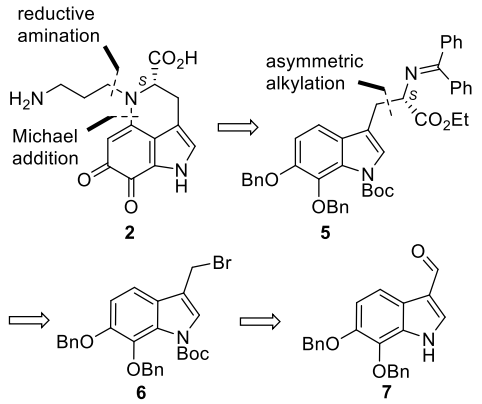
During our attempts to synthesise mycenarubin A (**2**), we observed an acid-catalysed decarboxylation reaction of the protected mycenarubin A **27**. Thus, we synthesised a racemic, OH-protected mycenarubin F derivative **33** which was decarboxylated and deprotected in one step to obtain mycenaflavin B (**4b**). Additionally, we synthesised the indolo-6,7-quinone alkaloid sanguinolentaquinone (**3**). Both syntheses will be discussed later.



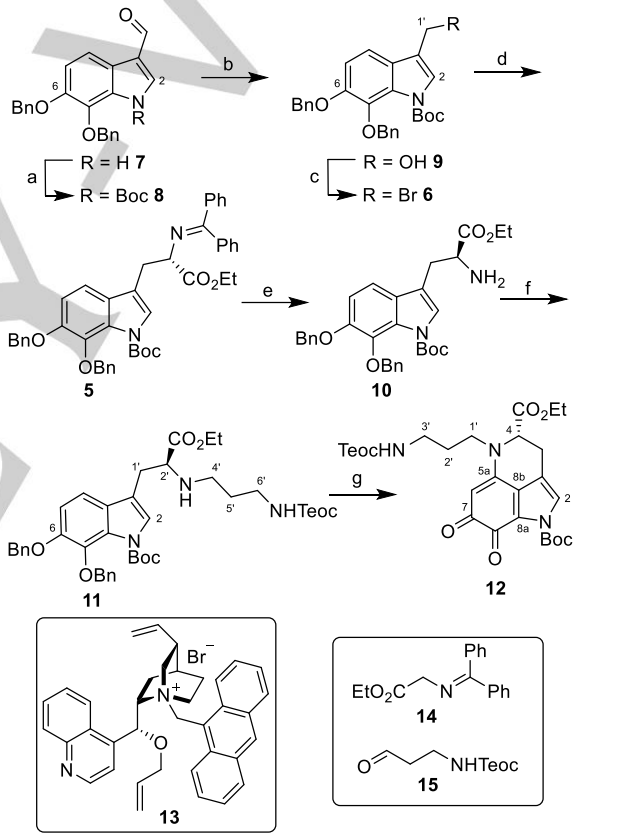
Scheme 1. Retrosynthetic analysis for the synthesis of mycenarubin A (**2**).

At first, the alkylating agent **6** for the enantioselective alkylation was prepared via three steps from the known 6,7-dibenzyloxyindole-3-carbaldehyde (**7**),[18] as outlined in Scheme 2. The Boc protection (Boc_2O, DMAP) of the carbaldehyde **7** gave the protected indole **8** (97 %). Reduction of the aldehyde with $NaBH_4$, followed by benzylic bromination with PBr_3 afforded the alkylation agent **6** in 94 % yield over two steps. The alkylation agent **6** is moisture- and heat-sensitive, thus purification and mass spectrometric analysis are not possible.

Recently, Ku *et al.* developed an asymmetric phase-transfer alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester in the presence of a cinchona alkaloid and successfully applied this strategy to the enantioselective synthesis of an (*S*)-tryptophan derivative (99 % ee).[20] Hence, we applied the above mentioned strategy to synthesise the (*S*)-tryptophan derivative **5**. In contrast to Ku *et al.* we used the known *N*-(diphenylmethylene)glycine ethyl ester (**14**)[21] for alkylation and Corey's cinchona catalyst **13**.[22] Phase-transfer catalytic conditions as described by Ku *et al.* (50 % aq. KOH in toluene/chloroform (7:3) at 0 °C) gave the tryptophan derivative **5** in 52 % yield.[20] When the alkylation was performed at −78 °C in dichloromethane and with $CsOH \times H_2O$, **5** was obtained in higher yields (91 %, 97% ee). The enantiopurity was determined by deprotection of the Schiff base under acidic conditions (2 M aq. HCl, THF), followed by derivatisation with (*R*)-Mosher's acid chloride (DMAP, Et_3N, CH_2Cl_2) and GC-MS analysis (see the SI).

The coupling product was converted into the free amine **10** by hydrolytic cleavage of the imine with aqueous HCl in THF (93 %). The Boc protective group was not removed under these conditions. Surprisingly, purification of the amine **10** by using acid-base extraction was not possible. Therefore, we purified the amine **10** by column chromatography (cyclohexane/EtOAc 5:1 to EtOAc/MeOH 19:1). In the next step, we intended to introduce the side chain via reductive amination. It was important to choose a protecting group for the amino group on the side chain which is selectively removable at the end of the total synthesis. Thus, we chose the Teoc protecting group which can be easily removed by fluoride ions. The corresponding aldehyde **15** was synthesised via two steps from 3-aminopropanol. First, 3-aminopropanol was *N*-Teoc protected using 4-nitrophenyl 2-(trimethylsilyl)ethyl carbonate and then the alcohol was oxidised to the aldehyde **15** by TEMPO oxidation (69 % yield over two steps).[23,24] The side chain **15** was introduced via reductive amination ($NaBH(OAc)_3$, AcOH, CH_2Cl_2, 91 %). Usage of $NaCNBH_3$ in MeOH afforded **11** in lower yield (54 %) and purity.

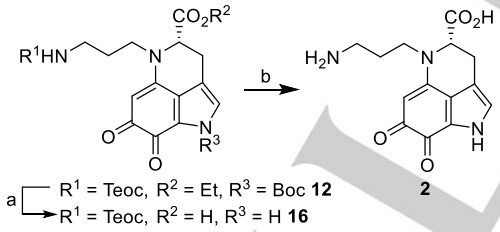
In the next step, the benzylic groups were deprotected under hydrogen atmosphere. Surprisingly, after removal of the catalyst and hydrogen atmosphere the resulting hydroquinone was not oxidised to the quinone by oxygen in the air atmosphere.



Scheme 2. Synthesis of the protected mycenarubin A **12**. *Reagents and conditions*: a) Boc_2O, DMAP, THF/CH_3CN (1:1), 12 h, rt, 97 %. b) $NaBH_4$, THF/EtOH (3:1), 3 h, rt, 98 %. c) PBr_3, Et_2O, 10 min, rt, 96 %. d) Corey's cinchona catalyst **13**, *N*-(diphenylmethylene)glycine ethyl ester (**14**), $CsOH \times H_2O$, CH_2Cl_2, 4 h, −78 °C, 91 % (97 % ee). e) 2 M aq. HCl, THF, 4 h, rt, 93 %. f) **15**, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, 12 h, rt, 91 % g) H_2, Pd/C, MeOH, 1 h, rt then Et_3N, MnO_2, air, 1 h, rt, 49 %.

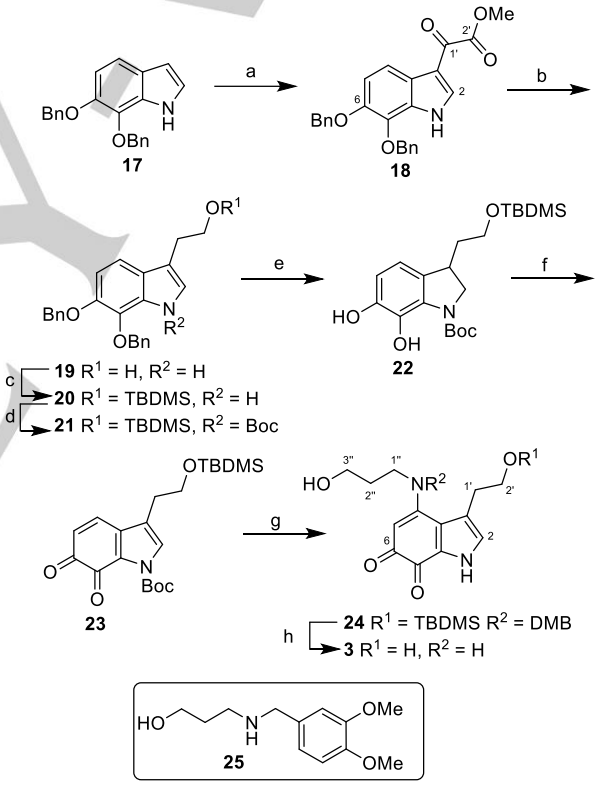
Presumably the 2,3-double bond of the pyrrole ring was also reduced during the hydrogenation due to the electron-withdrawing effect of the Boc protecting group.

After addition of MnO_2 the reaction mixture turned red immediately, indicating the formation of the pyrroloquinoline **12**. The pyrroloquinoline **12** was obtained in 49 % yield after column chromatography. LiOH-induced ester hydrolysis at 55 °C gave the *N*-Teoc protected mycenarubin A **16** in 89 % yield (Scheme 3). Finally, we intended to cleave the *N*-Teoc protective group with TBAF. First, we treated the *N*-Teoc protected mycenarubin A **16** with an excess of TBAF in DMF. These conditions led to Teoc deprotection but unfortunately the formed mycenarubin A (**2**) was mostly *N*-formyl protected. Suchý *et al.* have already described the formylation of amines in presence of DMF and a base.[25] To avoid the undesired formylation reaction, we treated the *N*-Teoc protected mycenarubin A **16** with an excess of TBAF in DMSO but we could not observe any conversion. Addition of CsF to the TBAF containing reaction mixture immediately led to the formation of mycenarubin A (**2**). Treatment of the *N*-Teoc protected mycenarubin A **16** with CsF alone did not result in deprotection. Thus, a mixture of CsF and TBAF is necessary for the Teoc deprotection. Purification of mycenarubin A (**2**) was achieved by ion exchange chromatography (DOWEX 50WX8, eluent: 25 % aq. NH_3; 76 % yield, 92 % ee). The enantiomeric excess of the synthesised mycenarubin A (**2**) was determined by *N*-Boc protection, derivatisation of the carboxylic acid with a proline derivative and separation of the resulting diastereomers by LC-MS (see the SI). The specific rotation of the synthesised mycenarubin A (**2**) ($[\alpha]_D^{20}$ = +647 (*c* = 0.0034, H_2O)) was lower than the specific rotation of the natural product reported in the literature ($[\alpha]_D^{25}$ = +1190 (*c* = 0.00807, H_2O)).[7] Thus, we isolated mycenarubin A (**2**) from an extract of *Mycena rosea* by the known procedure[7] and found a lower specific rotation for the natural product ($[\alpha]_D^{20}$ = +669 (*c* = 0.0055, H_2O)) which is in agreement with the specific rotation of the synthesised mycenarubin A (**2**). Mycenarubin A (**2**) slowly decomposes even at −40 °C, hence the optical rotation decreases gradually.



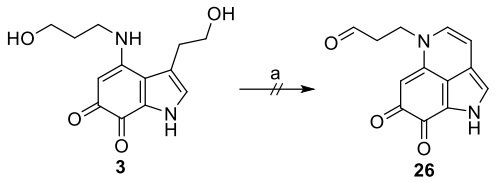
Scheme 3. Synthesis of mycenarubin A (**2**). *Reagents and conditions:* a) 0.1 M aq. LiOH, THF, 48 h, 55 °C, 89 %. b) CsF, TBAF (1 M in THF), DMSO, 5 min, rt, 76 % (92 % ee).

Different strategies for the synthesis of mycenaflavin B (**4b**) were applied (see the SI). The first generation synthesis (Scheme 4) started with the protected methyl indolyl-3-glyoxylic acid **18** which was prepared by the reaction of the indole **17** with oxalyl chloride followed by the addition of MeOH (yield 86 %). Reduction of **18** with an excess of lithium aluminium hydride at reflux in THF (92 %) yielded the alcohol **19**, which was protected as a TBDMS ether (yield 97 %). *N*-protection of **20** with Boc_2O and DMAP in THF gave the fully protected indole **21** in 93 % yield. Henceforward, we used the procedure of Steglich *et al.* as the guideline for our synthesis.[26] The benzylic groups of the protected alcohol **21** were removed by hydrogenation in the presence of Pd/C in EtOAc (98 %). Unfortunately, the 2,3 double bond of the pyrrole ring was also reduced due to electron-withdrawing effect of the Boc protective group. Moreover, the indoline **22** was not oxidised to the corresponding quinone by aerial oxygen. Using DDQ the double bond was reestablished and the catechol was oxidised to afford the quinone **23** in one step with 91 % yield. Next, we intended to introduce a side chain at the C-4 position using a Michael addition. We used the DMB-protected 3-aminopropanol **25**[26] as the nucleophile because primary amines do not react selectively with quinones. The resulting hydroquinone was oxidised to the quinone by oxygen in an air atmosphere. Additionally, a transamination reaction led to the removal of the Boc group. Treatment of the protected sanguinolentaquinone **24** with trifluoroacetic acid in dichloro-methane gave sanguinolentaquinone (**3**) in 72 % yield after purification by column and size exclusion chromatography.



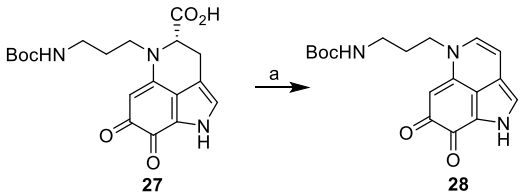
Scheme 4. Total synthesis of sanguinolentaquinone (**3**). *Reagents and conditions*: a) $(COCl)_2$, diethyl ether, 30 min, 0 °C then MeOH, 30 min, rt, 86 %. b) $LiAlH_4$, THF, 3 h, reflux, 92 %. c) TBDMSCl, imidazole, DMF, 12 h, rt, 97 %. d) Boc_2O, DMAP, THF, 12 h, rt, 92 %. e) H_2 (1 atm), Pd/C, EtOAc, 4 h, rt, 98 %. f) DDQ, toluene, 5 min, rt, 91 %. g) 3-[*N*-(3,4-dimethoxybenzyl)amino]-propan-1-ol (**25**), air, CH_3CN, 72 h, rt, 59 %. h) CF_3CO_2H, CH_2Cl_2, 1 h, rt, 72 %.

However, attempts to oxidatively cyclise sanguinolentaquinone (**3**) to obtain the mycenaflavin B derivative **26** by using Dess-Martin periodinane have not been successful (Scheme 5).



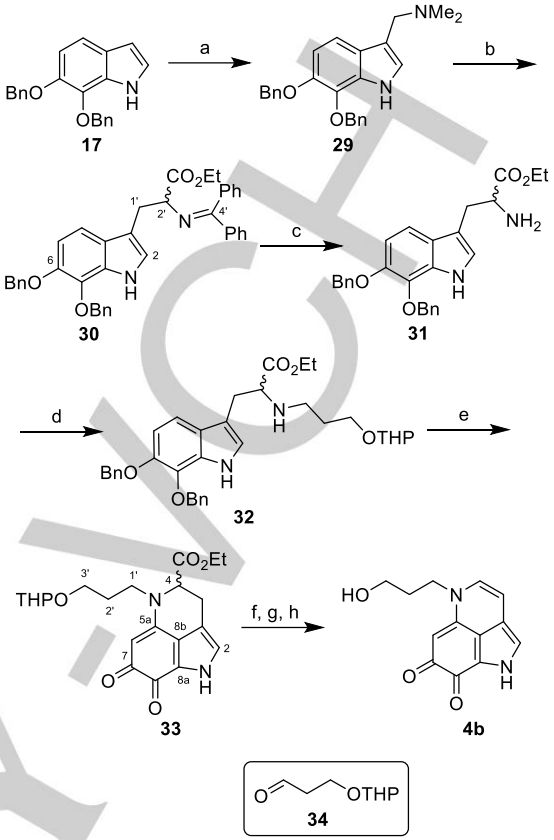
Scheme 5. Attempts to oxidise sanguinolentaquinone (**3**) to form the mycenaflavin B derivative **26**. *Reagents and conditions*. a) Dess-Martin periodinane, CH_2Cl_2, 2 h, 0 °C to rt.

During our attempts to synthesise mycenarubin A (**2**) we observed an unexpected side reaction (Scheme 6). When the *N*-Boc protected mycenarubin A **27** was treated with a Lewis or Brønsted acid, a decarboxylation reaction took place. Fortunately, we were able to use this strategy for the total synthesis of mycenaflavin B (**4b**).



Scheme 6. Attempted deprotection of the *N*-Boc protected mycenarubin A derivative **27** with a Lewis or Brønsted acid. *Reagents and conditions*: a) $SnCl_4$, DMF or AcOH, THF, H_2O.

Since the carboxylic acid should be removed in the last step of the synthesis of mycenaflavin B (**4b**), the synthesis of an enantiopure tryptophan derivative **5** was not necessary. Thus, we developed a shorter synthesis of a racemic tryptophan derivative **30** (Scheme 7). The synthesis started with Mannich reaction of the indole **17** with Eschenmoser's salt (96 %).[26] Somei-Kametani coupling of the known gramine **29** and *N*-(diphenylmethylene)glycine ethyl ester (**14**) in the presence of 0.5 eq. tributylphosphine gave the protected tryptophan derivative **30** in 92 % yield. Although tributylphosphine has only a catalytic effect on the reaction, 0.5 eq. tributylphosphine are advisable because residues of benzophenone (impurity from benzophenone imine used for the synthesis of **14**) deactivate the phosphine catalyst. The coupling product can be converted into the free amine **31** upon hydrolysis of the imine with aqueous hydrochloric acid (93 %). In the case of **31** purification by a simple acid-base extraction was possible (presumably, due to the absence of the *N*-Boc protecting group). Again the side chain was introduced via reductive amination (3-(tetrahydro-2*H*-pyran-2-yl)oxypropanal (**34**),[27] $NaCNBH_3$, 88 %). We used a THP-protected propanal derivative **34** because the THP group can be removed during the final acidic decarboxylation due to the acid labiality of the THP protecting group (Scheme 7).



Scheme 7. Total synthesis of mycenaflavin B (**4b**). *Reagents and conditions*: a) Eschenmoser's salt, CH_2Cl_2, 2 h, rt, 96 %. b) *N*-(Diphenylmethylene)glycine ethyl ester (**14**), PBu_3, CH_3CN, 12 h, reflux, 92 %. c) 2 M HCl, THF, 4 h, 0 °C to rt, 99 %. d) 3-(Tetrahydro-2*H*-pyran-2-yloxy)propan-1-al (**34**), $NaCNBH_3$, MeOH, 12 h, rt, 88 %. e) H_2, Pd/C, MeOH, 1 h, rt, then Et_3N, air, 1 h, 39 %. f) LiOH, THF/H_2O (1:1), 48 h, 55 °C. g) AcOH, MeOH/H_2O (2:1), 40 °C, 2 h. h) AcOH, rt, 72 h, 48 % over three steps.

The benzylic groups were removed by catalytic hydrogenation, subsequently the hydroquinone was oxidised to the corresponding quinone **33** under air atmosphere (39 % yield).

In this case the addition of MnO_2 was not necessary, presumably again due to the absence of the *N*-Boc protecting group. A one pot synthesis was finally used to synthesise mycenaflavin B (**4b**) from the pyrroloquinoline **33**. First, the ethyl ester was converted into the carboxylic acid using aq. LiOH in THF at 55 °C. After acidification with AcOH complete decarboxylation took place at 40 °C within 2 h. Finally, further addition of AcOH and stirring at rt for 3 days led to THP deprotection and to the formation of mycenaflavin B (**4b**) (48% over three steps). Purification of mycenaflavin B (**4b**) was achieved by HPLC. The ^{13}C chemical shifts and the width of ^{1}H and ^{13}C signals of mycenaflavin B (**4b**) strongly depend on the pH value. Only small changes of the pH value lead to shifting and broadening of the signals. Particularly, the signals of C-2 and C-8a are affected by a change of the pH value.

The resulting synthetic mycenarubin A (**2**) and mycenaflavin B (**4b**) were evaluated for their antimicrobial activity against three soil bacteria. Mycenarubin A (**2**) did not display antimicrobial activity against *Azospirillum brasilense*, *Azoarcus tolulyticus* and *Azovibrio restrictus* (1 µmol). Mycenaflavin B (**4b**) did not exhibit antimicrobial activity against *Azospirillum brasilense* and *Azoarcus tolulyticus* but revealed a moderate activity against *Azovibrio restrictus* (inhibition zone: Ø = 0.8 cm, 1 µmol).[10]

Additionally, we tested the cytotoxic activities of mycenarubin A (**2**) and mycenaflavin B (**4b**). Two fast growing cell lines, mouse fibroblast L929 and human malignant melanoma RPMI-7951, were incubated for up to 52 h using three different concentrations of each compound (up to 870 µM for mycenarubin A (**2**) and up to 1170 µM for mycenaflavin B (**4b**)).

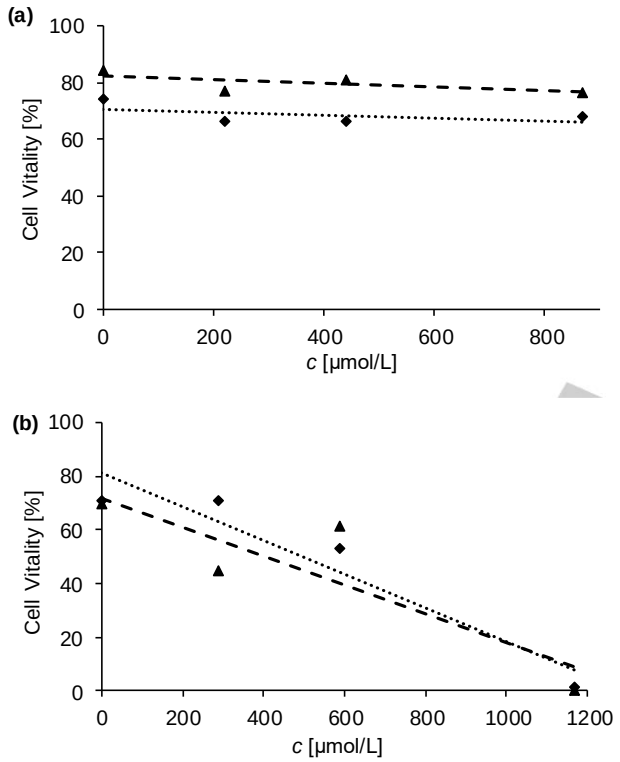


Figure 2. Concentration-dependent effects of mycenarubin A (**2**) or mycenaflavin B (**4b**) on the vitality of different cell lines. The mouse fibroblasts L929 (diamonds) and cells of the human malignant melanoma cell line RPMI-7951 (triangles) were incubated for up to 52 h with mycenarubin A (**2**) (a) or for up to 44 h with mycenaflavin B (**4b**) (b) with the concentrations indicated. The dotted and the dashed regression lines refer to the data points obtained for L929 cells and RPMI-7951 cells, respectively.

Incubation times of more than 50 h and concentrations of mycenarubin A (**2**) up to 870 µM had no adverse effects on the vitality of the fibroblasts and melanoma cells (Figure 2 (a)). A complete different behaviour is observable for mycenaflavin B (**4b**). The alkaloid **4b** revealed a moderate cytotoxicity with a 50 % cytotoxic concentration (CC_{50}) of 400 µM for fibroblasts and 500 µM for melanoma cells, respectively (Figure 2 (b)). Unfortunately, no anti-tumour activities were found for mycenaflavin B (**4b**). The cytotoxicity of mycenaflavin B (**4b**) could result from its planarity and therefore the possibility of DNA-intercalation.

Conclusions

The enantioselective total synthesis of mycenarubin A (**2**) and total syntheses of sanguinolentaquinone (**3**) and mycenaflavin B (**4b**) have been achieved in 10, 8 and 8 steps, respectively, starting from the key precursor 6,7-dibenzyloxyindole (**17**). Key steps to obtain mycenarubin A (**2**) were an enantioselective alkylation reaction with *N*-(diphenylmethylene)glycine ethyl ester (**14**) in the presence of a cinchona alkaloid derived catalyst and a biomimetic ring closure. The key step for the synthesis of mycenaflavin B (**4b**) was an acid catalysed decarboxylation reaction forming the enamine. The total yields are ranging from 21 % (92 % ee) for mycenarubin A (**2**), 28 % for sanguinolentaquinone (**3**) to 15 % for mycenaflavin B (**4b**). These efficient synthetic routes allowed the examination of the antimicrobial and anti-tumour activity of the synthesised compounds. Non-antimicrobial and non-cytotoxic properties were observed for mycenarubin A (**2**). Mycenaflavin B (**4b**) has shown a moderate activity against the soil bacterium *Azovibrio restrictus* (inhibition zone: Ø = 0.8 cm, 1 µmol) and a moderate cytotoxicity with a CC_{50} of 400 µM for fibroblasts and 500 µM for melanoma cells, respectively.

Experimental Section

General: Syntheses which are sensitive to oxygen or air humidity were performed in glassware dried by heating in vacuo and under an argon atmosphere. Dry CH_2Cl_2, CH_3CN, THF and toluene were directly taken from the solvent purification system SPS-800 constructed by M. Braun. DMF and DMSO were distilled over phosphorus pentoxide and stored over molecular sieve (3 Å). Methanol and ethanol were distilled over calcium oxide and also stored over molecular sieve (3 Å). Et_2O was stored over sodium. Purification of reaction products was carried out by column chromatography using silica gel 60 (40−63 µm) as stationary phase. Analytical thin-layer chromatography was performed with TLC aluminum foils coated with silica gel 60 F_{254} purchased from Merck. Visualisation was accomplished by UV light (254 nm and 366 nm) or staining with $KMnO_4$ solution. ^{1}H NMR spectra were recorded on an Avance WB-360, an Avance NB-360 (both 360 MHz) at 293 K or an Avance DRX-600 spectrometer (Bruker Daltonics, 600 MHz) at 300 K and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm, CD_3OD at 3.31 ppm, D_2O at 4.75 ppm[28] and *d*$_6$-DMSO at 2.50 ppm). Data are reported as s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). Coupling constants are quoted in Hz and signals were integrated. Proton-decoupled ^{13}C NMR spectra were recorded on an Avance WB-360 (91 MHz) at 293 K or an Avance DRX-600 (151 MHz) spectrometer at 300 K and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm, CD_3OD at 49.00 ppm and *d*$_6$-DMSO at 39.52 ppm). The ^{13}C chemical shifts measured in D_2O were calibrated by the IUPAC recommendations[29] using the conversion factor of 0.25144953 for calculating the absolute frequency of ^{13}C (0.0 ppm). EIMS and HR-EIMS spectra were obtained on a MAT 95 spectrometer (Finnigan MAT). ESIMS spectra were

recorded on an Esquire LC (Bruker). HR-ESIMS spectra were obtained on a QExactive Plus Orbitrap (Thermo Fisher Scientific). Infrared spectra were recorded on a Nicolet iS10 FT-IR spectrometer (Thermo Fisher Scientific). Melting points were measured with a melting point apparatus 530 from Büchi, UV-Vis spectra were recorded on a Genesys 10S UV-VIS spectrophotometer (Thermo Fisher Scientific). Optical rotation values were measured on a Perkin-Elmer 243 polarimeter and CD spectra were recorded on a Chirascan spectrometer (Applied Photophysics). Preparative HPLC separations were performed on Waters 510 pumps equipped with an automated gradient controller 680 and a Waters 486 UV/vis detector. The samples were separated on a Nucleodur C-18ec column (5 µm, 16 × 250 mm) by the use of the following gradient programm: 10 min at 100% H_2O (+ 0.1% AcOH) then within 20 min to MeOH-H_2O (50:50), then within 5 min linear to 100% MeOH (flow rate: 6 mL/min; UV/vis detection at 440 nm).

Cytotoxicity Tests: A Dulbecos Modified Eagle Medium (500 mL DMEM, 50 mL FCS and 1 g Ciprofloxacin) was used as the incubation medium. The cells were incubated for up to 52 h. After the incubation time, the cells were carefully washed and trypan blue solution was added to 100 µL cell suspension. The dead cells take up the dye and the rate between the healthy cells and the dead cells was determined by counting two loaded chambers (each with 9 squares) of a hemocytometer under the microscope (further details see the SI).

Antimicrobial Assay: For plate diffusion assays, **2** (0.29 mg, 1 µmol) or **4b** (0.24 mg, 1 µmol) was dissolved in H_2O and was dropped onto paper discs (Ø 6 mm, thickness 0.5 mm). These paper discs were dried under sterile conditions and then placed on agar plates inoculated with the respective test organism (*Azospirillum brasilense* (sp7), *Azoarcus tolulyticus* (Td-1) and *Azovibrio restrictus* (DSM 23866, DSMZ)). The plates were incubated at 37 °C for 24 h.

6,7-Dibenzyloxy-1-(*tert*-butyloxycarbonyl)indole-3-carbaldehyde (8). To a solution of aldehyde **7**[18] (0.40 g, 1.10 mmol) in a mixture of THF (10 mL) and CH_3CN (10 mL) Boc_2O (0.36 g, 1.65 mmol) and DMAP (0.13 g, 1.10 mmol) were added. The mixture was stirred at ambient temperature for 12 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, $CHCl_3$/MeOH 19:1) to afford **8** (0.49 g, 1.07 mmol, 97 %) as a yellow solid. R_f = 0.83 ($CHCl_3$/MeOH 19:1); m.p. 107 °C; ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 1.61 (s, 9H, Boc), 5.20 (s, 4H, C*H*$_2$Ph), 7.16 (d, ^3J(H-5,H-4) = 8.5 Hz, 1H, H-5), 7.27 − 7.49 (m, 10H, CH_2*Ph*), 7.98 (d, ^3J(H-4,H-5) = 8.5 Hz, 1H, H-4), 8.03 (s, 1H, H-2), 10.03 ppm (s, 1H, C*H*O); ^{13}C NMR (90.5 MHz, $CDCl_3$, 293 K): δ = 28.0 (Boc), 72.6 (*C*H$_2$Ph), 75.2 (*C*H$_2$Ph), 85.2 (Boc), 114.5 (C-5), 117.4 (C-4), 121.1 (C-3), 123.0 (C-3a), 127.9 (CH_2*Ph*), 128.0 (CH_2*Ph*), 128.1 (CH_2*Ph*), 128.3 (CH_2*Ph*), 128.6 (CH_2*Ph*), 128.9 (CH_2*Ph*), 130.4 (C-7a), 137.0 (C-7), 137.1 (CH_2*Ph*), 137.7 (CH_2*Ph*), 138.8 (C-2), 147.7 (C-6), 151.4 (Boc), 185.6 ppm (*C*HO); IR (ATR): ν = 695, 714, 735, 745, 772, 804, 817, 851, 905, 922, 1012, 1028, 1034, 1048, 1080, 1147, 1181, 1224, 1236, 1263, 1284, 1332, 1372, 1385, 1394, 1418, 1457, 1475, 1503, 1557, 1579, 1618, 1676, 1755, 2833, 2862, 2909, 2938, 2979 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 457 (0.5) $[M]^{+\cdot}$, 401 (0.5) $[M - C_4H_9]^+$, 357 (0.5) $[M - Boc]^+$, 266 (8) $[M - Boc - Bn]^+$, 91 (100) $[C_7H_7]^+$; HRMS (EI): calcd. for $C_{28}H_{27}NO_5$ $[M]^+$ 457.18837; found: 457.18885.

6,7-Dibenzyloxy-1-(*tert*-butyloxycarbonyl)-3-(hydroxymethyl)indole (9). The protected aldehyde **8** (1.25 g, 2.70 mmol) was dissolved in a mixture of THF (45 mL) and ethanol (15 mL). $NaBH_4$ (0.21 g, 5.46 mmol) was added and the mixture was stirred at ambient temperature for two hours. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL) and was washed with sat. aq. $NaHCO_3$ solution (100 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by flash column chromatography (SiO_2, $CHCl_3$/MeOH 19:1) to afford **9** (1.22 g, 2.65 mmol, 98 %) as a yellow solid. R_f = 0.45 ($CHCl_3$/MeOH 19:1); m.p. 122 °C; ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 1.60 (s, 9H, Boc), 1.83 (s_{br}, 1H, O*H*), 4.76 (s, 2H, H-1′), 5.18 (s, 4H, C*H*$_2$Ph), 7.05 (d, ^3J(H-5,H-4) = 8.3 Hz, 1H, H-5), 7.27 – 7.48 ppm (m, 12H, CH_2*Ph*, H-4, H-2); ^{13}C NMR (90.5 MHz, $CDCl_3$, 293 K): δ = 28.1 (Boc), 57.2 (C-1′), 73.1 (*C*H$_2$Ph), 75.3 (*C*H$_2$Ph), 83.3 (Boc), 113.6 (C-5), 114.5 (C-4), 119.8 (C-3), 125.9 (C-2), 127.0 (C-3a), 127.8 (CH_2*Ph*), 127.9 (CH_2*Ph*), 128.2 (CH_2*Ph*), 128.5 (CH_2*Ph*), 129.0 (CH_2*Ph*), 130.1 (C-7a), 137.5 (CH_2*Ph*), 138.0 (CH_2*Ph*, C-7), 148.6 (C-6), 150.6 ppm (Boc); IR (ATR): ν = 695, 717, 736, 771, 797, 836, 845, 853, 905, 925, 989, 1001, 1027, 1045, 1079, 1146, 1159, 1223, 1237, 1262, 1347, 1371, 1388, 1421, 1456, 1475, 1500, 1557, 1614, 1676, 1747, 2857, 2936, 2979, 3028, 3059, 3413 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 459 (3) $[M]^{+\cdot}$, 268 (14) $[M - Boc - Bn]^+$, 250 (7) $[M - Boc - Bn - H_2O]^+$, 222 (7), 91 (100) $[C_7H_7]^+$; HRMS (EI): calcd. for $C_{28}H_{29}NO_5$ $[M]^+$ 459.20402; found: 459.20385.

6,7-Dibenzyloxy-3-(bromomethyl)-1-(*tert*-butyloxycarbonyl)indole (6). Alcohol **9** (0.57 g, 1.25 mmol) was suspended in diethyl ether (20 mL) and treated with PBr_3 (44 µL, 0.45 mmol) at 0 °C. The mixture was stirred for 10 minutes at ambient temperature. Sat. aq. $NaHCO_3$ solution (20 mL) was added and the phases were separated. The organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo to afford **6** (0.63 g, 1.20 mmol, 96 %) as a yellow solid which was used immediately without further purification. ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 1.59 (s, 9H, Boc), 4.64 (s, 2H, H-1′), 5.17 (s, 2H, C*H*$_2$Ph), 5.19 (s, 2H, C*H*$_2$Ph), 7.10 (d, ^3J(H-5,H-4) = 7.7 Hz, 1H, H-5), 7.28 – 7.48 (m, 11H, CH_2*Ph*, H-4), 7.53 ppm (s, 1H, H-2); ^{13}C NMR (90.5 MHz, $CDCl_3$, 293 K): δ = 24.9 (C-1′), 28.1 (Boc), 73.1 (*C*H$_2$Ph), 75.4 (*C*H$_2$Ph), 83.7 (Boc), 113.7 (C-5), 114.5 (C-4), 116.5 (C-3), 126.4 (C-3a), 127.2 (C-2), 127.9 (CH_2*Ph*), 128.0 (CH_2*Ph*), 128.2 (CH_2*Ph*), 128.6 (CH_2*Ph*), 129.0 (CH_2*Ph*), 130.2 (C-7a), 137.5 (CH_2*Ph*), 138.0 (CH_2*Ph*, C-7), 148.3 (C-6), 151.0 ppm (Boc); IR (ATR): ν = 674, 695, 718, 740, 759, 767, 796, 821, 839, 855, 906, 928, 991, 1001, 1009, 1027, 1042, 1080, 1152, 1198, 1211, 1226, 1240, 1260, 1348, 1378, 1419, 1439, 1456, 1477, 1497, 1572, 1596, 1615, 1638, 1676, 1754, 2862, 2946, 2978, 3023, 3059, 3399 cm^{-1}.

(*S*)-6,7-Dibenzyloxy-1-(*tert*-butyloxycarbonyl)-*N*-(diphenylmethylene)tryptophan ethyl ester (5). A solution of bromide **6** (0.71 g, 1.36 mmol) in dry CH_2Cl_2 (20 mL) was cooled to −78 °C. Subsequently, *N*-(diphenylmethylene)glycine ethyl ester (**14**)[21] (0.37 g, 1.36 mmol), *O*-allyl-*N*-9-anthracenylmethylcinchonidium bromide (**13**)[22] (84 mg, 0.0136 mmol) and CsOH×H_2O (0.78 g, 5.17 mmol) were added and the reaction mixture was stirred at −78 °C for four hours. Water (20 mL) and EtOAc (20 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (2×20 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 5:1) to afford **5** (0.88 g, 1.24 mmol, 91 %) as a yellow viscous oil. The enantioselectivity was determined by GC-MS (97 % ee, see the SI). R_f = 0.37 (cyclohexane/EtOAc 5:1); $[\alpha]_D^{20}$ = −85.5 (*c* = 1.446, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 1.30 (t, $^3J(CH_3,CH_2)$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.55 (s, 9H, Boc), 3.24 (dd, ^2J(H-1′,H-1′) = 14.2 Hz, ^3J(H1′,H-2′) = 9.1 Hz, 1H, H-1′), 3.35 (dd, ^2J(H-1′,H-1′) = 14.2 Hz, ^3J(H-1′,H-2′) = 4.4 Hz, 1H, H-1′), 4.17 (m, 2H, $CO_2CH_2CH_3$), 4.39 (dd, ^3J(H-2′,H-1′) = 9.1 Hz, ^3J(H-2′,H-1′) = 4.4 Hz, 1H, H-2′), 5.17 (s, 2H, C*H*$_2$Ph), 5.23 (s, 2H, C*H*$_2$Ph), 6.69 (d, ^3J(H,H) = 7.2 Hz, 2H, Ph), 6.90 (m, 1H, H-4, H-5), 7.17 − 7.65 ppm (m, 18H, CH_2*Ph*, Ph); ^{13}C NMR (90.5 MHz, $CDCl_3$, 293 K): δ = 14.2 ($CO_2CH_2CH_3$), 27.9 (Boc), 28.6 (C-1′), 61.0 ($CO_2CH_2CH_3$), 65.2 (C-2′), 72.9 (*C*H$_2$Ph), 75.0 (*C*H$_2$Ph), 82.6 (Boc), 113.1 (C-5), 114.0 (C-4), 115.9 (C-3), 126.4 (C-2), 127.5 (Ph), 127.6 (Ph), 127.7 (Ph), 127.8 (Ph), 127.9 (Ph), 128.0 (Ph), 128.2 (Ph), 128.3 (C-3a),

128.4 (Ph), 128.7 (Ph), 128.8 (Ph), 129.3 (C-7a), 130.2 (Ph), 135.7 (Ph), 137.4 (Ph), 137.6 (C-6), 137.9 (Ph), 139.2 (Ph), 148.4 (Boc), 150.1 (C-5), 170.9 (C-4'), 171.7 ppm (CO_2Et); IR (ATR): ν = 694, 742, 781, 796, 853, 907, 1023, 1066, 1105, 1151, 1233, 1255, 1351, 1368, 1419, 1446, 1496, 1575, 1597, 1615, 1733, 2850, 2925, 2977 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 708 (2) $[M]^+$, 608 (8) $[M - Boc]^+$, 517 (19) $[M - Boc - Bn]^+$, 489 (9) $[M - Boc - Bn - CO]^+$, 342 (14), 307 (14), 266 (10), 193 (17), 91 (100) $[C_7H_7]^+$; HRMS (EI): calcd. for $C_{45}H_{44}N_2O_6$ $[M]^+$ 708.31939; found: 708.32019.

(*S*)-6,7-Dibenzyloxy-1-(*tert*-butyloxycarbonyl)tryptophan ethyl ester (10). To a solution of the protected tryptophan **5** (0.53 g, 0.75 mmol) in THF (14 mL) 1 M HCl (14 mL) was added and the mixture was stirred at ambient temperature for four hours. THF was removed under reduced pressure. The residue was neutralised with sat. aq. $NaHCO_3$ solution and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic phases were dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash column chromatography (SiO_2, first cyclohexane/EtOAc 5:1 to remove impurities like benzophenone then EtOAc/MeOH 19:1) to afford **10** (0.38 g, 0.68 mmol, 93 %) as a brown oil which slowly solidifies. $[\alpha]_D^{20}$ = +2.5 (c = 0.264, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 1.24 (t, $^3J(CH_3,CH_2)$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.60 (s, 9H, Boc), 1.66 (s_{br}, 2H, NH_2), 2.94 (dd, ^2J(H-1',H-1') = 14.4 Hz, ^3J(H-1',H-2') = 7.5 Hz, 1H, H-1'), 3.14 (dd, ^2J(H-1',H-1') = 14.4 Hz, ^3J(H-1',H-2') = 5.3 Hz, 1H, H-1'), 3.80 (dd, ^3J(H-2',H-1') = 7.5 Hz, ^3J(H-2',H-1') = 5.3 Hz, 1H, H-2'), 4.16 (q, $^3J(CH_2,CH_3)$ = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 5.17 (s, 2H, CH_2Ph), 5.20 (s, 2H, CH_2Ph), 7.04 (d, ^3J(H-5,H-4) = 8.5 Hz, 1H, H-5), 7.22 (d, ^3J(H-4,H-5) = 8.5 Hz, 1H, H-4), 7.27 – 7.49 ppm (m, 11H, CH_2Ph, H-2); ^{13}C NMR (91 MHz, $CDCl_3$, 293 K): δ = 14.1 ($CO_2CH_2CH_3$), 27.9 (Boc), 30.4 (C-1'), 54.3 (C-2'), 60.8 ($CO_2CH_2CH_3$), 72.7 (CH_2Ph), 75.0 (CH_2Ph), 82.8 (Boc), 113.1 (C-5), 113.9 (C-4), 115.3 (C-3), 125.9 (C-2), 127.5 (CH_2Ph), 127.6 (CH_2Ph), 127.7 (CH_2Ph), 127.9 (CH_2Ph), 128.1 (C-3a), 128.3 (CH_2Ph), 128.7 (CH_2Ph), 129.6 (CH_2Ph), 137.3 (CH_2Ph), 137.7 (C-7a), 137.8 (C-7), 148.3 (C-6), 150.3 (Boc), 174.8 ppm (CO_2Et); IR (ATR): ν = 695, 718, 737, 756, 770, 795, 837, 846, 854, 905, 925, 1010, 1027, 1079, 1149, 1188, 1224, 1238, 1262, 1329, 1350, 1369, 1392, 1419, 1456, 1475, 1499, 1570, 1600, 1614, 1677, 1746, 2856, 2904, 2935, 2978, 3025, 3058, 3387 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 544 (2) $[M]^+$, 444 (4) $[M - Boc]^+$, 353 (9) $[M - Boc - Bn]^+$, 342 (23), 252 (12), 189 (4), 161 (4), 132 (4), 91 (100) $[C_7H_7]^+$; HRMS (EI): calcd. for $C_{32}H_{36}N_2O_6$ $[M]^{+\cdot}$: 544.25679; found: 544.25726.

(*S*)-*N*-[(*N*-(2-(Trimethylsilyl)ethyloxycarbonyl)-3-aminopropyl]-6,7-dibenzyloxy-1-(*tert*-butyloxycarbonyl)tryptophan ethyl ester (11). To a solution of the tryptophan derivative **10** (0.20 g, 0.37 mmol) in CH_2Cl_2 (5 mL) sodium triacetoxyborohydride (0.11 g, 0.51 mmol) and acetic acid (24 µL) were added. After five minutes a solution of *N*-(2-(trimethylsilyl)ethyloxycarbonyl)-3-aminopropan-1-al (**15**)[23,24] (0.092 g, 0.42 mmol) in CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred at ambient temperature overnight. Sat. aq. $NaHCO_3$ solution (10 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$), the solvent was removed in vacuo and the crude product was purified by flash column chromatography (SiO_2, $CHCl_3$/MeOH 49:1) to afford **11** (0.25 g, 0.34 mmol, 91 %) as a yellow oil. R_f = 0.13 ($CHCl_3$/MeOH 49:1); $[\alpha]_D^{20}$ = +1.85 (c = 1.328, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ = −0.02 (s, 9H, $Si(CH_3)_3$), 0.91 (t, $^3J(CH_2Si,CH_2)$ = 8.5 Hz, 2H, $CH_2Si(CH_3)_3$), 1.05 (t, $^3J(CH_3,CH_2)$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.53 (s, 9H, Boc), 1.76 − 1.80 (m, 2H, H-5'), 2.68 – 2.80 (m, 2H, H-4'), 3.10 − 3.24 (m, 4H, H-1', H-6'), 3.71 (t, ^3J(H-2',H-1') = 7.1 Hz, 1H, H-2'), 3.99 − 4.09 (m, 4H, $CO_2CH_2CH_3$, OCH_2CH_2Si), 5.10 (s, 2H, CH_2Ph), 5.11 (s, 2H, CH_2Ph), 5.42 (s_{br}, 1H, NH), 6.97 (d, ^3J(H-5,H-4) = 8.4 Hz, 1H, H-5), 7.20 (d, ^3J(H-4,H-5) = 8.4 Hz, 1H, H-4), 7.21 − 7.40 ppm (m, 11H, CH_2Ph, H-2); ^{13}C NMR (151 MHz, $CDCl_3$, 300 K): δ = −1.4 ($Si(CH_3)_3$), 14.1 ($CO_2CH_2CH_3$), 17.8 ($CH_2Si(CH_3)_3$), 28.1 (Boc, C-1'), 28.6 (C-5'), 38.7 (C-6'), 45.4 (C-4'), 61.1 (C-2'), 61.5 ($CH_2CH_2Si(CH_3)_3$), 63.1 ($CO_2CH_2CH_3$), 72.9 (CH_2Ph), 75.2 (CH_2Ph), 83.2 (Boc), 113.3 (C-5), 114.0 (C-4), 114.3 (C-3), 126.4 (C-2), 127.7 (CH_2Ph), 127.8 (CH_2Ph), 127.9 (C-3a), 128.1 (CH_2Ph), 128.5 (CH_2Ph), 128.9 (CH_2Ph), 129.7 (C-7a), 137.4 (CH_2Ph), 137.8 (CH_2Ph), 138.0 (C-7), 148.5 (C-6), 150.5 (Boc), 157.2 ($SiCH_2CH_2OC$=O), 172.2 ppm (CO_2Et); IR (ATR): ν = 695, 734, 801, 836, 934, 1023, 1152, 1232, 1350, 1369, 1421, 1454, 1498, 1608, 1716, 1751, 2951, 3321 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 745 (5) $[M]^{+\cdot}$, 645 (10) $[M - Boc]^+$, 554 (4) $[M - Boc - Bn]^+$, 527 (7), 436 (6), 408 (7), 342 (100) $[M - Boc - CH(CO_2Et)NHCH_2CH_2NHC(O)OCH_2CH_2Si(CH_3)_3]^+$, 303 (18), 275 (16), 185 (23), 174 (8), 116 (12) $[HOCH_2CH_2Si(CH_3)_3]$, 91 (81) $[C_7H_7]^+$, 73 (23) $[Si(CH_3)_3/CO_2Et]^+$; HRMS (EI): calcd. for $C_{41}H_{55}N_3O_8Si$ $[M]^{+\cdot}$ 745.37529; found: 745.37499.

1-(*tert*-Butyloxycarbonyl)-*N*-[2-(trimethylsilyl)ethoxycarbonyl]-mycenarubin A ethyl ester (12). An argon-purged suspension of the tryptophan derivative **11** (0.13 g, 0.174 mmol) and 10 % Pd/C (40 mg) in MeOH (90 mL) was stirred under a hydrogen atmosphere (1 atm, balloon) at ambient temperature. After one hour, the catalyst was filtered off. Subsequently, triethylamine (100 µL) and MnO_2 (1.0 g) were added to the filtrate which was stirred for an additional hour under air atmosphere. The reaction mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, $CHCl_3$/MeOH 49:1) to afford **12** (48 mg, 85 µmol, 49 %) as a red solid. R_f = 0.19 ($CHCl_3$/MeOH 49:1); $[\alpha]_D^{20}$ = +511 (c = 0.009, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$, 300 K): δ = 0.01 (s, 9H, $Si(CH_3)_3$), 0.95 (t, $^3J(CH_2Si,CH_2)$ = 8.6 Hz, 2H, $CH_2Si(CH_3)_3$), 1.20 (t, $^3J(CH_3,CH_2)$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.61 (Boc), 1.73 − 1.78 (m, 1H, H-2'), 1.92 − 1.96 (m, 2H, H-2'), 3.14 − 3.25 (m, 4H, H-3, H-1', H-3'), 3.29 − 3.34 (m, 1H, H-3'), 3.65 − 3.67 (m, 1H, H-1'), 4.10 − 4.13 (m, 4H, $CO_2CH_2CH_3$, CH_2CH_2Si), 4.37 − 4.41 (m, 1H, H-4), 5.13 (t, ^3J(NH,H-3') = 6.2 Hz, 1H, NH), 5.46 (s, 1H, H-6), 7.32 ppm (s, 1H, H-2); ^{13}C NMR (151 MHz, $CDCl_3$, 300 K): δ = −1.4 ($Si(CH_3)_3$), 14.2 ($CO_2CH_2CH_3$), 17.9 ($CH_2Si(CH_3)_3$), 24.0 (C-3), 27.8 (Boc), 27.9 (C-2'), 38.4 (C-3'), 49.6 (C-1'), 62.1 (C-4), 62.4 ($CO_2CH_2CH_3$), 63.3 (CH_2CH_2Si), 86.6 (Boc), 96.3 (C-6), 114.3 (C-2a), 125.1 (C-8b), 125.8 (C-2), 129.6 (C-8a), 147.8 (Boc), 151.7 (C-5a), 157.3 ($SiCH_2CH_2OC$=O), 169.0 (C-8), 170.4 (CO_2Et), 179.2 ppm (C-7); IR (ATR): ν = 695, 719, 737, 769, 796, 837, 906, 921, 1027, 1080, 1150, 1186, 1238, 1261, 1311, 1348, 1370, 1392, 1420, 1455, 1475, 1500, 1528, 1558, 1603, 1683, 1746, 2935, 2978, 3327 cm^{-1}; UV/vis (MeOH): λ^{max} (ε) = 507 (2416), 336 (17265), 254 (20580), 202 nm (25993 mol^{-1} dm^3 cm^{-1}); MS (ESI$^+$): *m/z*: 562 $[M + H]^+$, 584 $[M + Na]^+$; HRMS (ESI$^+$): calcd. for $C_{27}H_{39}N_3O_8SiNa^+$ $[M + Na]^+$ 584.23986; found: 584.24023.

***N*-[2-(Trimethylsilyl)ethoxycarbonyl]mycenarubin A (16).** The pyrroloquinoline **12** (52 mg, 93 µmol) was dissolved in THF (5 mL) and 0.1 M aq. LiOH solution (5 mL) was added. The reaction mixture was stirred for 16 h at 55 °C. Subsequently, AcOH (31 µL) was added and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH 3:2) to afford **16** (36 mg, 83 µmol, 89 %) as a purple solid. R_f = 0.75 (CH_2Cl_2/MeOH 3:2); $[\alpha]_D^{20}$ = +249 (c = 0.007, MeOH); ^{1}H NMR (600 MHz, CD_3OD, 300 K): δ = 0.04 (s, 9H, $Si(CH_3)_3$), 0.97 (t, $^3J(CH_2Si,CH_2)$ = 8.3 Hz, 2H, $CH_2Si(CH_3)_3$). 1.86 − 1.98 (m, 2H, H-2'), 3.14 − 3.41 (m, 6H, H-3, H-1', H-3'), 3.79 − 3.83 (m, 1H, H-3'), 4.12 (t, $^3J(CH_2,CH_2Si)$ = 8.3 Hz, CH_2CH_2Si), 4.23 (d, ^3J(H-4,H-3) = 7.2 Hz, 1H, H-4), 5.42 (s, 1H, H-6), 6.95 ppm (s, 1H, H-2). ^{13}C NMR (151 MHz, CD_3OD, 300 K): δ = −1.4 ($Si(CH_3)_3$), 18.6 ($CH_2Si(CH_3)_3$), 25.5 (C-3), 29.2 (C-2'), 39.3 (C-1'), 50.4 (C-3'), 63.9 (CH_2CH_2Si), 66.9 (C-4), 93.4 (C-6), 117.9 (C-2a), 125.9 (C-8b), 126.1 (C-2), 127.0 (C-8a), 157.4 ($SiCH_2CH_2OC$=O), 159.3 (C-5a), 173.1 (C-8), 176.5 (CO_2H), 180.5 ppm (C-6). IR (ATR): ν = 668, 694, 719, 738, 755, 769, 795, 857, 905, 926,

941, 1027, 1034, 1044, 1066, 1078, 1106, 1151, 1187, 1225, 1240, 1261, 1328, 1352, 1368, 1393, 1418, 1442, 1455, 1476, 1498, 1574, 1599, 1725, 1745, 2901, 2976, 3057, 3388, 3675 cm^{-1}. UV/vis (MeOH): λ^{max} (ε) = 529 (1590), 357 (16965), 245 (24612), 216 nm (12536 $mol^{-1}dm^3cm^{-1}$); MS (ESI^-): *m/z* = 432 [*M* − H]$^-$, 866 [2*M* − H]$^-$. HRMS (ESI^-): calcd. for $C_{20}H_{26}N_3O_6Si^-$ [*M* − H]$^-$ 432.15964; found: 432.15988.

Mycenarubin A (2). To a solution of the protected pyrroloquinoline **16** (10.0 mg, 21 µmol) in DMSO (2 mL) CsF (14.0 mg, 92 µmol) and 1 M TBAF in THF (0.1 mL, 100 µmol) were added. The reaction mixture was stirred for 5 minutes. The solvent was removed in vacuo. The crude product was purified by ion-exchange chromatography (DOWEX 50WX8, eluent: 25% aq. NH_3) to afford **2** (5.1 mg, 17.6 µmol, 76 %, 92 % ee) as a red solid. $[\alpha]_D^{20}$ = +647 (*c* = 0.0034, H_2O) (natural product: $[\alpha]_D^{20}$ = +669 (*c* = 0.0055, H_2O)); CD (H_2O): λ (Δε) = 243 (−3.2), 263 (+1.0), 280 (+1.0), 310 (+1.4), 363 (−3.5), 514 nm (+1.3 L mol^{-1} cm^{-1}); ^{1}H NMR (600 MHz, D_2O, 300 K): δ = 2.01 – 2.12 (m, 2H, H-2'), 3.08 − 3.22 (m, 4H, H-3, H-3'), 3.34 (ddd, ^2J(H-1',H-1') = 14.1 Hz, ^3J(H-1',H-2') = 7.1 Hz, ^3J(H-1',H-2') = 7.1 Hz, 1H, H-1'), 3.75 (ddd, ^2J(H-1',H-1') = 14.1 Hz, ^3J(H-1',H-2') = 7.1 Hz, ^3J(H-1',H-2') = 7.1 Hz, 1H, H-1'), 4.26 (d, ^3J(H-4,H-3) = 6.8 Hz, 1H, H-4), 5.36 (s, 1H, H-6), 6.96 ppm (s, 1H, H-2); ^{13}C NMR (151 MHz, D_2O, 300 K): δ = 26.9 (C-3), 28.0 (C-2'), 39.8 (C-3'), 51.2 (C-1'), 68.2 (C-4), 95.3 (C-6), 118.9 (C-2a), 127.0 (C-8b), 127.8 (C-8a), 128.8 (C-2), 159.3 (C-5a), 174.3 (C-8), 179.3 (*C*O_2H), 182.3 ppm (C-7); (ATR): *v* = 666, 694, 738, 766, 808, 998, 1024, 1106, 1152, 1235, 1246, 1326, 1370, 1417, 1442, 1455, 1498, 1519, 1548, 1579, 1606, 1651, 1672, 1716, 1751, 2951, 3032, 3065, 3324 cm^{-1}; UV/vis (MeOH): λ^{max} (ε) = 527 (377), 355 (4000), 246 (7088), 200 nm (4211 $mol^{-1}dm^3cm^{-1}$); MS (ESI^+): *m/z* = 290 [*M* + H]$^+$, 312 [*M* + Na]$^+$. HRMS (ESI^+): calcd. for $C_{14}H_{15}N_3O_4Na^+$ [*M* + Na]$^+$ 312.09548; found: 312.09541.

Methyl 6,7-dibenzyloxyindole-3-glyoxylate (18). To a solution of the key precursor **17** (3.28 g, 10.0 mmol) in diethyl ether (50 mL) oxalyl chloride (1.5 mL, 17.2 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then quenched with MeOH (2 mL, 50 mmol). The mixture was allowed to warm to ambient temperature over 30 min. The resulting yellow precipitate was collected by filtration, washed with cold diethyl ether and dried in vacuo to afford **18** (3.58 g, 8.6 mmol, 86 %) as a yellow solid. m.p. 146 °C; ^{1}H NMR (360 MHz, *d*$_6$-DMSO, 293 K): δ = 3.88 (s, 3H, CO_2CH_3), 5.18 (s, 2H, CH_2Ph), 5.20 (s, 2H, CH_2Ph), 7.20 (d, ^3J(H-5,H-4) = 8.7 Hz, 1H, H-5), 7.29 − 7.52 (m, 10H, CH_2*Ph*), 7.80 (d, ^3J(H-4,H-5) = 8.7 Hz, 1H, H-4), 8.28 (d, ^3J(H-2,NH) = 3.3 Hz, 1H, H-2), 12.43 ppm (s_{br}, 1H, N*H*); ^{13}C NMR (90.5 MHz, *d*$_6$-DMSO, 293 K): δ = 52.6 (CO_2CH_3), 71.3 (*C*H_2Ph), 74.4 (*C*H_2Ph), 112.5 (C-5), 112.8 (C-3), 116.3 (C-4), 121.7 (C-3a), 127.8 (CH_2*Ph*), 127.9 (CH_2*Ph*), 128.0 (CH_2*Ph*), 128.1 (CH_2*Ph*), 128.4 (CH_2*Ph*), 128.5 (CH_2*Ph*), 131.4 (C-7a), 133.7 (C-7), 137.2 (CH_2*Ph*), 137.3 (C-2), 147.5 (C-6), 163.9 (C-2'), 178.5 ppm (C-1'); IR (ATR): *v* = 682, 695, 717, 743, 773, 840, 879, 906, 959, 974, 1026, 1062, 1104, 1121, 1143, 1222, 1237, 1254, 1278, 1296, 1330, 1366, 1383, 1416, 1453, 1470, 1507, 1610, 1640, 1733, 2862, 2950, 3031, 3150, 3313 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 415 (17) [*M*]$^{+\cdot}$, 356 (3) [*M* – CO_2CH_3]$^+$, 324 (15) [*M* – Bn]$^+$, 296 (6) [*M* – Bn – CO]$^+$, 264 (4), 236 (4), 91 (100) [C_7H_7]$^+$; HRMS (EI): calcd. for $C_{25}H_{21}NO_5$ [*M*]$^{+\cdot}$: 415.14142; found: 415.14088.

6,7-Dibenzyloxy-3-(2-hydroxyethyl)indole (19). A suspension of lithium aluminum hydride (2.6 g, 68 mmol) in THF (100 mL) was heated to reflux. To this suspension a solution of the ester **18** (2.0 g, 4.8 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for three hours under reflux and afterwards allowed to cool to ambient temperature. Excess $LiAlH_4$ was quenched with water. The reaction mixture was filtered and the residue was washed with hot THF. The filtrate was dried over $MgSO_4$ and evaporated to afford **19** (1.64 g, 4.4 mmol, 92 %) as violet crystals. m.p. 86 °C; ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 1.55 (s_{br}, 1H, O*H*), 2.97 (t, ^3J(H-1',H-2') = 6.3 Hz, 2H, H-1'), 3.87 (t, ^3J(H-2',H-1') = 6.3 Hz, 2H, H-2'), 5.21 (s, 2H, CH_2Ph), 5.22 (s, 2H, CH_2Ph), 6.92 (s, 1H, H-2), 6.93 (d, ^3J(H-5,H-4) = 8.7 Hz, 1H, H-5), 7.24 (d, ^3J(H-4,H-5) = 8.7 Hz, 1H, H-4), 7.34 − 7.51 (m, 10H, CH_2*Ph*), 7.93 ppm (s_{br}, 1H, N*H*); ^{13}C NMR (90.5 MHz, $CDCl_3$, 293 K): δ = 28.9 (C-1'), 62.7 (C-2'), 73.1 (*C*H_2Ph), 75.6 (*C*H_2Ph), 110.6 (C-5), 112.5 (C-3), 114.0 (C-4), 122.3 (C-2), 124.6 (C-3a), 127.8 (CH_2*Ph*), 128.0 (CH_2*Ph*), 128.3 (CH_2*Ph*), 128.5 (CH_2*Ph*), 128.7 (CH_2*Ph*), 131.6 (C-7a), 134.6 (C-7), 137.7 (CH_2*Ph*), 138.1 (CH_2*Ph*), 146.5 ppm (C-6); IR (ATR): *v* = 666, 695, 751, 910, 929, 955, 991, 1020, 1042, 1065, 1184, 1217, 1257, 1305, 1335, 1347, 1369, 1440, 1453, 1467, 1505, 1628, 2864, 2924, 3033, 3061, 3242, 3399 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 373 (18) [*M*]$^{+\cdot}$, 282 (25) [*M* − Bn]$^+$,255 (5) [*M* – Bn – H_2O]$^+$, 254 (30) [*M* – Bn – CO]$^+$, 236 (5) [*M* – Bn – CO – H_2O]$^+$, 91 (100) [C_7H_7]$^+$; HRMS (EI): calcd. for $C_{24}H_{23}NO_3$ [*M*]$^{+\cdot}$: 373.16725; found: 373.16622.

6,7-Dibenzyloxy-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)indole (20). To a solution of the alcohol **19** (0.84 g, 2.25 mmol) in DMF (20 mL) imidazole (0.34 g, 5.00 mmol) and TBDMSCl (0.51 g, 3.37 mmol) were added. The reaction mixture was stirred for 12 h at ambient temperature. Water (50 mL) was added and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic phases were washed with water (3×50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, $CHCl_3$) to afford **20** (1.07 g, 2.20 mmol, 97 %) as a colorless oil. R_f = 0.57 ($CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 0.19 (s, 6H, SiCH_3), 1.07 (s, 9H, SiC(CH_3)$_3$), 3.08 (t, ^3J(H-1',H-2') = 7.3 Hz, 2H, H-1'), 4.01 (t, ^3J(H-2',H-1') = 7.3 Hz, 2H, H-2'), 5.31 (s, 2H, CH_2Ph), 5.33 (s, 2H, CH_2Ph), 6.94 (d, ^3J(H-2,NH) = 2.2 Hz, 1H, H-2), 7.05 (d, ^3J(H-5,H-4) = 8.6 Hz, 1H, H-5), 7.38 (d, ^3J(H-4,H-5) = 8.6 Hz, 1H, H-4), 7.44 −7.63 (m, 10H, CH_2*Ph*), 7.99 ppm (s_{br}, 1H, N*H*); ^{13}C NMR (90.5 MHz, $CDCl_3$, 293 K): δ = –5.2 (Si*C*H_3), 18.5 (Si*C*(CH$_3$)$_3$), 26.1 (SiC(*C*H_3)$_3$), 29.2 (C-1'), 63.9 (C-2'), 73.0 (*C*H_2Ph), 75.4 (*C*H_2Ph), 110.3 (C-5), 113.3 (C-3), 114.0 (C-4), 121.9 (C-2), 125.0 (C-3a), 127.7 (CH_2*Ph*), 127.9 (CH_2*Ph*), 128.1 (CH_2*Ph*), 128.4 (CH_2*Ph*), 128.5 (CH_2*Ph*), 131.2 (C-7a), 134.4 (C-7), 137.8 (CH_2*Ph*), 138.2 (CH_2*Ph*), 146.2 ppm (C-6); IR (ATR): *v* = 662, 696, 714, 729, 750, 756, 771, 789, 809, 834, 853, 913, 938, 1005, 1014, 1030, 1067, 1083, 1098, 1131, 1185, 1225, 1254, 1276, 1303, 1348, 1372, 1390, 1439, 1451, 1466, 1477, 1498, 1509, 1576, 1631, 2856, 2884, 2928, 2951, 3426 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 487 (33) [*M*]$^{+\cdot}$, 396 (10) [*M* – Bn]$^+$, 368 (21) [*M* – Bn – CO]$^+$, 264 (18) [*M* – Bn – OTBDMS]$^+$, 236 (32) [*M* – Bn – CO – OTBDMS]$^+$, 208 (14), 91 (100) [C_7H_7]$^+$; HRMS (EI): calcd. for $C_{30}H_{37}O_3NSi$ [*M*]$^+$: 487.25372, found: 487.25392.

6,7-Dibenzyloxy-1-(*tert*-butyloxycarbonyl)-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)indole (21). To a solution of the protected alcohol **20** (1.13 g, 2.32 mmol) in THF (100 mL) Boc_2O (0.76 g, 3.48 mmol) and a catalytic amount of DMAP were added. The reaction mixture was stirred at ambient temperature for 12 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 3:1) to afford **21** (1.26 g, 2.15 mmol, 92 %) as a colorless solid. R_f = 0.59 (cyclohexane/EtOAc 3:1); m.p. 106 °C; ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 0.12 (s, 6H, SiCH_3), 1.01 (s, 9H, SiC(CH_3)$_3$), 1.68 (s, 9H, Boc), 2.94 (t, ^3J(H-1',H-2') = 6.7 Hz, 2H, H-1'), 3.97 (t, ^3J(H-2',H-1') = 6.7 Hz, 2H, H-2'), 5.24 (s, 2H, CH_2Ph), 5.27 (s, 2H, CH_2Ph), 7.10 (d, ^3J(H-5,H-4) = 8.5 Hz, 1H, H-5), 7.25 (d, ^3J(H-4,H-5) = 8.5 Hz, 1H, H-4), 7.36 – 7.58 ppm (m, 11H, CH_2*Ph*, H-2); ^{13}C NMR (90.5 MHz, $CDCl_3$, 293 K): δ = −5.3 (Si*C*H_3), 18.4 (Si*C*(CH$_3$)$_3$), 26.0 (SiC(*C*H$_3$)$_3$), 28.1 (Boc), 28.5 (C-1'), 62.7 (C-2'), 73.1 (*C*H_2Ph), 75.2 (*C*H_2Ph), 82.7 (Boc), 113.3 (C-5), 114.0 (C-4), 117.2 (C-3), 125.5 (C-2), 127.7 (CH_2*Ph*), 127.8 (CH_2*Ph*), 128.1 (CH_2*Ph*), 128.4 (CH_2*Ph*), 128.8 (C-3a), 128.9 (CH_2*Ph*), 129.6 (C-7a), 137.6 (C-7), 138.1 (CH_2*Ph*), 148.7 (C-6), 150.3 ppm (Boc); IR (ATR): *v* = 663, 695, 716, 730,

739, 749, 757, 770, 781, 797, 811, 837, 912, 925, 935, 975, 1010, 1025, 1042, 1061, 1097, 1134, 1160, 1224, 1239, 1255, 1316, 1349, 1372, 1388, 1424, 1439, 1455, 1465, 1495, 1509, 1746, 2856, 2884, 2908, 2927, 2950, 3426 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 587 (2) $[M]^{+\cdot}$, 487 (3) $[M - Boc]^+$, 396 (13), 368 (6), 264 (10), 236 (15), 208 (7), 91 (100) $[C_7H_7]^+$, 73 (9) $[Si(CH_3)_3]^+$, 57 (15) $[C_4H_9]^+$; HRMS (EI): calcd. for $[M]^+$ $C_{35}H_{45}NO_5Si$: 587.30615, found: 587.30695.

1-(*tert*-Butyloxycarbonyl)-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)-6,7-dihydroxyindoline (22). An argon-purged suspension of compound **21** (1.02 g, 1.74 mmol) and 10 % Pd/C (0.20 g) in EtOAc (200 mL) was stirred under a hydrogen atmosphere (1 atm, balloon) at ambient temperature. After four hours, the catalyst was filtered off and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 9:1) to afford **22** (0.70 g, 1.7 mmol, 98 %) as a colorless solid. R_f = 0.32 (cyclohexane/EtOAc 9:1); m.p. 65 °C; ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 0.07 (s, 3H, SiC*H*$_3$), 0.08 (s, 3H, SiC*H*$_3$), 0.92 (s, 9H, SiC(C*H*$_3$)$_3$), 1.55 (s, 9H, Boc), 1.55 – 1.63 (m, 1H, H-1'), 1.96 (dddd, ^2J(H-1',H-1') = 14.3 Hz, ^3J(H-1',H-2') = 5.1 Hz, ^3J(H-1',H-2') = 5.1 Hz, ^3J(H-1',H-3) = 5.1 Hz, 1H, H-1'), 3.28 – 3.35 (m, 1H, H-3), 3.67 – 3.79 (m, 3H, H-2, H-2'), 4.13 (dd, ^2J(H-2,H-2) = 11.5 Hz, ^3J(H-2,H-3) = 9.3 Hz, 1H, H-2) 5.80 (s_{br}, 1H, O*H*), 6.53 (d, ^3J(H-5,H-4) = 8.0 Hz, 1H, H-5), 6.64 (d, ^3J(H-4,H-5) = 8.0 Hz, H-4), 11.46 ppm (s, 1H, O*H*); ^{13}C NMR (91 MHz, $CDCl_3$, 293 K): δ = −5.3 ($SiCH_3$), 18.3 (Si*C*(CH$_3$)$_3$), 26.0 (SiC(*C*H$_3$)$_3$), 28.4 (Boc), 37.6 (C-3), 37.9 (C-1'), 56.1 (C-2), 61.6 (C-2'), 82.9 (Boc), 110.3 (C-5), 114.5 (C-4), 127.2 (C-3a), 128.2 (C-7a), 132.2 (C-7), 145.9 (C-6), 154.9 ppm (Boc); IR (ATR): *v* = 660, 721, 776, 807, 825, 883, 907, 938, 965, 986, 1005, 1024, 1080, 1097, 1155, 1202, 1219, 1250, 1294, 1309, 1339, 1366, 1376, 1417, 1472, 1613, 1655, 2855, 2884, 2928, 2952, 3476 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 409 (17) $[M]^{+\cdot}$, 353 (28) $[M - C(CH_3)_3]^+$, 309 (100) $[M - Boc]^+$, 296 (94), 252 (87) $[M - Boc - C(CH_3)_3]^+$, 176 (73), 57 (43) $[C(CH_3)_3]^+$; HRMS (EI): calcd. for $^{\cdot}C_{21}H_{35}NO_5Si$ $[M]^{+\cdot}$ 409.22845; found: 409.22984.

1-(*tert*-Butoxycarbonyl)-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1*H*-indolo-6,7-quinone (23). To a solution of the indoline **22** (0.39 g, 0.95 mmol) in toluene (40 mL) DDQ (0.48 g, 2.14 mmol) was added. The reaction mixture was stirred at ambient temperature for five minutes. The suspension was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 1:1) to afford **23** (0.35 g, 0.86 mmol, 91 %) as a red solid. R_f = 0.76 (cyclohexane/EtOAc 1:1); m.p. 110 °C; ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = −0.04 (s, 6H, SiC*H*$_3$), 0.81 (s, 9H, SiC(C*H*$_3$)$_3$), 1.57 (s, 9H, Boc), 2.63 (t, ^3J(H-1',H-2') = 6.1 Hz, 2H, H-1'), 3.70 (t, ^3J(H-2',H-1') = 6.1 Hz, 2H, H-2'), 6.09 (d, ^3J(H-5,H-4) = 9.9 Hz, 1H, H-5), 7.30 (d, ^3J(H-4,H-5) = 9.9 Hz, 1H, H-4), 7.37 ppm (s, 1H, H-2); ^{13}C NMR (91 MHz, $CDCl_3$, 293 K): δ = −5.4 ($SiCH_3$), 18.3 (Si*C*(CH$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 27.4 (Boc), 27.6 (C-1'), 63.1 (C-2'), 86.4 (Boc), 122.7 (C-3), 125.7 (C-5), 127.1 (C-7a), 130.8 (C-2), 134.8 (C-3a), 137.0 (C-4), 147.6 (Boc), 167.0 (C-7), 183.0 ppm (C-6); IR (ATR): *v* = 660, 679, 702, 765, 774, 791, 836, 860, 920, 941, 1005, 1038, 1079, 1101, 1127, 1153, 1256, 1273, 1291, 1325, 1370, 1391, 1418, 1445, 1460, 1473, 1490, 1612, 1664, 1738, 2854, 2883, 2927, 2957, 3136 cm^{-1}; UV/vis (MeOH): λ^{max} (ε) = 380 (5538), 218 (21420), 204 nm (18803 $mol^{-1}dm^3cm^{-1}$); MS (ESI^+): *m/z* = 428 $[M + Na]^+$, 444 $[M + K]^+$, 833 $[2M + Na]^+$; HRMS (ESI^+): calcd. for $C_{21}H_{31}NO_5SiNa^+$ $[M + Na]^+$ 428.1864; found: 428.1865.

4-(*N*-(3-Hydroxypropyl)-*N*-(3,4-dimethoxybenzyl)amino)-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)indolo-6,7-quinone (24). To a solution of the quinone **23** (0.30 g, 0.74 mmol) in acetonitrile (30 mL) 3-[*N*-(3,4-dimethoxybenzyl)amino]propan-1-ol[26] (**25**) (0.33 g, 1.48 mmol) was added. The reaction mixture was stirred three days at ambient temperature under air atmosphere. Subsequently, water (100 mL) was added and the aqueous phase was extracted with chloroform (6×20 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, $CHCl_3$/MeOH 9:1) to afford **24** (0.23 g, 0.44 mmol, 59 %) as a red oil. R_f = 0.37 ($CHCl_3$/MeOH 9:1); ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = −0.03 (s, 6H, SiC*H*$_3$), 0.82 (s, 9H, SiC(C*H*$_3$)$_3$), 1.85 – 1.88 (m, 2H, H-2''), 2.81 (t, ^3J(H-1',H-2') = 6.8 Hz, 2H, H-1'), 3.38 (s_{br}, 2H, H-1''), 3.72 – 3.87 (m, 10H, DMB, H-3", H-2'), 4.46 (s, 2H, DMB), 5.57 (s, 1H, H-5), 6.75 – 6.79 (m, 3H, DMB), 7.14 (s, 1H, H-2), 11.90 ppm (s_{br}, 1H, N*H*); ^{13}C NMR (90.5 MHz, $CDCl_3$, 293 K): δ = −5.3 ($SiCH_3$), 18.3 (Si*C*(CH$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 29.5 (C-2''), 30.4 (C-1'), 47.5 (C-1''), 55.9 (DMB), 59.2 (C-3"), 63.3 (C-2'), 104.5 (C-5), 111.0 (DMB), 111.1 (DMB), 120.8 (C-3), 121.2 (DMB), 126.0 (C-3a), 128.1 (DMB), 128.9 (C-2), 130.0 (C-7a), 148.7 (DMB), 149.2 (DMB), 163.1 (C-4), 170.0 (C-7), 179.6 ppm (C-6); IR (ATR): *v* = 660, 749, 774, 809, 831, 918, 1025, 1058, 1090, 1139, 1154, 1223, 1257, 1359, 1402, 1461, 1506, 1557, 1593, 1658, 2855, 2927, 3150 cm^{-1}; UV/vis (MeOH): λ^{max} (ε) = 541 (478), 380 (5274), 252 (5691), 231 (7622), 204 nm (17886 $mol^{-1}dm^3cm^{-1}$); MS (ESI^+): *m/z* = 529 $[M + H]^+$, 551 $[M + Na]^+$; HRMS (ESI^+): calcd. for $C_{28}H_{41}N_2O_6Si^+$ $[M + H]^+$ 529.2728; found: 529.2728.

Sanguinolentaquinone (3). To a stirred solution of the compound **24** (50 mg, 94 µmol) in dichloromethane (3 mL) trifluoroacetic acid (300 µL) was added. The reaction mixture was stirred for one hour at ambient temperature. The solvent was removed under reduced pressure, the residue was dissolved in toluene and the solution was concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, $CHCl_3$/MeOH 9:1 to MeOH) and size exclusion chromatography (sephadex LH-20, MeOH) to afford **3** (18 mg, 68 µmol, 72 %) as a red solid. ^{1}H NMR (600 MHz, CD_3OD, 300 K): δ = 1.96 (tt, ^3J(H-2'',H-1'') = 6.4 Hz, ^3J(H-2'',H-3'') = 6.4 Hz, 2H, H-2''), 2.88 (t, ^3J(H-1',H-2') = 5.5 Hz, 2H, H-1'), 3.52 (t, ^3J(H-1'',H-2'') = 6.4 Hz, 2H, H-1''), 3.73 (t, ^3J(H-3",H-1'') = 6.4 Hz, 2H, H-3"), 3.83 (t, ^3J(H-2',H-1') = 5.5 Hz, 2H, H-2'), 5.40 (s, 1H, H-5), 7.04 ppm (s, 1H, H-2); ^{13}C NMR (151 MHz, CD_3OD, 300 K): δ = 30.2 (C-1'), 31.9 (C-2''), 42.5 (C-1''), 60.7 (C-3''), 64.4 (C-2'), 93.6 (C-5), 122.9 (C-3), 124.1 (C-3a), 129.1 (C-2), 130.4 (C-7a), 160.4 (C-4), 174.1 (C-7), 178.6 ppm (C-6); IR (ATR): *v* = 668, 702, 798, 863, 1019, 1089, 1260, 1410, 1559, 1653, 2962 cm^{-1}; UV/vis (MeOH): λ^{max} (ε) = 522 (222), 333 (3220), 241 (5806), 203 nm (3982 $mol^{-1}dm^3cm^{-1}$); MS (ESI^+): *m/z* = 265 $[M + H]^+$, 287 $[M + Na]^+$, 303 $[M + K]^+$, 551 $[2M + Na]^+$; HRMS (ESI^+): calcd. for $C_{13}H_{17}N_2O_4^+$ $[M + H]^+$ 265.11841; found: 265.11828.

***rac*-6,7-Dibenzyloxy-*N*-(diphenylmethylene)tryptophan ethyl ester (30).** To a solution of the gramine **29**[26] (0.20 g, 0.52 mmol) and *N*-(diphenylmethylene)glycine ethyl ester (**14**)[21] (0.18 g, 0.64 mmol) in acetonitrile (6 mL) tributylphosphine (0.64 mL, 0.26 mmol) was added. The mixture was stirred at reflux for 12 h. Subsequently, the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 5:1) to afford **30** (0.30 g, 0.48 mmol, 92 %) as a yellow viscous oil. R_f = 0.17; ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 1.22 (t, ^3J(CH_3,CH_2) = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 3.29 (dd, ^2J(H-1',H-1') = 14.2 Hz, ^3J(H-1',H-2') = 8.9 Hz, 1H, H-1'), 3.47 (dd, ^2J(H-1',H-1') = 14.2 Hz, ^3J(H-1',H-2') = 4.6 Hz, 1H, H-1'), 4.11 – 4.25 (m, 2H, $CO_2CH_2CH_3$), 4.43 (dd, ^3J(H-2',H-1') = 4.6 Hz, ^3J(H-2',H-1') = 8.9 Hz, 1H, H-2'), 5.17 – 5.26 (m, 4H, C*H*$_2$Ph), 6.57 – 6.58 (m, 2H, *Ph*), 6.76 – 6.79 (m, 2H, H-2, H-5), 6.91 (d, ^3J(H-4,H-5) = 8.5 Hz, 1H, H-4), 7.11 (t, ^3J(H,H) = 7.6 Hz, 2H, *Ph*), 7.21 – 7.66 (m, 16H, *Ph*), 8.06 ppm (s_{br}, 1H, N*H*); ^{13}C NMR (91 MHz, $CDCl_3$, 293 K): δ = 14.0 ($CO_2CH_2CH_3$), 29.2 (C-1'), 60.7 ($CO_2CH_2CH_3$), 65.9 (C-2'), 72.6 (CH_2Ph), 75.0 (CH_2Ph), 109.9 (C-5), 111.7 (C-3), 113.8 (C-4), 122.9 (C-2), 124.7 (C-3a), 127.4 (CH_2*Ph*), 127.5 CH_2*Ph*), 127.8 (CH_2*Ph*), 127.9 (CH_2*Ph*), 128.1 (CH_2*Ph*), 128.2 (CH_2*Ph*), 128.3 (CH_2*Ph*), 128.6 (CH_2*Ph*), 130.0 (CH_2*Ph*), 130.8 (C-7a), 133.8 (C-7), 135.7 (CH_2*Ph*), 137.6 (CH_2*Ph*),

137.8 (CH_2*Ph*), 139.3 (CH_2*Ph*), 145.8 (C-6), 170.3 (C-3'), 172.0 ppm (CO_2Et); IR (ATR): ν = 693, 735, 782, 846, 908, 936, 1027, 1067, 1137, 1177, 1212, 1257, 1298, 1314, 1340, 1372, 1442, 1508, 1575, 1596, 1623, 1728, 2924, 2978, 3029, 3060, 3433 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 608 (21) $[M]^{+\cdot}$, 517 (38) $[M - Bn]^+$, 489 (22) $[M - Bn - CO]^+$, 342 (37), 307 (31), 91 (100) $[C_7H_7]^+$; HRMS (EI): calcd. for $C_{40}H_{36}O_4N_2$ $[M]^{+\cdot}$ 608.26696; found: 608.26750.

***rac*-6,7-Dibenzyloxytryptophan ethyl ester (31).** To a solution of the protected tryptophan **30** (0.76 g, 1.25 mmol) in THF (5 mL) 1 M HCl (20 mL) was added dropwise at 0 °C. The reaction mixture was stirred for four hours at ambient temperature. Subsequently, THF was removed under reduced pressure and the aqueous residue was washed with diethyl ether (2×20 mL). The pH was adjusted to 9 with saturated $NaHCO_3$ solution and the aqueous phase was extracted with dichloromethane (3×20 mL). The combined dichloromethane phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford **31** (0.55 g, 1.23 mmol, 99 %) as a brownish viscous oil. ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 1.22 (t, $^3J(CH_3,CH_2)$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.99 (dd, ^2J(H-1',H-1') = 14.5 Hz, ^3J(H-1',H-2') = 7.5 Hz, 1H, H-1'), 3.21 (dd, ^2J(H-1',H-1') = 14.5 Hz, ^3J(H-1',H-2') = 4.7 Hz, 1H, H-1'), 3.79 (m, 1H, H-2'), 4.13 (q, $^3J(CH_2,CH_3)$ = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 5.18 (s, 2H, CH_2Ph), 5.20 (s, 2H, CH_2Ph), 6.91 (d, ^3J(H-5,H-4) = 8.5 Hz, 1H, H-5), 6.92 (s, 1H, H-2), 7.23 (d, ^3J(H-4,H-5) = 8.5 Hz, 1H, H-4), 7.32 – 7.60 (m, 10H, CH_2*Ph*), 7.97 (s_{br}, 1H, N*H*); ^{13}C NMR (91 MHz, $CDCl_3$, 293 K): δ = 14.3 ($CO_2CH_2CH_3$), 30.8 (C-1'), 55.1 (C-2'), 61.1 ($CO_2CH_2CH_3$), 73.1 (CH_2Ph), 75.5 (CH_2Ph), 110.6 (C-5), 111.5 (C-3), 114.0 (C-4), 122.9 (C-2), 124.7 (C-3a), 127.8 (CH_2*Ph*), 128.0 (CH_2*Ph*), 128.3 (CH_2*Ph*), 128.5 (CH_2*Ph*), 128.6 (CH_2*Ph*), 131.5 (C-7a), 134.5 (C-7), 137.8 (CH_2*Ph*), 138.1 (CH_2*Ph*), 146.5 (C-6), 175.1 ppm (CO_2Et); IR (ATR): ν = 696, 736, 791, 844, 967, 903, 1021, 1067, 1119, 1136, 1181, 1200, 1217, 1259, 1301, 1351, 1441, 1453, 1509, 1576, 1630, 1728, 2868, 2939, 3309 cm^{-1}; MS (ESI^+): *m/z* = 445 $[M + H]^+$, 467 $[M + Na]^+$, 483 $[M + K]^+$; HRMS (ESI^+): calcd. for $C_{27}H_{29}N_2O_4$ $[M + H]^+$ 445.21218; found: 445.21221.

***rac*-6,7-Dibenzyloxy-*N*-(3-(tetrahydro-2*H*-pyran-2-yloxy)propyl)-tryptophan ethyl ester (32).** To a solution of the tryptophan **31** (0.23 g, 0.52 mmol) in MeOH (5 mL) 3-(tetrahydro-2*H*-pyran-2-yloxy)propan-1-al (**34**)[27] (0.13 g, 0.79 mmol) and sodium cyanoborohydride (0.10 g, 1.56 mmol) were added. The reaction mixture was stirred at ambient temperature for 12 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, $CHCl_3$/MeOH 49:1) to afford **32** (0.27 g, 0.46 mmol, 88 %) as a brownish oil. R_f = 0.2 ($CHCl_3$/MeOH 49:1); ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 1.11 (t, $^3J(CH_3,CH_2)$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.49 – 1.80 (m, 8H, THP), 2.58 – 2.78 (m, 2H, H-3'), 3.08 (d, ^3J(H-1',H-2') = 6.7 Hz, 2H, H-1'), 3.37 – 3.44 (m, 1H, H-5'), 3.46 – 3.50 (m, 1H, THP), 3.57 – 3.62 (m, 1H, H-2'), 3.74 – 3.86 (m, 2H, H-5', THP), 4.07 (q, $^3J(CH_2,CH_3)$ = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.52* (t, ^3J(H-1',H-2') = 3.5 Hz, 0.5H, H-1'), 4.55* (t, ^3J(H-1',H-2') = 3.5 Hz, 0.5H, H-1'), 5.19 (s, 2H, CH_2Ph), 5.21 (s, 2H, CH_2Ph), 6.89 (d, ^3J(H-2,NH) = 2.1 Hz, 1H, H-2), 6.92 (d, ^3J(H-5,H-4) = 8.6 Hz, 1H, H-5), 7.25 (d, ^3J(H-4,H-5) = 8.6 Hz, 1H, H-4), 7.31 – 7.51 (m, 10H, CH_2*Ph*), 8.16 ppm (s_{br}, 1H, N*H*); ^{13}C NMR (91 MHz, $CDCl_3$, 293 K): δ = 14.1 ($CO_2CH_2CH_3$), 19.5+19.5* (THP), 25.4 (THP), 29.4 (C-1'), 30.1+30.1* (C-4'), 30.6 (THP), 45.5+45.6* (C-3'), 60.5 ($CO_2CH_2CH_3$), 62.1+62.2* (THP), 62.3 (C-2'), 65.7+65.8* (C-5'); 72.9 (CH_2Ph), 75.3 (CH_2Ph), 98.7+98.8* (THP), 110.3 (C-5), 111.5 (C-3), 113.8 (C-4), 122.6 (C-2), 124.7 (C-3a), 127.6 (CH_2*Ph*), 127.8 (CH_2*Ph*), 128.0 (CH_2*Ph*), 128.3 (CH_2*Ph*), 128.4 (CH_2*Ph*), 131.2 (C-7a), 134.3 (C-7), 137.6 (CH_2*Ph*), 138.0 (CH_2*Ph*), 146.2 (C-6), 174.9 ppm (CO_2Et) (*two diastereomeric pairs of enantiomers); IR (ATR): ν = 695, 735, 790, 845, 906, 941, 1026, 1067, 1084, 1183, 1216, 1260, 1301, 1350, 1377, 1443, 1497, 1509, 1575, 1629, 1657, 1728, 2869, 2930, 3030, 3062, 3362 cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 586 (10) $[M]^{+\cdot}$, 342 (100) $[M - CH(CO_2Et)NHCH_2CH_2CH_2OTHP]^+$, 160 (58) $[THPOCH_2CH_2CH_2NH_2]^+$, 91 (100) $[C_7H_7]^+$; HRMS (EI): calcd. for $C_{35}H_{42}O_6N_2$ $[M]^{+\cdot}$ 586.30429; found: 586.30318.

***rac*-*O*-(Tetrahydro-2*H*-pyran-2-yl)mycenarubin E ethyl ester (33).** An argon-purged suspension of the tryptophan derivative **32** (0.19 g, 0.72 mmol) and 10 % Pd/C (65 mg) in MeOH (90 mL) was stirred under a hydrogen atmosphere (1 atm, balloon) at ambient temperature. After one hour, the catalyst was filtered off. Subsequently, triethylamine (100 µL) was added to the filtrate which was stirred for an additional hour under air atmosphere. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, $CHCl_3$/MeOH 49:1) to afford **33** (0.11 g, 0.27 mmol, 39 %) as a red solid. R_f = 0.02 ($CHCl_3$/MeOH 49:1); ^{1}H NMR (360 MHz, $CDCl_3$, 293 K): δ = 1.24 (t, $^3J(CH_3CH_2)$ = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.57 – 2.08 (m, 8H, H-2', THP), 3.18 – 3.36 (m, 3H, H-3, H-1'), 3.47 – 3.56 (m, 2H, H-3', THP), 3.77 – 3.95 (m, 3H, H-1', H-3', THP), 4.16 (q, $^3J(CH_2CH_3)$ = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.35* (dd, ^3J(H-4,H-3) = 6.7 Hz, ^3J(H-4,H-3) = 1.8 Hz, 0.5H, H-4), 4.46* (dd, ^3J(H-4,H-3) = 6.5 Hz, ^3J(H-4,H-3) = 1.5 Hz, 0.5H, H-4), 4.53 – 4.55* (m, 0.5H, THP), 4.58 – 4.60* (m, 0.5H, THP), 5.48 (s, 0.5H, H-6), 5.49 (s, 0.5H, H-6), 7.08 (m, 1H, H-2), 11.45 ppm (s_{br}, 1H, N*H*); ^{13}C NMR (91 MHz, $CDCl_3$, 293 K): δ = 14.3 ($CO_2CH_2CH_3$), 20.0+20.5* (THP), 24.4+24.6* (C-3), 25.5 (THP), 27.8+27.9* (C-2'), 30.9+31.0* (THP), 48.7+49.1* (C-1'), 62.4+62.4* ($CO_2CH_2CH_3$), 62.8+63.0* (C-4), 63.0+63.7* (THP), 64.2+64.6* (C-3'), 94.6+94.6* (C-6), 99.6+99.9* (THP), 114.2+114.4* (C-2a), 125.2 (C-2), 125.3 (C-8a), 126.1 (C-8b), 153.2 (C-5a), 170.7+170.9 (C-8), 170.9+171.0 (CO_2Et), 180.5 ppm (C-7) (*two diastereomeric pairs of enantiomers); IR (ATR): ν = 668, 693, 716, 734, 765, 866, 880, 901, 924, 940, 1027, 1058, 1066, 1184, 1241, 1250, 1320, 1378, 1394, 1410, 1442, 1522, 1559, 1593, 1617, 1670, 1734, 2901, 2972, 2988, 3675 cm^{-1}; UV/vis (MeOH): λ^{max} (ε) = 520 (323), 350 (3909), 242 (5828), 200 nm (4323 $mol^{-1}dm^3cm^{-1}$); MS (ESI^+): *m/z* = 403 $[M + H]^+$, 425 $[M + Na]^+$, 441 $[M + K]^+$, 827 $[2M + Na]^+$; MS (ESI^-): *m/z* = 401 $[M - H]^-$; HRMS (ESI^+): calcd. for $C_{21}H_{27}N_2O_6^+$ $[M + H]^+$ 403.18636; found: 403.18628.

Mycenaflavin B (4b). The pyrroloquinoline **33** (31 mg, 77 µmol) was dissolved in THF (4 mL) and 0.1 M aqueous LiOH solution (4 mL) was added. The solution was stirred for 48 hours at 55 °C (ester hydrolysis). Subsequently, the solution was neutralised with AcOH and the solvents were removed under reduced pressure. The residue was dissolved in a mixture of MeOH (2 mL), H_2O (1 mL) and AcOH (5 mL). The solution was stirred for two hours at 40 °C (decarboxylation step). After cooling to ambient temperature the reaction mixture was stirred 72 h at ambient temperature (THP deprotection). The solvents were removed under reduced pressure and the crude product was purified by HPLC to afford **4b** (9 mg, 37 µmol, 48 % over three steps) as a brown solid. $HPLC_{prep}$: R_t = 30.2 min; ^{1}H NMR (600 MHz, d_6-DMSO, 300 K): δ = 1.88 (tt, ^3J(H-2',H-3') = 5.8 Hz, ^3J(H-2',H-1') = 6.2 Hz, 2H, H-2'), 3.47 (t, ^3J(H-3',H-2') = 5.8 Hz, 2H, H-3'), 4.09 (t, ^3J(H-1',H-2') = 6.2 Hz, 2H, H-1'), 4.72 (s, 1H, N*H*); 5.58 (s, 1H, H-6), 6.81 (d, ^3J(H-3,H-4) = 6.8 Hz, 1H, H-3), 7.28 (d, ^3J(H-4,H-3) = 6.8 Hz, 1H, H-4), 7.71 ppm (s, 1H, H-2); ^{13}C NMR (151 MHz, d_6-DMSO, 300 K): δ = 31.5 (C-2'), 49.1 (C-1'), 57.5 (C-3'), 91.1 (C-6), 104.5 (C-3), 119.8 (C-8b), 120.4 (C-2a), 125.4 (C-8a), 126.5 (C-2), 131.5 (C-4), 145.8 (C-5a), 170.6 (C-8), 179.0 ppm (C-7); IR (ATR): ν = 668, 757, 811, 911, 984, 1051, 1148, 1196, 1264, 1310, 1374, 1394, 1456, 1559, 1577, 1653, 2901, 2988 cm^{-1}; UV/vis (MeOH): λ^{max} (ε) = 522 (3896), 435 (5202), 418 (4883). 241 (11457), 225 (14395), 201 nm (10085 $mol^{-1}dm^3cm^{-1}$); MS (ESI^+): *m/z* = 245 $[M + H]^+$, 267 $[M + Na]^+$; MS (ESI^-): *m/z* = 243 $[M - H]^-$; HRMS (ESI^+): calcd. for $C_{13}H_{13}N_2O_3^+$ $[M + H]^+$ 245.09207; found: 245.09190.

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Text for Table of Contents

Total Synthesis*

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Total Synthesis of Mycenarubin A, Sanguinolentaquinone and Mycenaflavin B and their Cytotoxic Activities

The first total synthesis of the fungal pyrroloquinoline alkaloids mycenarubin A, sanguinolentaquinone and mycenaflavin B are described. Key steps for the synthesis of mycenarubin A are an enantioselective alkylation and a biomimetic Michael addition leading to the pyrrolo[4,3,2-*de*]quinoline core. Mycenaflavin B has been obtained via a biomimetic ring closure and an acidic decarboxylation reaction. Moreover, the cytotoxic activities of mycenarubin A and mycenaflavin B have been evaluated against mouse fibroblasts (L929) and human malignant melanoma cells (RPMI-7951).