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Total Synthesis of Lavendamycin by a [2+2+2] Cycloaddition

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Dedicated to Prof. Dr. Horst Kunz on the occasion of his 70th birthday

Keywords: Natural products / Total synthesis / Cycloaddition / Regioselectivity / Nitrogen heterocycles

The total synthesis of the bacterial-derived, pentacyclic, antitumor antibiotic lavendamycin has been achieved through a highly convergent strategy. The key step of this synthesis is a ruthenium-catalyzed [2+2+2] cycloaddition of an electron-deficient nitrile to an alkynyl-ynamide to prepare the carboline scaffold. The elaborate cycloaddition substrate is obtained in few steps by an *N*-ethynylation using alkynyliodonium salt chemistry and two palladium-catalyzed cross-coupling reactions. An efficient synthesis of a halogenated quinoline-5,8-dione building block starting from hydroquinone is presented.

Introduction

Lavendamycin (**1**, Figure 1), a bacterial-derived antitumor antibiotic, was isolated and characterized from *Streptomyces lavendulae* in 1981 by Doyle and Balitz.[1] In initial studies lavendamycin showed activity against several cancer cell lines and significant activity against topoisomerase I.[2]

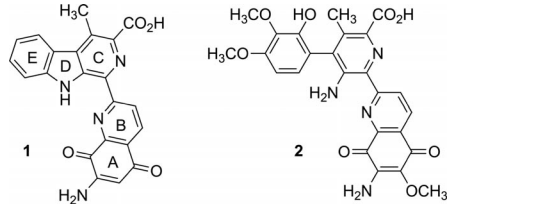

Figure 1. Lavendamycin (**1**) and streptonigrin (**2**).

These promising biological properties as well as the complex structural features of lavendamycin (**1**), a highly functionalized pentacyclic structure containing a β-carboline[3] and a quinoline-5,8-dione moiety, have sparked considerable research activities directed toward its total synthesis. As a result of these efforts, the first total synthesis of lavendamycin was reported in 1984 by Kende and Ebetino, and additional total syntheses followed within the next few years.[4–11] Closely related in structure and biological activity to streptonigrin (**2**),[12] another potent antitumor agent, lavendamycin's beneficial effects are unfortunately associated with a high general toxicity, which has precluded its potential clinical use. Therefore, a substantial interest in a flexible strategy for the total synthesis of lavendamycin arose recently, elicited by the potential application of structurally related analogs having comparable efficacy but diminished toxicity.

A key to the synthesis of lavendamycin lies in the preparation of the highly substituted pyridine ring of the carboline core. Several strategies have been applied to the synthesis of this heterocyclic system, that is, annulation of a pyridine ring to a preformed indole structure through classic Pictet–Spengler[13] or Bischler–Napieralski condensation,[14] ring-closure of the pyrrole ring through a Pd-mediated[7] or nucleophilic[11] substitution, tandem aza-Wittig/electrocyclic ring-closure followed by construction of the pyrrole ring through a thermolytic nitrene insertion,[10] and modified Knoevenagel–Stobbe reaction.[9] However, low yields, not readily available starting materials, or a lack of generality make these strategies unattractive for the systematic synthesis of structurally related analogs. Recently, Behforouz reported an efficient total synthesis of lavendamycin through a Pictet–Spengler condensation of 7-(acylamino)-2-formylquinoline-5,8-dione and β-methyltryptophan.[8] Based on this approach, over 100 analogs, varied predominantly by esterification as well as acylation of the 7-amino group, were synthesized and biologically evaluated. Several lavendamycin analogues showed a higher specific toxicity against human cancer cells,[15] as well as anti-HIV reverse transcriptase activity,[16] compared to the parent molecule.

Inspired by the highly flexible approach to the formation of annulated pyridines from tethered diynes or cyanoalkynes in transition-metal-mediated [2+2+2] cycloadditions,[17,18] we investigated the possibility of simulta-

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neously constructing the pyrrole and the pyridine ring in the carboline core with a cocycloaddition of a 1,6-diyne and a nitrile.[19]

Results and Discussion

Our synthetic strategy for lavendamycin is based on the retrosynthetic analysis shown in Figure 2. The key step of this synthesis is the formation of the β-carboline core by a transition-metal-catalyzed [2+2+2] cycloaddition. Additional masking of the 7-aminoquinoline-5,8-dione unit by appropriate group transformations leads retrosynthetically to the electron-deficient nitrile methyl cyanoformate and the *o*,*N*-dialkynylanilide (alkynyl-ynamide) **3**.[20,21] Continuing with the simplification of the structure, diyne **3** can be traced back by straightforward retrosynthetic disconnections to the small and readily available starting materials 2-iodoaniline, hydroquinone, propyne, 3,3-dimethoxypropanoic acid, and ethynyl(phenyl)iodonium triflate **4**.[22]

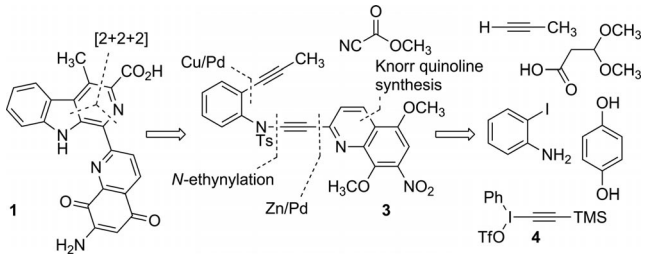
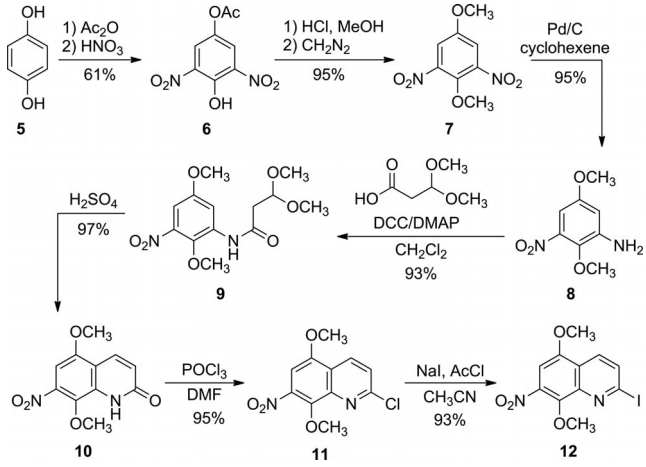


Figure 2. Retrosynthetic analysis for lavendamycin (**1**).

An important intermediate for the synthesis of the quinoline-5,8-dione moiety of lavendamycin was the known compound **8** (Scheme 1). With some improvements, the synthesis of **8** followed published procedures (see Exp. Sect. for details). Briefly, this unit was prepared from hydroquinone (**5**) by acetylation,[23a] nitration,[23b] methanolysis, and subsequent methylation with diazomethane[23c] to yield 1,4-dimethoxy-2,6-dinitrobenzene (**7**) in 55% yield over 4 steps. Thereafter, a selective reduction of one of the nitro groups was achieved by transfer hydrogenation with cyclohexene in the presence of 5 mol-% Pd/C (10%) in ethanol at 50 °C (95% yield).[24]

Once the substitution pattern of the A-ring of lavendamycin was established, a DCC (*N*,*N*′-dicyclohexylcarbodiimide)/DMAP (4-dimethylaminopyridine)-mediated amidation of **8** with 3,3-dimethoxypropanoic acid afforded **9** in 93% yield.[25] The projected Knorr cyclization[26] proceeded efficiently by treating **9** with concentrated H_2SO_4 at room temperature for 2 h to give quinolinone **10** in 97% yield. Chlorination of **10** with 10 equiv. of $POCl_3$ in DMF (dimethylformamide) cleanly furnished **11** (95% yield). To optimize the cross-coupling reactivity, **11** was converted to the more reactive 2-iodoquinoline **12**. A series of experiments were carried out to find an optimal catalyst for this reaction. Treatment of **11** with sodium iodide in acetonitrile at 60 °C for 2 h in the presence of either acetyl chloride,[27] trimethylsilyl chloride (TMSCl),[28] or hydrochloric acid,[29]



Scheme 1. Reaction sequence leading to **12**.

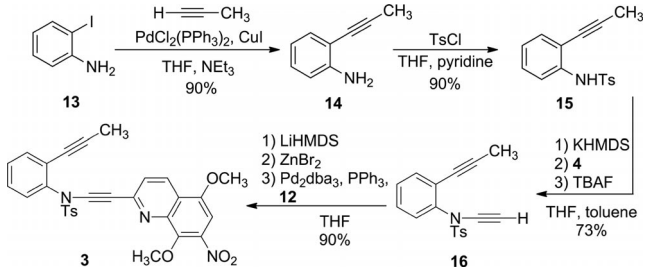
common catalysts for halogen exchange in 2- or 4-chloropyridines, afforded iodoquinoline **12** in excellent yields (Table 1, Entries 1–3, 87–93%). Remarkably, the use of acid-free acetyl chloride (distilled from PCl_5 followed by distillation from quinoline) under the same conditions led to only 10% conversion after 24 h (Entry 4), which shows for this reaction the importance of an initially formed protonated species.

Table 1. Investigation of the reaction conditions for the chlorine/iodine exchange leading to iodoquinoline **12**.

Run	Catalyst	Time [h]	Isolated yield [%]
1	2 equiv. AcCl	4	93
2	0.5 equiv. HCl (aqueous)	4	87
3	0.5 equiv. TMSCl	4	91
4	2 equiv. AcCl (acid-free)	24	10[a]

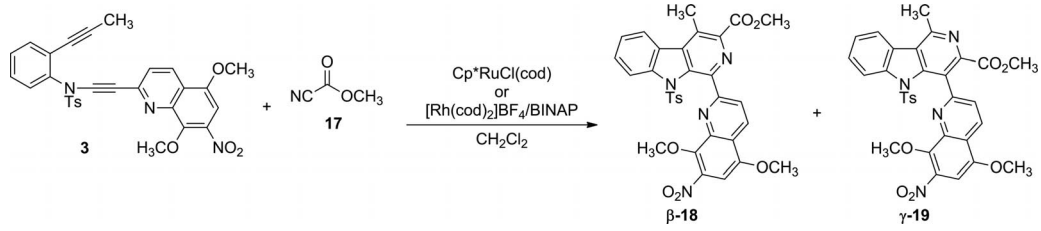
[a] Not isolated; conversion determined by ^{1}H NMR.

Having established a convenient procedure for the construction of the quinoline-5,8-dione part of lavendamycin, we next turned our attention to the preparation of 1,6-diyne **3**. Based on Witulski's route to carbazoles through a rhodium-catalyzed cross-cyclotrimerization,[30] 1,6-diyne **16** was synthesized in three steps starting from 2-iodoaniline (**13**) (Scheme 2). A Sonogashira reaction with propyne followed by *N*-tosylation afforded sulfonamide **15**, which was then deprotonated with potassium hexamethyldisilazane (KHMDS) and alkynylated with alkynyliodonium salt **4** to



Scheme 2. Reaction sequence leading to **3**.

Table 2. Transition-metal-catalyzed [2+2+2] cycloaddition of diyne **3** and methyl cyanoformate (**17**).

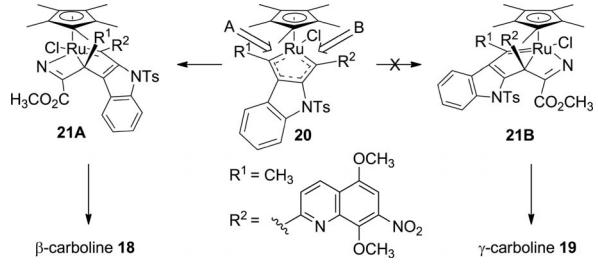


Run	Catalyst (amount [mol-%])	Temperature [°C]	Nitrile **17** [equiv.]	Regioisomeric ratio (**β-18**/**γ-19**)	Isolated yield (%)
1	$[Rh(cod)_2]BF_4$/BINAP (6)	20	10	27:73	92
2	$[Rh(cod)_2]BF_4$/BINAP (6)	60	10	30:70	87
3	$[Rh(cod)_2]BF_4$/BINAP (6)	80	10	38:62	81
4	Cp*RuCl(cod) (2)	20	5	100:0	92

obtain 1,6-diyne **16**. This diyne was coupled smoothly under Negishi conditions[31] with the 2-iodoquinoline building block **12** to finally give diyne **3** in 53% overall yield.

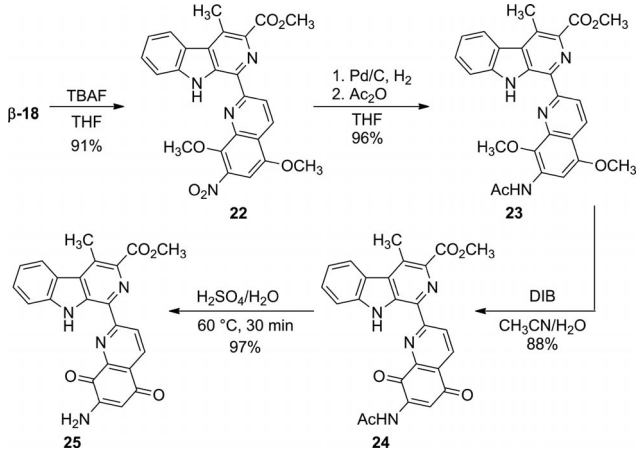
With 1,6-diyne **3** in hand, we began investigating its reaction with methyl cyanoformate (**17**) to give the desired pentacyclic precursor of lavendamycin. Although reactions of α,ω-diynes with electron-deficient nitriles are known to be efficiently mediated by Cp*RuCl(cod)[32] or cationic Rh^I catalysts,[33] this case was complicated by the sterically and electronically complex features of 1,6-diyne **3**. Assuming that the presence of the electronically modified alkyne unit and the fully unsymmetrical substitution of 1,6-diyne **3** would facilitate the chemo- and regioselective outcome of this reaction, we carried out the [2+2+2] cycloaddition with **17** in the presence of 6 mol-% $[Rh(cod)_2]BF_4$/BINAP [2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl] in CH_2Cl_2 at room temperature (Table 2). A regioisomeric mixture of the corresponding β-carboline **18** and its γ-isomer **19** was obtained in excellent yield (92%), but with the undesired γ-carboline **19** as the major product (Table 2; Entry 1; β/γ = 27:73). Attempts to influence the regiochemical outcome of this reaction by varying the temperature were unsuccessful (Table 2, Entries 2 and 3). Remarkably, the regioselectivity of this reaction was completely reversed when the cycloaddition was promoted by the ruthenium(II) complex Cp*RuCl(cod).

With a catalyst loading of only 2 mol-% Cp*RuCl(cod), the desired β-carboline **18** was formed under mild conditions (room temperature, 5 equiv. of nitrile in CH_2Cl_2) in very high yield (92%) without any detectable trace of γ-isomer **19** (Entry 4). In agreement with previously reported Cp*RuCl-catalyzed cycloadditions of unsymmetrical α,ω-diynes,[32] the origin of this excellent regioselectivity might be rationalized by considering the [2+2] addition of the electron-deficient nitrile to asymmetric metallacyclic intermediate **20** leading to the intermediates **21A** or **21B** (Scheme 3). If the nitrile attacks the Ru–C-α bond B, intermediate **21B** will form, but the sterically more demanding substituent R^2 will come close to the bulky Cp* ligand. Addition to the Ru–C-α bond A will avoid this steric repulsion and lead to the formation of β-carboline **18** via intermediate **21A**.



Scheme 3. Proposed reaction path leading to β-carboline **18**.

Having demonstrated the synthesis of the pentacyclic core of lavendamycin through a [2+2+ 2] cycloaddition, only a few remaining group transformations were needed to complete the total synthesis of lavendamycin (Scheme 4). Removal of the *N*-tosyl protecting group with 3 equiv. of tetrabutylammonium fluoride (TBAF) in tetrahyrofuran (THF) at room temperature afforded **22** in 91% yield.[34] Then, the C-7 nitro group was reduced with hydrogen in the presence of Pd/C, and the resulting amino group was acetylated. First attempts at the direct oxidative demethylation of **23** to generate the quinoid system were carried out with cerium ammonium nitrate (CAN) in a mixture of acetonitrile and water.[35] Although the CAN oxidation af-



Scheme 4. Reaction sequence leading to lavendamycin methyl ester (**25**).

forded the corresponding quinoline-5,8-dione **24** in an acceptable yield of 64%, this process was significantly improved when **23** was treated with 4 equiv. of (diacetoxyiodo)benzene (DIB) to give **24** in 88% yield.[36] Finally, to complete the formal total synthesis of lavendamycin, the C-7 acetamido group was hydrolyzed in a mixture of H_2SO_4/water (4:3) at 60 °C according to a procedure reported by Behforouz.[8a]

Lavendamycin methyl ester (**25**) was obtained in 97% yield, and the physical and spectroscopic data were identical to those reported in the literature.[1a,7a,8a] In addition, structure and connectivity was unequivocally evidenced by two-dimensional NMR spectroscopy and X-ray crystal structure analysis (Figure 3).

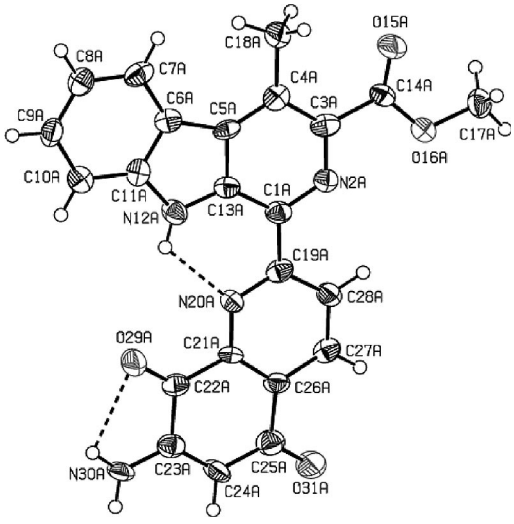


Figure 3. X-ray crystallographic structure of lavendamycin methyl ester (**25**).

The crystals of **25** contain two independent molecules **25A** and **25B**, and the unit cell is filled with two **25A**, two **25B**, and two molecules of the solvent (Figure 4). Molecules **25A** and **25B** are nearly identical with the largest deviation being the angle between the planes of the ester and the carboline unit [**25A**: N-2–C-3–C-14–O-15 178.2(9)°; **25B**: N-2–C-3–C-14–O-15 144.7(9)°]. A highly coplanar arrangement of the carboline and the quinolinone unit results from hydrogen-bond formation between the pyrrole NH group and the quinoline N atom, as well as from the amino N-30 group adjacent to the quinine O-29 – the dihedral angle of the mean planes of the carboline and the quinoline units amounts to only θ = 3.44°. This hydrogen-bond-stabilized coplanarity is closely analogous to the structure of streptonigrin (**2**) in the solid state[37] and in solution.[38] Intermolecular hydrogen bonds from the amine to the ester (N-30–H–O-15) connect coplanar molecules of **25A** to form linear strands. On both sides of the strand, the **25B** molecules are attached with hydrogen bonds from the amine N-30A to the quinone O-31B and O-31A to N-30B. Layers with parallel strands of **25A** are arranged in a herringbone fashion, and the distances of the mean planes of **25A** [4.029(5) Å] and **25B** [3.496(5) Å] indicate π-stacking interaction. These layers are separated from the next layer of **25A** by a layer of parallel **25B** molecules with an interstrand distance of half of the *b*-axis. Channels between the B-layers are filled with two molecules of the solvent $CHCl_3$.

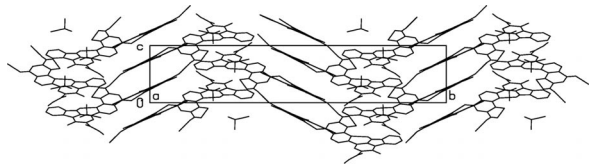


Figure 4. Arrangement of lavendamycin methyl ester (**25**) in the crystal.

Conclusions

The regio- and chemoselective transition-metal-catalyzed [2+2+2] cycloaddition of a 1,6-diyne and an electron-deficient nitrile is a new and efficient route for the synthesis of β- and γ-carbolines. We have proven the efficiency of this method in the key step for the total synthesis of lavendamycin. Forming three bonds in a single step, this convergent approach allows the flexible preparation of the highly substituted pyridine ring of lavendamycin. This method requires simple starting materials and a sequence of reliable reactions, which should enable the synthesis of a broad variety of derivatives and analogs for this promising antitumor antibiotic.

Experimental Section

General Information: Commercially available reagents were used without further purification. Solvents and gases were dried by standard procedures. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded with Bruker AC 300 (300 MHz), AV 400, and ARX 400 (400 MHz) spectrometers in $CDCl_3$ and [D_6]DMSO. The proton and carbon signals were assigned on the basis of DEPT, COSY45, HMQC (Heteronuclear Multiple Quantum Coherence), and HMBC experiments. Melting points were measured with a Büchi HWS SG 200, and IR spectra were recorded with a JASCO 4100 FTIR (ATR). FD mass spectra were recorded with a Mat 95 (Finnigan), and HR-ESI mass spectra were obtained by using a Q-TOF-ULTIMA 3 with a Lock Spray device (Waters–Micromass) and NaICsI standard as a reference. Elemental analyses were carried out with a Vario EL. X-ray crystal structure analyses were performed by using a Turbo CAD-4 with Cu-K_α radiation and data collection with CAD-4 software (Enraf–Nonius, 1989), structure solution with SIR97 (direct methods), structure refinement with SHELXL97, and molecular graphics with PLATON.[39]

4-Hydroxy-3,5-dinitrophenyl Acetate (6): 1,4-Diacetoxybenzene[21] (50 g, 0.26 mol) was added in small portions to fuming HNO_3 (150 mL) at –5 °C. After stirring at –5 °C for 30 min, the mixture was poured on ice and filtered. The residue was washed with water and dried in air to yield **6** (38 g, 0.16 mol, 61%) as a yellow solid. M.p. 95–96 °C (ref.[22] 94 °C).

1,4-Dimethoxy-3,5-dinitrobenzene (7): HCl (12 M, 0.2 mL, 0.24 mmol, 6 mol-%) was added to **6** (10 g, 41 mmol) in methanol

(80 mL), and the mixture was heated at reflux for 3 h. The solvent was removed in vacuo, and the residue was dissolved in diethyl ether (35 mL) and methanol (35 mL). At 5 °C diazomethane[40] (approximately 1 M in diethyl ether, 250 mL) was added, and the reaction mixture was stirred for 4 h. After the addition of acetic acid (30 mL), the mixture was stirred for an additional 4 h. The solution was concentrated. Diethyl ether was added, and the mixture was neutralized with NaOH (2 M solution). The organic layer was separated and then washed with NaOH (2 M solution, 3 × 30 mL), water, and brine. The organic layer was dried with $MgSO_4$ and then concentrated to yield **7** (8.97 g, 39 mmol, 95%) as a yellow solid. M.p. 109–110 °C (hexane/diethyl ether) (ref.[23] 109–111 °C). R_f = 0.50 (SiO_2; hexane/ethyl acetate, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS, 25 °C): δ = 7.58 (s, 2 H), 4.03 (s, 3 H), 3.92 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9 (C), 145.9 (C), 141.1 (C), 114.8 (CH), 65.1 (CH_3), 56.8 (CH_3) ppm. IR (neat, ATR): $\tilde{\nu}$ = 3092, 1524, 1486, 1417, 1346, 1042, 973, 873, 787 cm^{-1}. FD-MS: *m*/*z* (%) = 228 (100) $[M]^+$.

2,5-Dimethoxy-3-nitroaniline (8): Pd/C (10%, 1.17 g, 1.1 mmol, 5 mol-%) and cyclohexene (13 mL, 10.5 g, 0.13 mol, 6 equiv.) were added to a solution of **7** (5 g, 22 mmol) in ethanol (150 mL) at 45 °C. The starting material was completely consumed after 5 h (TLC), and the mixture was filtered through silica and concentrated in vacuo. The resulting residue was redissolved in diethyl ether and then filtered a second time through silica. Concentration of the mixture, and recrystallization of the solid from diethyl ether yielded **8** (4.13 g, 21 mmol, 95%) as dark-red solid. M.p. 88–89 °C (ref.[23] 87.5–89.5 °C). R_f = 0.38 (SiO_2; diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$/TMS, 25 °C): δ = 6.73 (d, $^4J_{H,H}$ = 3.0 Hz, 1 H), 6.50 (d, $^4J_{H,H}$ = 3.0 Hz, 1 H), 4.11 (br. s, 2 H, NH_2), 3.86 (s, 3 H), 3.77 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS, 25 °C): δ = 155.8 (C), 144.1 (C), 143.0 (C), 135.1 (C), 106.3 (CH), 98.4 (CH), 61.3 (CH_3), 55.9 (CH_3) ppm. FD-MS: *m*/*z* (%) = 198 (100) $[M]^+$. HRMS (ES+): calcd. for $[M + H]^+$ 199.0713; found 199.0712. IR (neat, ATR): $\tilde{\nu}$ = 3485, 3387, 2941, 1631, 1598, 1518, 1340, 1235, 1038, 991 cm^{-1}. $C_8H_{10}N_2O_4$ (198.18): calcd. C 48.48, H 5.09, N 14.14; found C 48.48, H 5.09, N 14.06.

***N*-(2,5-Dimethoxy-3-nitrophenyl)-3,3-dimethoxypropanamide (9):** To a solution of **8** (1.37 g, 6.9 mmol) and 3,3-dimethoxypropanoic acid (1.11 g, 8.3 mmol, 1.2 equiv.) in CH_2Cl_2 (7 mL) at 0 °C was added DMAP (82 mg, 0.7 mmol, 10 mol-%) and a solution of DCC (1.71 g, 8.3 mmol, 1.2 equiv.) in CH_2Cl_2 (3.5 mL). The mixture was stirred at 0 °C for 30 min and at room temperature for an additional 14 h. Diethyl ether was added, and the precipitated urea was removed by filtration through a pad of silica. After removal of the solvent under reduced pressure, the residue was crystallized from diethyl ether/hexane to give **9** (2.03 g, 6.5 mmol, 95%) as a colorless solid. M.p. 75–76 °C. R_f = 0.21 (SiO_2; hexane/ethyl acetate, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$/TMS, 25 °C): δ = 9.12 (s, 1 H, NH), 8.34 (d, $^4J_{H,H}$ = 3.1 Hz, 1 H), 7.10 (d, $^4J_{H,H}$ = 3.1 Hz, 1 H), 4.71 (t, $J_{H,H}$ = 4.5 Hz, 1 H), 3.89 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.48 (s, 6 H), 2.80 (d, $^3J_{H,H}$ = 4.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS, 25 °C): δ = 167.8 (C), 155.8 (C), 143.1 (C), 136.7 (C), 134.7 (C), 111.4 (CH), 104.3 (CH), 102.0 (CH), 62.7 (CH_3), 56.2 (CH_3), 54.8 (CH_3), 42.2 (CH_2) ppm. FD-MS: *m*/*z* (%) = 314 (100) $[M]^+$. IR (neat, ATR): $\tilde{\nu}$ = 3252, 2945, 2836, 1656, 1583, 1527, 1477, 1112, 1081, 1052 cm^{-1}. $C_{13}H_{18}N_2O_7$ (314.29): calcd. C 49.68, H 5.77, N 8.91; found C 49.82, H 5.77, N 8.95.

5,8-Dimethoxy-7-nitroquinolin-2(1*H*)-one (10): Compound **9** (9.0 g, 29 mmol) was introduced portionwise to concentrated H_2SO_4 (90 mL), and the resulting solution was stirred at room temperature. After 2 h, the mixture was poured into ice-cold water (1.5 L). The precipitate was filtered and washed with ice-cold water until the filtrate was neutral. The resulting solid was dried under vacuum in a desiccator over P_2O_5 to provide **10** (6.95 g, 28 mmol, 97%) as a yellow solid. M.p. 294–297 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 11.73 (br. s, 1 H, NH), 8.04 (d, $^3J_{H,H}$ = 9.7 Hz, 1 H), 7.20 (s, 1 H), 6.64 (d, $^3J_{H,H}$ = 9.7 Hz, 1 H), 3.94 (s, 3 H), 3.82 (s, 3 H) ppm. FD-MS: *m*/*z* (%) = 250 (100) $[M]^+$. HRMS (ES+): calcd. for $[M + H]^+$ 251.0662; found 251.0659. IR (neat, ATR): $\tilde{\nu}$ = 3045, 1671, 1574, 1521, 1490, 1357, 1336, 1156, 112, 957, 832 cm^{-1}.

2-Chloro-5,8-dimethoxy-7-nitroquinoline (11): A solution of **10** (10 g, 40 mmol) in DMF (10 mL) was treated with $POCl_3$ (36.7 mL, 62 g, 0.4 mol, 10 equiv.) and heated at 120 °C for 30 min. After cooling to room temperature, the reaction mixture was poured into ice-cold water, and $NaHCO_3$ (saturated aqueous solution) was added until a neutral pH was reached. The precipitate was isolated by suction filtration, washed with water, and dried under vacuum in a desiccator over P_2O_5 to yield **11** (10.22 g, 38 mmol, 95%) as a yellow solid. M.p. 181–182 °C (diethyl ether). R_f = 0.43 (SiO_2; hexane/ethyl acetate, 2:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 8.60 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H), 7.77 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H), 7.47 (s, 1 H), 4.10 (s, 3 H), 4.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 151.6 (C), 150.9 (C), 143.6 (C), 142.0 (C), 141.4 (C), 135.1 (CH), 124.5 (CH), 121.8 (C), 100.2 (C), 63.7 (CH_3), 56.9 (CH_3) ppm. FD-MS: *m*/*z* (%) = 268 (100) $[M]^+$. HRMS (ES+): calcd. for $[M + H]^+$ 269.0324; found 269.0320. IR (neat, ATR): $\tilde{\nu}$ = 3111, 3084, 2953, 1601, 1577, 1521, 1359, 1161, 1081, 832 cm^{-1}.

2-Iodo-5,8-dimethoxy-7-nitroquinoline (12): A suspension of **11** (5.0 g, 19 mmol) and NaI (11.2 g, 75 mmol, 4 equiv.) in acetonitrile (100 mL) was treated with acetyl chloride (0.7 mL, 10 mmol, 0.5 equiv.), and the reaction mixture was heated to 60 °C. After 3.5 h, the starting material had been consumed (^{1}H NMR), and a 5% aqueous $NaHCO_3$/NaS_2O_3 solution was added. The aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic phases were washed with water (2×), dried with $MgSO_4$, and filtered through silica. After removal of the solvent under reduced pressure and crystallization of the residue from CH_2Cl_2/hexane, **12** (6.22 g, 17 mmol, 93%) was obtained as a dark yellow solid. M.p. 166–167 °C. R_f = 0.43 (SiO_2; hexane/ethyl acetate, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 8.15 (d, *J* = 8.8 Hz, 1 H), 7.86 (d, *J* = 8.8 Hz, 1 H), 7.14 (s, 1 H), 4.27 (s, 3 H), 4.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 151.1 (C), 144.4 (C), 143.8 (C), 142.8 (C), 134.0 (CH), 132.3 (CH), 123.1 (C), 120.7 (C), 99.8 (CH), 64.2 (CH_3), 56.5 (CH_3) ppm. FD-MS: *m*/*z* (%) = 359 (100) $[M]^+$. HRMS (ES+): calcd. for $[M + H]^+$ 360.9680; found 360.9673. IR (neat, ATR): $\tilde{\nu}$ = 3106, 2941, 1566, 1520, 1455, 1350, 1319, 1161, 979, 923 cm^{-1}. $C_{11}H_9IN_2O_4$ (360.10): calcd. C 36.69, H 2.52, N 7.78; found C 36.67, H 2.53, N 7.75.

2-(Prop-1-yn-1-yl)aniline (14): Into a Schlenk tube were introduced 2-iodoaniline (5.0 g, 23 mmol), $PdCl_2(PPh_3)_2$ (800 mg, 1.15 mmol, 5 mol-%), CuI (435 mg, 2.3 mmol, 10 mol-%), dry Et_3N (50 mL), and dry DMF (30 mL). The reaction mixture was cooled to –78 °C, and condensed propyne (1.75 mL, 1.17 g, 29 mmol, 1.3 equiv.), measured by condensing the gas in a precooled (–78 °C) graduated cylinder, was added. The reaction mixture was stirred at room temperature for 13 h. Then the mixture was worked up by evaporating the solvent, adding diethyl ether and water, and extracting with diethyl ether (3×). The organic phases were washed with brine and then dried with $MgSO_4$. Purification by column chromatography (SiO_2; pentane/diethyl ether, 10:1) afforded **14** (2.71 g, 21 mmol, 90%) as a yellow oil. R_f = 0.45 (SiO_2; pentane/diethyl ether, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.42 (dd, *J* = 7.8 Hz, *J* =

1.5 Hz, 1 H), 7.25 (dt, J = 7.8 Hz, J = 1.5 Hz, 1 H), 6.80–6.88 (m, 2 H), 4.33 (s, 2 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 148.2 (C), 132.4 (CH), 129.3 (CH), 118.2 (CH), 114.6 (CH), 109.4 (C), 91.4 (C), 76.7 (C), 4.9 (CH_3) ppm. FD-MS: m/z (%) = 131 (100) [M$^+$]. MS (ES+): m/z = 132 [M + H]$^+$. HRMS (ES+): calcd. for [M + H]$^+$ 132.0808; found 132.0806. IR (KBr): $\tilde{\nu}$ = 3470, 3375, 3029, 1613, 1493, 1455, 1306 cm^{-1}.

***N*-[2-(Prop-1-yn-1-yl)phenyl]toluenesulfonamide (15):** Tosyl chloride (3.68 g, 19 mmol, 2 equiv.) was added to a solution of **14** (1.25 g, 9.5 mmol) in THF (100 mL) and pyridine (50 mL). The mixture was stirred at room temperature for 3 d. The solution was concentrated, and CH_2Cl_2 (50 mL) and water (100 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 ×), and the combined organic layers were washed with brine and dried with $MgSO_4$. Purification by column chromatography (SiO_2; pentane/diethyl ether, 5:1) afforded **15** (2.44 g, 8.6 mmol, 90%) as colorless crystals. M.p. 111–113 °C. R_f = 0.35 (SiO_2; pentane/diethyl ether, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 2.05 (s, 3 H, CH_3), 2.35 (s, 3 H, $TsCH_3$), 6.97 (dt, J = 7.6 Hz, J = 1.1 Hz, 1 H), 7.16–7.28 (m, 5 H), 7.53 (d, J = 7.6 Hz, 1 H), 7.67 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 143.8 (C), 137.5 (C), 136.2 (C), 131.8 (CH), 129.4 (CH), 128.7 (CH), 127.2 (CH), 124.1 (CH), 119.4 (CH), 114.9 (C), 93.1 (C), 74.5 (C), 21.4 (CH_3), 4.4 (CH_3) ppm. MS (ES+): m/z = 308.0688 [M + Na]$^+$, 593.1538 [2M + Na]$^+$. HRMS (ES+): calcd. for [M + Na]$^+$ 308.0716; found 308.0721. IR (KBr): $\tilde{\nu}$ = 3278, 3257, 2917, 1493, 1397, 1158 cm^{-1}.

***N*-Ethynyl-*N*-[2-(prop-1-yn-1-yl)phenyl]toluenesulfonamide (16):** KHMDS (0.5 M solution) in toluene (18.9 mL, 9.5 mmol, 1.2 equiv.) was added dropwise at 0 °C to a solution of **15** (2.25 g, 7.9 mmol) in toluene (760 mL) . After 15 min of stirring at 0 °C, a solution of alkynyliodonium salt **4**[22] (4.75 g, 11 mmol, 1.3 equiv.) in CH_2Cl_2 (380 mL) was added dropwise, and the reaction mixture was stirred at room temperature overnight. The mixture was worked up by concentration, addition of CH_2Cl_2 (50 mL) and water (100 mL), and extraction with CH_2Cl_2. The organic layer was dried with $MgSO_4$. Column chromatography (SiO_2; pentane/diethyl ether, 4:1) yielded a colorless oil (2.31 g, 6.1 mmol, 77%). The oil was dissolved in wet THF (240 mL), and at 0 °C TBAF (1 M solution) in THF (7.9 mL, 7.9 mmol, 1.3 equiv.) was added dropwise. After 15 min, diethyl ether and brine were added, and the layers were separated. The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried with $MgSO_4$. Purification by column chromatography (SiO_2; pentane/diethyl ether, 10:1) afforded **16** (1.79 g, 5.8 mmol, 73% over 2 steps) as a white solid. M.p. 57–58 °C. R_f = 0.3 (SiO_2; pentane/diethyl ether, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 7.73 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, Ts), 7.25–7.40 (m, 6 H), 2.83 (s, 1 H, CCH), 2.45 (s, 3 H, $TsCH_3$), 1.81 (s, 3 H, $CCCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 144.8 (C), 138.6 (C), 135.0 (C), 133.5 (CH), 129.5 (CH), 129.4 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 123.9 (C), 92.8 (C), 76.1 (CH), 75.3 (C), 58.6 (C), 21.7 (CH_3), 4.5 (CH_3) ppm. MS (ES+): m/z = 332.0703 [M + Na]$^+$, 641.1520 [2 M + Na]$^+$. HRMS (ES+): calcd. for [M + Na]$^+$ 332.0721; found: 332.0703. IR (KBr): $\tilde{\nu}$ = 3259, 2229, 2123, 1595, 1484, 1446, 1366, 1183, 1163, 1091, 926, 762, 669, 584 cm^{-1}.

***N*-[(5,8-Dimethoxy-7-nitroquinolin-2-yl)ethynyl]-*N*-[2-(prop-1-ynyl)-phenyl]tolouenesulfonamide (3):** A freshly prepared solution of LiHMDS (0.5 M in THF, 19.4 mL, 9.7 mmol, 1.5 equiv.) was added to a solution of **16** (2.0 g, 6.5 mmol, 1.1 equiv.) in THF (90 mL) at –78 °C over 3 min. The mixture was stirred at –40 °C for 30 min, and a solution of anhydrous $ZnBr_2$ (1.60 g, 7.1 mmol, 1.1 equiv.) in THF (4 mL) was added. The mixture was stirred without cooling for 30 min, and thereafter the reaction mixture was treated with a solution of Pd_2dba_3·$CHCl_3$ (148 mg, 0.16 mmol, 2.5 mol-%), PPh_3 (170 mg, 0.64 mmol, 10 mol-%), and **12** (2.18 g, 6.1 mmol, 1 equiv.) in THF (60 mL). After 3 h, the solvent was removed under reduced pressure, and the residue was dissolved in water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 ×), and the combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The resulting solution was applied to a short silica column and eluted with CH_2Cl_2 followed by diethyl ether. Removal of the solvent under reduced pressure and washing of the residue with a small amount of diethyl ether yielded **3** (2.97 g, 5.5 mmol, 90%) as a bright yellow solid. M.p. 165–167 °C (CH_2Cl_2/hexane). R_f = 0.61 (SiO_2; hexane/ethyl acetate, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 8.46 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 7.84 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H), 7.51 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 7.32–7.43 (m, 6 H), 7.09 (s, 1 H), 4.27 (s, 3 H, CO_2CH_3), 4.02 (s, 3 H, OCH_3), 2.46 (s, 3 H, $TsCH_3$), 1.75 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 150.9 (C), 145.4 (C), 145.3 (C), 144.1 (C), 143.7 (C), 142.8 (C), 138.3 (C), 134.6 (C), 133.5 (CH), 131.2 (CH), 129.8 (CH), 129.6 (CH), 129.5 (CH), 128.8 (CH), 128.5 (CH), 125.4 (CH), 123.9 (C), 122.3 (C), 99.1 (CH), 93.2 (C), 85.8 (C), 75.2 (C), 72.7 (C), 64.2 (CH_3), 56.4 (CH_3), 21.8 (CH_3), 4.6 (CH_3) ppm. FD-MS: m/z (%) = 541 (100) [M]$^+$. HRMS (ES+): calcd. for [M + H]$^+$ 542.1380; found 542.1370. IR (neat, ATR): $\tilde{\nu}$ = 2949, 2232, 1604, 1576, 1518, 1350, 1163, 1072, 984, 766 cm^{-1}. $C_{25}H_{18}N_4O_5$ (454.43): calcd. C 64.31, H 4.28, N 7.76, S 5.92; found C 63.91, H 4.28, N 7.56, S 5.49.

Methyl 1-(5,8-Dimethoxy-7-nitroquinolin-2-yl)-4-methyl-9-tosyl-β-carboline-3-carboxylate (β-18): To a solution of **3** (1.0 g, 1.8 mmol) and methyl cyanoformate (**17**, 0.44 mL, 5.5 mmol, 3 equiv.) in CH_2Cl_2 (10 mL) was added Cp*RuCl(cod) (35 mg, 92 μmol, 5 mol-%). The mixture was stirred at room temperature for 14 h, and diethyl ether (20 mL) was added. The resulting precipitate was isolated by suction filtration and recrystallized from CH_2Cl_2/diethyl ether to yield **18** (1.06 g, 1.7 mmol, 92%) as a bright yellow solid. M.p. 268–269 °C. R_f = 0.47 (SiO_2; hexane/ethyl acetate, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$/TMS): δ = 8.81 (d, $^3J_{H,Hv}$ = 8.6 Hz, 1 H), 8.44 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H), 8.16 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 8.07 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.55–7.63 (m, 1 H), 7.40–7.46 (m, 1 H), 7.18 (s, 1 H), 7.10 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 6.91 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H), 4.44 (s, 3 H), 4.06 (s, 3 H), 4.05 (s, 3 H), 2.96 (s, 3 H), 2.21 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/TMS): δ = 167.1 (C), 160.1 (C), 151.0 (C), 146.3 (C), 145.3 (C), 145.2 (C), 144.1 (C), 142.9 (C), 142.6 (C), 142.0 (C), 138.0 (C), 135.7 (C), 132.8 (C), 132.5 (CH), 129.7 (CH), 129.3 (CH), 129.1 (C), 127.3 (C), 126.9 (CH), 125.8 (CH), 124.1 (C), 123.7 (C), 123.4 (CH), 118.4 (CH), 99.3 (CH), 65.2 (CH_3), 56.4 (CH_3), 53.0 (CH_3), 21.6 (CH_3), 16.3 (CH_3) ppm. FD-MS: m/z (%) = 626 (100) [M]$^+$. HRMS (ES+): calcd. for [M + H]$^+$ 627.1544; found 627.1557. IR (neat, ATR): $\tilde{\nu}$ = 2943, 1721, 1603, 1530, 1457, 1364, 1236, 1173, 1092, 936, 765, 741 cm^{-1}. $C_{32}H_{26}N_4O_8S$ (626.64): calcd. C 61.33, H 4.18, N 8.94, S 5.12; found C 60.92, H 4.16, N 8.71, S 4.60.

Methyl 4-(5,8-Dimethoxy-7-nitroquinolin-2-yl)-1-methyl-5-tosyl-γ-carboline-3-carboxylate (γ-19): In a Schlenk tube, $[Rh(cod)_2]BF_4$ (2.7 mg, 6 mol-%) and BINAP (4.1 mg, 6 mol-%) were dissolved in dry, nitrogen-saturated CH_2Cl_2 (1.2 mL). The solution was stirred vigorously under H_2 for 20 min and then concentrated to dryness. The residue was dissolved in CH_2Cl_2 (1.2 mL), and methyl cyanoformate (**17**) (88 μL, 1.1 mmol, 10 equiv.) and a solution of **3** (60 mg, 0.22 mmol) in CH_2Cl_2 (2.4 mL) were added. After 13 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; hexane/ethyl acetate, 3:2) to yield **β-18** (17 mg, 0.27 mmol, 25%) and **γ-19** (46 mg,

0.08 mmol, 67%) as bright yellow solids. **γ-19**: M.p. 226–229 °C (CH_2Cl_2/diethyl ether). R_f = 0.33 (SiO_2; hexane/ethyl acetate, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 8.68 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 8.30 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H), 7.99 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H), 7.92 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 7.58 (t, $^3J_{H,H}$ = 7.6 Hz, 1 H), 7.49 (t, $^3J_{H,H}$ = 7.6 Hz, 1 H), 7.19 (s, 1 H), 7.13 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H), 6.91 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H), 4.35 (s, 3 H), 4.07 (s, 3 H), 3.72 (s, 3 H), 3.01 (s, 3 H), 2.21 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 167.9 (C), 157.4 (C), 153.6 (C), 151.1 (C), 148.9 (C), 145.4 (C), 145.0 (C), 144.2 (C), 143.1 (C), 142.5 (C), 141.3 (C), 132.4 (C), 131.1 (CH), 129.4 (CH), 128.6 (CH), 126.9 (CH), 126.3 (C), 126.2 (CH), 125.4 (C), 125.0 (CH), 124.0 (C), 123.3 (C), 122.8 (CH), 118.7 (CH), 99.3 (CH), 64.2 (CH_3), 56.4 (CH_3), 52.9 (CH_3), 24.1 (CH_3), 21.6 (CH_3) ppm. FD-MS: *m/z* (%) = 626 (100) $[M]^+$. IR (neat, ATR): $\tilde{\nu}$ = 3066, 2939, 1739, 1601, 1523, 1379, 1325, 1173, 750 cm^{-1}.

Methyl 1-(5,8-Dimethoxy-7-nitroquinolin-2-yl)-4-methyl-β-carboline-3-carboxylate (22): A suspension of **18** (600 mg, 0.96 mmol) in THF (90 mL) was treated with TBAF (1 M in THF, 2.88 mL, 2.88 mmol, 3 equiv.), and the reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated to dryness, and the residue was dissolved in water and chloroform. The organic phase was washed with water (3×) and dried with $MgSO_4$. The solvent was removed under reduced pressure. Crystallization from chloroform yielded **22** (411 mg, 0.87 mmol, 91%) as a yellow solid. M.p. 261–262 °C. R_f = 0.47 (SiO_2; hexane/ethyl acetate/methanol, 6:3:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 12.11 (s, 1 H), 9.01 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H), 8.71 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H), 8.37 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.71 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 7.62–7.67 (m, 1 H), 7.37–7.41 (m, 1 H), 7.24 (s, 1 H), 4.38 (s, 3 H), 4.090 (s, 3 H), 4.088 (s, 3 H), 3.22 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 168.0 (C), 159.1 (C), 151.7 (C), 144.3 (C), 142.7 (C), 142.6 (C), 141.2 (C), 137.8 (C), 136.0 (C), 134.3 (C), 132.9 (C), 132.2 (CH), 130.6 (C), 128.6 (CH), 124.3 (CH), 123.7 (C), 122.5 (C), 121.4 (CH), 121.1 (CH), 112.3 (CH), 99.5 (CH), 63.7 (C), 56.5 (CH_3), 52.5 (CH_3), 17.0 (CH_3) ppm. FD-MS: *m/z* (%) = 472 (100) $[M]^+$. IR (neat, ATR): $\tilde{\nu}$ = 3338, 3028, 1715, 1601, 1528, 1459, 1338, 1244, 1211, 988, 730 cm^{-1}.

Methyl 1-(7-Acetamido-5,8-dimethoxyquinolin-2-yl)-4-methyl-β-carboline-3-carboxylate (23): Pd/C (10%, 47 mg, 44 μmol, 5 mol-%) was added to a suspension of **22** (405 mg, 0.86 mmol) in THF (170 mL), and the mixture was stirred for 13 h under H_2. Ac_2O (5.0 mL) was added, and the mixture was heated to 50 °C. After 3 h, the solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2. The mixture was filtered through a pad of Celite, and the filtrate was washed with $NaHCO_3$ (8% aqueous solution, 8 mL). The organic layer was dried with $MgSO_4$ and concentrated. Crystallization from chloroform/diethyl ether yielded **23** (399 mg, 0.82 mmol, 96%) as a bright yellow solid. M.p. 194–195 °C. R_f = 0.12 (SiO_2; hexane/ethyl acetate/ethanol, 6:3:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 12.26 (s, 1 H, NH), 8.72 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 8.58 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H), 8.34 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H), 8.09–8.13 (m, 2 H), 7.60–7.66 (m, 2 H), 7.34–7.39 (m, 1 H, CH), 4.19 (s, 3 H), 4.09 (s, 3 H), 4.02 (s, 3 H), 3.19 (s, 3 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ = 168.7 (C), 166.7 (C), 157.3 (C), 151.7 (C), 140.8 (C), 140.6 (C), 136.9 (C), 135.7 (C), 135.4 (C), 135.0 (C), 132.3 (C), 131.8 (CH), 129.8 (C), 128.0 (CH), 124.0 (CH), 122.3 (C), 120.6 (CH), 117.3 (C), 117.0 (CH), 111.9 (C), 98.8 (CH), 61.6 (CH_3), 56.1 (CH_3), 52.4 (CH_3), 25.2 (CH_3), 16.8 (CH_3) ppm. FD-MS: *m/z* (%) = 484 (100) $[M]^+$. IR (neat, ATR): $\tilde{\nu}$ = 3246, 2948, 1702, 1653, 1618, 1596, 1446, 1334, 1275, 1212, 834, 846, 732 cm^{-1}. $C_{25}H_{18}N_4O_5$ (454.43): calcd. C 66.93, H 4.99, N 11.56; found C 66.39, H 4.96, N 11.50.

7-*N*-Acetyllavendamycin Methyl Ester (24): Compound **23** (240 mg, 0.50 mmol) and diacetoxyiodobenzene (DIB, 636 mg, 2 mmol, 4 equiv.) were suspended in a mixture of water (9 mL), acetonitrile (9 mL), and methanol (0.45 mL), and the mixture was stirred at room temperature. After 12 h, water (50 mL) was added, and the aqueous phase was extracted with $CHCl_3$ (4 × 50 mL). The combined organic phases were washed with brine and dried with $MgSO_4$, and the resulting mixture was filtered through a pad of aluminium oxide. The solvent was removed under reduced pressure, and the residue was washed and centrifuged with diethyl ether (2×) to yield **24** (198 mg, 0.44 mmol, 84%) as an orange solid. Spectroscopic and analytical data are in accordance with those in the literature.[8a] M.p. 335 °C. R_f = 0.22 (Al_2O_3 activity II; CH_2Cl_2/methanol, 100:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 11.90 (br. s, 1 H, NH), 9.14 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H), 8.55 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H), 8.44 (br. s, 1 H, NHAc), 8.35 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 8.00 (s, 1 H), 7.78 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.68 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H), 7.43 (t, $^3J_{H,H}$ = 8.0 Hz, 1 H), 4.09 (s, 3 H, CO_2CH_3), 3.23 (s, 3 H), 2.38 (s, 3 H, Ac) ppm. FD-MS: *m/z* (%) = 454 (100) $[M]^+$. HRMS (ES+): calcd. for $[M + Na]^+$ 477.1169; found 477.1176. IR (neat, ATR): $\tilde{\nu}$ = 3309, 3078, 2950, 1722, 1708, 1503, 1305, 1227, 1074, 1051, 863 cm^{-1}.

Lavendamycin Methyl Ester (25): Compound **24** (105 mg, 0.23 mmol) was dissolved in a mixture of H_2SO_4/water (4:3, 11 mL) at 0 °C, and the mixture was heated to 60 °C under N_2. After 30 min, $NaHCO_3$ (9% aqueous) was added until pH = 9. The mixture was extracted with $CHCl_3$ (5 × 30 mL), and the combined organic phases were dried with $MgSO_4$. Removal of the solvent followed by washing and centrifuging the residue with diethyl ether gave lavendamycin methyl ester (**25**) (92 mg, 0.22 mmol, 97%) as a red solid. Spectroscopic and analytical data are in accordance with those in the literature.[1a,7a,8a] M.p. 310 °C. R_f = 0.29 (Al_2O_3; CH_2Cl_2/methanol, 20:1). ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 11.97 (br., 1 H, NH), 9.07 (d, *J* = 8.5 Hz, 1 H, 4′-H), 8.54 (d, *J* = 8.5 Hz, 1 H, 3′-H), 8.37 (d, *J* = 8.5 Hz, 1 H, 5-H), 7.79 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.66 (t, *J* = 7.4 Hz, 1 H, 7-H), 7.40 (t, *J* = 7.4 Hz, 1 H, 6-H), 6.12 (s, 1 H, 6′-H), 5.32 (br. s, 2 H, NH_2), 4.09 (s, 3 H, OCH_3), 3.22 (s, 1 H, 1′-H) ppm. ^{1}H NMR (400 MHz, $[D_6]$DMSO): δ = 11.90 (s, 1 H, NH), 8.77 (d, *J* = 8.3 Hz, 1 H, 3′-H), 8.44 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H, 4′-H), 8.36 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H, 5-H), 7.72 (m, $^3J_{H,H}$ = 8.3 Hz, 1 H, 8-H), 7.67 (dt, $^3J_{H,H}$ = 7.5 Hz, $J_{H,H}$ = 1.2 Hz, 1 H, 7-H), 7.39 (dt, $^3J_{H,H}$ = 7.5 Hz, $J_{H,H}$ = 1.2 Hz, 1 H, 6-H), 5.96 (s, 1 H, 6′-H), 3.97 (s, 3 H, OCH_3), 3.05 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 180.4 (s, C-5′), 179.8 (s, C-8′), 166.8 (s, CO_2), 158.0 (s, C-2′), 150.5 (s, C-7′), 145.4 (s, C-8a′), 140.2 (s, C-8a), 137.4 (s, C-3), 134.4 (s, C-8b), 134.3 (d, C-4′), 133.0 (s, C-1), 130.7 (s, C-4a), 129.2 (s, C-4), 128.6 (s, C-4a′), 128.4 (d, C-7), 124.3 (d, C-3′), 123.6 (d, C-5), 121.1 (s, C-4b), 120.7 (d, C-6), 111.9 (d, C-8), 102.2 (d, C-6′), 51.8 (q, OCH_3), 15.9 (q, CH_3) ppm. FD-MS: *m/z* (%) = 412 (100) $[M]^+$. MS (ES+): *m/z* = 435.1068 $[M + Na]^+$. HRMS (ES+): calcd. for $[M + Na]^+$ 435.1069; found 435.1068. IR (KBr): $\tilde{\nu}$ = 3451, 3329, 1713, 1618, 1335, 738 cm^{-1}.

X-ray Crystal Structure Analysis of 25: The analysis was performed with an Enraf–Nonius Turbo-Cad 4 instrument equipped with a rotating anode by using a red block. Crystal data: $C_{23}H_{16}N_4O_4 \cdot 0.5CHCl_3$, M = 944.2 g mol^{-1}, 0.064 × 0.256 × 0.512 mm, monoclinic, space group $P2_1/c$, Cu-K_α radiation (graphite-monochromated; λ = 1.54180 Å), T = 193 K, unit-cell dimensions: a = 14.314(4) Å, b = 38.714(5) Å, c = 7.4958(2) Å, β = 92.16(2)°, V = 4159(2) Å^3, Z = 4, $d_{calcd.}$ = 1.511 g cm^{-3}, absorption μ = 2.581 mm^{-1}. The θ range for data collection was 2–70°; index ranges were $-17 \le h \le 17$, $-47 \le k \le 0$, $-9 \le l \le 0$. Number of

reflections collected: 8634, independent reflections: 7853 (R_{int} = 0.0837). The structure was solved by direct methods (program SIR 92, refinement by SHELXL 97).[39] Structure refinement was performed by full-matrix least squares on 599 parameters, weighted refinement: $w = 1/[\sigma^2(F_o^2) + (0.1945\,P)^2]$ with $P = [\max(F_o^2,0) + 2\,F_o^2]/3$, and hydrogen atoms were located from difference Fourier synthesis and refined isotropically by assuming a riding-motion model, non-hydrogen atoms were improved with anisotropic refinement. Goodness-of-fit on $S = 0.991$, maximum range of parameters 0.001 e.s.d, final R indices: $R_1 = 0.1258$, $wR_2 = 0.3849$; the final difference Fourier map showed minimum and maximum values of 1.09 and –0.81 e Å^{-3}, respectively. CCDC-805338 (for **25**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of compounds.

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