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Synthesis of Amide Isosteres of Schweinfurthin-based Stilbenes

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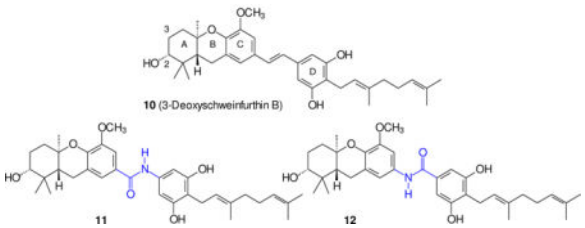
Abstract

The schweinfurthins are plant-derived stilbenes with an intriguing profile of anti-cancer activity. To obtain analogues of the schweinfurthins that might preserve the biological activity but have greater water solubility, a formal replacement of the central olefin with an amide has been explored. Two pairs of amides have been prepared, each containing the same hexahydroxanthene "left half" joined through an amide linkage to two different "right halves." In each series, the amide has been inserted in both possible orientations, placing the carbonyl group on the tricyclic ABC ring system and the amine on the D-ring, or placing the amine on the hexahydroxanthene and the carbonyl group on the D-ring. The four new schweinfurthin analogues have been tested in the NCI 60 cell line screen, and in both cases the more active isomer carried the carbonyl group on the C-ring.

TOC image



Keywords

Schweinfurthin; stilbene; amide isostere; cancer

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Supporting Information Available: The ^{1}H and ^{13}C NMR spectra of all new compounds, and the full 60 cell assay data (including the GI_{50}, TGI, and LC_{50} values for each cell line) for compounds **11**, **12**, **33**, and **35**, can be found here. This material is available free of charge via the Internet at

Competing financial interests. JAB and DFW are named inventors on several patents that describe schweinfurthin analogues, held by the University of Iowa and/or NIH.

Introduction

The natural products commonly grouped as schweinfurthins include six compounds isolated from the plant *Macaranga schweinfurthii*[1–3] (A–D, **1–4**, I and J), four isolated from the plant *Macaranga alnifolia*[4] (E–H, **5–8**), and vedelianin (**9**) which was isolated much earlier from *Macaranga vedeliana*.[5] When tested in the National Cancer Institute screen of 60 human cancer cell lines, those containing a hexahydroxanthene substructure as the ABC ring system showed an intriguing pattern of biological activity. Their unique fingerprint of activity does not parallel that of any chemotherapeutic agent in current clinical use, and approximates those of only a few, far more complex natural products (notably cephalostatins,[6] OSW-1,[7] ritterazines,[8] and stellettins[9]). Mechanistic investigations from several groups have suggested that the schweinfurthins may engage several different targets, including oxysterol binding proteins,[10] trans-Golgi-network trafficking,[11] and cholesterol biosynthesis and its cellular export.[12] The combination of a unique profile of activity with the limited success of efforts to obtain more of the schweinfurthins by isolation from the plant source, has led us to an extended effort to prepare these natural products by chemical synthesis. Our efforts to date have afforded seven of the natural products (schweinfurthins A,[13] B,[14] C,[15] E,[14] F,[16] G[16] and vedelianin[17]), as well as 3-deoxyschweinfurthin B[18] (**10**) which we have used as a lead for a number of structure-activity studies.[19,20] All of the optically active synthetic materials were prepared in high ee through reagent level control of absolute stereochemistry via an enantioselective epoxidation followed by a cascade cyclization to the tricyclic core. In fact, both enantiomers of schweinfurthin F were prepared,[16] and the significantly different selectivity of the two enantiomers in the 60 cell line screen was used to assign the natural absolute stereochemistry as *R, R, R* and not *S, S, S*.

A possible drawback to the use of schweinfurthin-based drugs in chemotherapy is their limited solubility in water. Based on the activity of various analogues we have prepared, it appears that features essential for activity include a trans-fused A-B ring system, an oxygen substituent at C-5 of the C-ring, at least one free phenol on the D-ring, and conjugation from the C-ring to the D-ring as found in the trans (but not the cis[19]) olefin. On the other hand, the C-3 oxygen of schweinfurthin B is expendable without significant loss of activity and the 6′-position in the D-ring can accommodate a wide variety of substituents. Thus we have come to view the hexahydroxanthene found in the ABC ring system as the primary pharmacophore, although the D ring substituents contribute to activity in a lesser way. These observations led us to examine whether the central stilbene olefin could be replaced with a more polar group such as an amide to maintain activity while improving water solubility. The restricted rotation around the amide bond should favor a transoid structure, and may allow some communication of electronic effects from the C-ring to the D-ring. As a test of that hypothesis, in this paper we report the preparation of four new “schweinfurthin amides” as well as our initial studies on their biological activity.

Results and Discussion

From the outset of this effort, it was viewed as essential to prepare the new schweinfurthin analogues as a matched pair (Scheme 1), that is, one analogue with the carbonyl group on the tricyclic ABC ring system and the amide nitrogen on the D-ring (**11**), and a second

isomeric analogue where the substituents were reversed (**12**). The obvious disconnection at the amide bond leads to the acids **13** and **16** and the amines **14** and **15**. If some variation on the Curtius or Hoffman reaction[21] could be employed despite the presence of a variety of other functional groups, it would be possible to derive the amine **14** from the acid **16** and the amine **15** from the acid **13**. This would enhance the efficiency of the overall effort by the dual use of these carboxylic acids. While the ether and acetal groups in compound **13** were viewed as relatively stable to both acidic and basic conditions, the stability of the isoprenoid olefins in compounds of the general structure **16** was of more concern. Nevertheless, given the possibility for use of compound **16** in both target amides, the initial goal became preparation of a protected acid **16**.

The synthetic sequence used to prepare the target “right half” acid began with commercial 3,5-dihydroxybenzoic acid (**17**). Treatment of this resorcinol with bromine under acidic conditions gave the para bromo derivative **18** in nearly quantitative yield.[22] Treatment of compound **18** with MOMCl and diisopropylethylamine resulted in smooth formation of the triMOM derivative **19**. While acyloxy esters commonly have been employed in prodrugs,[23] application of the MOM group as a carboxylic acid protecting group in place of a methyl ester or protected primary alcohol shortened the synthetic sequence significantly relative to our previous efforts. The MOM ester **19** proved to be sufficiently stable to allow halogen-metal exchange and alkylation with geranyl bromide to give the ester **20** in moderate yield.[24]

Selective hydrolysis of the MOM ester by treatment with LiOH gave the free carboxylic acid **21**, and set the stage for preparation of an aryl amine via C-C bond cleavage and a formal insertion. One might consider either a Hoffmann or Curtius rearrangement to accomplish this transformation, but the presence of the isoprenoid olefin led us to favor the Curtius strategy. While there is precedent for conversion of an olefin to an aziridine via reaction with a nitrene,[25,26] the prevailing view is that the Curtius rearrangement is a concerted process rather than one which involves discrete nitrene formation.[21] In the event, reaction of the acid **21** with diphenyl phosphoryl azide (DPPA) followed by treatment with LiOH, gave the desired amine **22** in moderate yield. The complementary carboxylic acid **24** could be prepared by simple oxidation of the aldehyde **23**, a hexahydroxanthene we have used in past syntheses of numerous schweinfurthin analogues.[14] An EDC-mediated condensation of the acid **24** and the amine **22** gave the expected amide **25**, and a final acid-catalyzed hydrolysis of the MOM protecting groups gave the target compound **11**.

After amide **11** was prepared, synthesis of amide **12** was relatively straightforward because the second sequence could take advantage of some intermediates already in hand. As shown in Scheme 3, the carboxylic acid **24** gave the desired amine **26** upon treatment with DPPA. An EDC mediated condensation of acid **21** and amine **26** gave the desired amide framework (**27**), and MOM hydrolysis gave the final target, amide **12**, in reasonable yield.

For a more robust comparison of the impact of formal replacement of the stilbene olefin with an amide unit, a second pair of schweinfurthin amides was prepared. We recently reported the synthesis and biological activity of some indole schweinfurthin analogues[27,28] and used that effort as an inspiration for this second pair. As shown in Scheme 4, the parent indole carboxylic acid ester **28** was first dimethylated (**29**) to protect potentially sensitive

functionality and to allow direct comparison with the activity of an indole schweinfurthin previously prepared. After hydrolysis of the methyl ester **29**, the resulting carboxylic acid **30** was converted to the corresponding amine **31** by reaction with DPPA. Formation of the amide **32** was accomplished under standard conditions, as was final hydrolysis of the MOM protecting groups. The “reversed” amide **34** was obtained upon condensation of the amine **26** with the carboxylic acid **30**, and a final hydrolysis of the MOM groups gave the target amide **35**.

Once the four new schweinfurthin amides were in hand, each was tested in the NCI’s 60 cell line assay.[29] These compounds showed schweinfurthin-like activity as measured by similar patterns of selectivity, with Pearson correlation coefficients of 0.65 to 0.78 (Table 1), and with the potency of compounds **11** and **33** comparable to the parent stilbenes. Both of the isomeric amides **12** and **35** were less potent and demonstrated a lower differential activity across the 60 cell lines assayed. In terms of calculated logP, there is no difference in water solubility between the two amide isomers in each pair, so the observed differences in biological activity must track to other molecular properties.

In conclusion, we have developed synthetic sequences that allow formal replacement of the central stilbene olefin of the schweinfurthins with an amide linkage. This substitution preserves the selectivity and potency of the parent schweinfurthins, and should increase the water solubility of these analogues relative to the parent compounds as measured by calculated logP values. In both series tested, the more active isomers **11** and **33** bore the carbonyl group on the C-ring, and the amine on the D-ring, suggesting that electron donation to the D-ring is more beneficial to activity than electron withdrawal. Further studies will be needed to determine if this is a consistent trend, but these findings provide some guidance to the design of still more pharmaceutically useful schweinfurthin analogues.

Experimental Section

General Experimental Procedures

Both tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium and benzophenone, whereas methylene chloride (CH_2Cl_2) was distilled from calcium hydride prior to use. The solutions of *n*–BuLi were purchased from a commercial source and titrated with diphenylacetic acid prior to use. All other reagents and solvents were purchased from commercial sources and used without further purification. All reactions in nonaqueous solvents were conducted in flame-dried glassware under a positive pressure of argon and with a magnetic stir bar. NMR spectra were obtained at 400 or 500 MHz for ^1H, 101 or 126 MHz for ^{13}C NMR, in $CDCl_3$ with $(CH_3)_4Si$ (^1H, 0.00 ppm) or $CDCl_3$ (^1H, 7.26 ppm; ^{13}C NMR; 77.16 ppm) or CD_3OD (^1H, 3.31 ppm; ^{13}C NMR; 49.00 ppm), as the internal standards. High-resolution mass spectra were obtained by GC-TOF. Silica gel (60 Å, 0.040 – 0.063 mm) was used for flash column chromatography.

(2R,4aR,9aR)-*N*-(4-((*E*)-3,7-Dimethylocta-2,6-dienyl)-3,5-dihydroxyphenyl)-2-hydroxy-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene-7-carboxamide (11). NSC#791211

To a stirred solution of the acetal **25** (39 mg, 56 μmol) in MeOH (5.6 mL) was added *p*-TsOH·H_2O (61 mg, 0.32 mmol). The flask was sealed and stirred for 28 hours at rt. Analysis by tlc suggested that the reaction was not complete so additional *p*-TsOH·H_2O (15 mg, 79 μmol) was added and the solution was stirred for an additional 17 hours. The solution was diluted with EtOAc and then washed with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered, and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 80% EtOAc in hexanes) afforded amide **11** (16.3 mg, 52%) as an off-white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.33 (d, *J* = 1.9 Hz, 1H), 7.30 (d, *J* = 1.8 Hz, 1H), 6.71 (s, 2H), 5.29 – 5.21 (m, 1H), 5.12 – 5.05 (m, 1H), 3.85 (s, 3H), 3.38 – 3.32 (m, 1H), 3.28 (d, *J* = 7.4 Hz, 2H), 2.79 – 2.73 (m, 2H), 2.10 – 2.01 (m, 3H), 1.99 – 1.91 (m, 2H), 1.84 – 1.74 (m, 5H), 1.67 – 1.62 (m, 5H), 1.57 (s, 3H), 1.22 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (101 MHz, CD 13 3OD) δ C NMR (101 MHz, CD_3OD) δ 168.6, 157.2 (2C), 149.9, 147.2, 138.0, 134.8, 132.0, 127.3, 125.6, 124.8, 123.8, 122.8, 113.1, 110.0, 101.4 (2C), 78.9, 78.6, 56.5, 48.2, 41.0, 39.5, 38.8, 28.9, 27.9, 27.8, 25.9, 24.1, 23.0, 20.3, 17.7, 16.3, 14.9; HRMS (TOF MS ES+) *m/z* calculated for $C_{34}H_{46}NO_6$ $(M + H)^+$ 564.3325, found 564.3326.

4-((*E*)-3,7-Dimethylocta-2,6-dienyl)-3,5-dihydroxy-*N*-((2R,4aR,9aR)-2-hydroxy-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-7-yl)benzamide (12), NSC#791210

To a stirred solution of the acetal **27** (32 mg, 46 μmol) in MeOH (4.6 mL) was added *p*-TsOH·H_2O (50 mg, 0.26 mmol). The flask was sealed and stirred for 27 hours at rt. After tlc analysis suggested that the reaction was not complete, additional *p*-TsOH·H_2O (15 mg, 79 μmol) was added and the solution was stirred for an additional 18 hours. The solution was diluted with EtOAc and then washed with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered, and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 80% EtOAc in hexanes) afforded amide **12** (19.2 mg, 74%) as an off-white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.13 (s, 1H), 6.95 (s, 1H), 6.80 (s, 2H), 5.25 (t, *J* = 7.1 Hz, 1H), 5.08 (t, *J* = 7.0 Hz, 1H), 3.80 (s, 3H), 3.35 (d, *J* = 7.2 Hz, 3H), 2.72 (s, 1H), 2.70 (s, 1H), 2.11 – 2.00 (m, 3H), 2.00 – 1.91 (m, 2H), 1.84 – 1.74 (m, 5H), 1.69 – 1.64 (m, 2H), 1.63 (s, 3H), 1.57 (s, 3H), 1.21 (s, 3H), 1.08 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 169.4, 157.4 (2C), 149.7, 140.9, 135.5, 134.8, 132.0, 131.9, 125.5, 124.0, 123.8, 120.6, 115.6, 106.8 (2C), 105.6, 78.7, 77.9, 56.4, 48.5, 41.0, 39.5, 38.9, 29.0, 27.9, 27.8, 25.9, 24.3, 23.4, 20.1, 17.7, 16.3, 14.8. HRMS (TOF MS ES+) *m/z* calculated for $C_{34}H_{46}NO_6$ $(M + H)^+$ 564.3325, found 564.3336.

Methoxymethyl 4-bromo-3,5-bis(methoxymethoxy)benzoate (19)

To a stirred solution of 4-bromo-3,5-dihydroxybenzoic acid (1.64 g, 7.0 mmol) and *N,N*-diisopropylethylamine (4.0 mL 23.2 mmol) in CH_2Cl_2 (24 mL) at 0 °C was added chloromethyl methyl ether (2.14 mL, 28.2 mmol) dropwise via syringe. The solution was allowed to equilibrate to rt overnight and then washed with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The organic layers were combined and washed with brine, and then dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 30% EtOAc in hexanes) afforded **19** (1.16 g, 89%) as an off-white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 2H), 5.48 (s, 2H), 5.31 (s, 4H), 3.54 (s, 3H), 3.53 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 155.0 (2C), 130.2, 110.3 (2C), 110.1, 95.3 (2C), 91.4, 58.1, 56.7 (2C). HRMS (TOF MS ES+) *m/z* calculated for $C_{13}H_{17}{}^{79}BrO_7Na$ $(M + Na)^+$ 387.0055, found 387.0060.

(*E*)-Methoxymethyl 4-(3,7-dimethylocta-2,6-dienyl)-3,5-bis(methoxymethoxy)benzoate (20).

An oven-dried flask was charged with ester **19** (0.5 g, 1.37 mmol) in anhydrous THF (10 mL) at –78 °C. To this solution was added *n*-BuLi (2.5M in hexanes, 0.58 mL, 1.4 mmol) dropwise via syringe. The resulting solution was stirred at –78 °C for 20 minutes and then CuBr·DMS (0.31 g, 1.5 mmol) was added. The solution was stirred an additional 20 minutes at –78 °C and then geranyl bromide (0.33 g, 1.5 mmol) was added dropwise via syringe. The solution was allowed to equilibrate to rt overnight and then the reaction was quenched by the addition of saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The organic extracts were combined, washed with brine, and dried (Na_2SO_4). The mixture was filtered and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 30% EtOAc in hexanes) afforded compound **20** (0.34 g, 60%) as a yellow oil: ^{1}H NMR (500 MHz, CDCl3) δ 7.47 (s, 2H), 5.46 (s, 2H), 5.24 (s, 4H), 5.20 – 5.15 (m, 1H), 5.05 (t, J = 6.9 Hz, 1H), 3.53 (s, 3H), 3.48 (s, 6H), 3.45 (d, J = 7.1 Hz, 2H), 2.03 (dd, J = 14.7, 6.9 Hz, 2H), 1.99 – 1.90 (m, 2H), 1.79 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 155.7 (2C), 135.6, 131.5, 128.7, 126.5, 124.4, 121.8, 109.4 (2C), 94.7 (2C), 91.0, 57.9, 56.3 (2C), 39.9, 26.9, 25.8, 23.2, 17.8, 16.3. HRMS (TOF MS ES+) *m/z* calculated for $C_{23}H_{34}O_7Na$ $(M + Na)^+$ 445.2202, found 445.2197.

(*E*)-4-(3,7-Dimethylocta-2,6-dienyl)-3,5-bis(methoxymethoxy)benzoic acid (21)

To a stirred solution of ester **20** (0.470 g, 1.11 mmol) in THF (5 mL) and H_2O (5 mL) was added $LiOH·H_2O$ (93 mg, 2.23 mmol). The flask was stirred at rt overnight and then the solution was acidified with HCl. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered, and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 40% EtOAc in hexanes) afforded compound **21** (0.421 g, 81%) as a white powder: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 2H), 5.25 (s, 4H), 5.21 – 5.16 (m, 1H), 5.05 (t, *J* = 6.8 Hz, 1H), 3.49 (s, 6H), 3.46 (d, *J* = 7.0 Hz, 2H), 2.07 – 2.00 (m, 2H), 1.99 – 1.93 (m, 2H), 1.79 (s, 3H), 1.64 (s, 3H), 1.56 (s,

3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 155.7 (2C), 135.7, 131.5, 128.1, 126.9, 124.4, 121.7, 109.8 (2C), 94.7 (2C), 56.3 (2C), 39.9, 26.8, 25.8, 23.2, 17.8, 16.3. HRMS (TOF MS ES+) *m/z* calculated for $C_{21}H_{30}O_6Na$ $(M + Na)^+$ 401.1940, found 401.1946.

(*E*)-4-(3,7-Dimethylocta-2,6-dienyl)-3,5-bis(methoxymethoxy)aniline (22)

An oven-dried flask was charged with carboxylic acid **21** (100 mg, 0.26 mmol) in anhydrous benzene (26 mL). To this stirred solution was added triethylamine (0.368 mL, 2.60 mmol) followed by the dropwise addition of DPPA (0.569 mL, 2.60 mmol) via syringe. The solution was stirred at rt for 15 minutes, and then the flask was fitted with a reflux condenser and heated at reflux overnight. The benzene was removed under reduced pressure and the residue was dissolved in THF (2.6 mL). To this solution was added aqueous 4N LiOH (1.3 mL, 5.30 mmol) and the resulting mixture was stirred vigorously at rt for 1 hour. The mixture was diluted with H_2O and the layers were separated. The aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were washed with brine, and dried (Na_2SO_4). The mixture was filtered and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 40% EtOAc in hexanes) afforded amine **22** (45 mg, 49%) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 2H), 5.22 – 5.18 (m, 1H), 5.15 (s, 4H), 5.13 – 5.06 (m, 1H), 3.48 (s, 6H), 3.30 (d, *J* = 7.0 Hz, 2H), 2.10 – 2.01 (m, 2H), 2.00 – 1.92 (m, 2H), 1.78 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (2C), 145.8, 134.0, 131.3, 124.6, 123.8, 110.7, 96.0 (2C), 94.6 (2C), 56.0 (2C), 40.0, 26.9, 25.8, 22.2, 17.8, 16.1. HRMS (TOF MS ES+) *m/z* calculated for $C_{20}H_{32}NO_4$ $(M + H)^+$ 350.2331, found 350.2324.

(2R,4aR,9aR)-5-Methoxy-2-(methoxymethoxy)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene-7-carboxylic acid (24)

To a stirred solution of aldehyde **23** (250 mg, 0.72 mmol) and 2-methyl-2-butene (1.50 mL, 14.4 mmol) in *t*-BuOH (7 mL) was added NaH_2PO_4 (301 mg, 2.50 mmol) and $NaClO_2$ (390 mg, 4.3 mmol) in H_2O (2.4 mL) via syringe. The solution was stirred vigorously at rt for 3.5 hours and then washed with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (3x) and the combined organic extracts were washed with brine and dried (Na_2SO_4). The mixture was filtered and filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 40% EtOAc in hexanes) afforded carboxylic acid **24** (138 mg, 53%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.42 (s, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 6.9 Hz, 1H), 3.90 (s, 3H), 3.41 (s, 3H), 3.28 (dd, *J* = 11.6, 3.9 Hz, 1H), 2.80 – 2.69 (m, 2H), 2.16 (d, *J* = 12.8 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.86 – 1.77 (m, 1H), 1.71 (dd, *J* = 11.5, 6.5 Hz, 1H), 1.65 – 1.54 (m, 1H), 1.27 (s, 3H), 1.10 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 148.8, 148.0, 125.3, 122.5, 120.3, 110.5, 96.3, 84.1, 78.2, 56.2, 55.8, 47.0, 38.4, 37.6, 27.5, 25.4, 23.2, 20.1, 15.3. HRMS (TOF MS ES-) *m/z* calculated for $C_{20}H_{27}O_6$ $(M - H)^-$ 363.1808, found 363.1798.

(2R,4aR,9aR)-*N*-(4-((*E*)-3,7-Dimethylocta-2,6-dienyl)-3,5-bis(methoxymethoxy)phenyl)-5-methoxy-2-(methoxymethoxy)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene-7-carboxamide (25)

To a stirred solution of carboxylic acid **24** (49 mg, 0.13 mmol) and amine **22** (39 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (1 mL) was added EDC (64 mg, 0.34 mmol) and 4-(dimethylamino)pyridine (2.7 mg, 22 μmol). The solution was stirred at rt for 19 hours and then washed with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered, and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 50% EtOAc in hexanes) afforded amide **25** (42 mg, 54%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.31 (d, *J* = 1.9 Hz, 1H), 7.21 (d, *J* = 1.8 Hz, 1H), 7.18 (s, 2H), 5.23 – 5.16 (m, 5H), 5.11 – 5.04 (m, 1H), 4.76 (d, *J* = 6.9 Hz, 1H), 4.64 (d, *J* = 6.9 Hz, 1H), 3.87 (s, 3H), 3.50 – 3.46 (m, 6H), 3.40 (s, 3H), 3.37 (d, *J* = 7.1 Hz, 2H), 3.26 (dd, *J* = 11.5, 4.0 Hz, 1H), 2.76 – 2.68 (m, 2H), 2.15 – 2.10 (m, 1H), 2.08 – 1.99 (m, 3H), 1.98 – 1.93 (m, 3H), 1.85 – 1.79 (m, 1H), 1.78 (s, 3H), 1.69 – 1.66 (m, 1H), 1.65 (s, 3H), 1.61 – 1.52 (m, 4H), 1.24 (s, 3H), 1.08 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 155.9 (2C), 149.1, 146.1, 137.3, 134.6, 131.3, 126.1, 124.5, 122.9, 122.4, 120.4, 116.4, 108.7, 100.4 (2C), 96.3, 94.7 (2C), 84.0, 77.8, 56.2, 56.2 (2C), 55.7, 47.0, 39.9, 38.4, 37.5, 27.5, 26.9, 25.8, 25.4, 23.3, 22.5, 20.0, 17.7, 16.2, 15.2. HRMS (TOF MS ES+) *m/z* calculated for $C_{40}H_{58}NO_9$ $(M + H)^+$ 696.4112, found 696.4116.

2R,4aR,9aR)-5-Methoxy-2-(methoxymethoxy)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-7-amine (26)

An oven-dried flask was charged with carboxylic acid **24** (75 mg, 0.21 mmol) in anhydrous benzene (21 mL). To this stirred solution was added triethylamine (0.287 mL, 2.10 mmol) followed by the dropwise addition of DPPA (0.443 mL, 2.10 mmol) via syringe. The resulting solution was stirred at rt for 15 minutes, and then the flask was fitted with a reflux condenser and heated at reflux overnight. The benzene was removed under reduced pressure and the residue was dissolved in THF (2.0 mL). To this solution was added aqueous 4N LiOH (1.0 mL, 4.12 mmol) and the resulting mixture was stirred vigorously at rt for 1 hour. The mixture was diluted with H_2O and the layers were separated. The aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were washed with brine, and dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (20 to 60% EtOAc in hexanes) afforded amine **26** (37 mg, 54%) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (d, *J* = 2.5 Hz, 1H), 6.06 (d, *J* = 2.4 Hz, 1H), 4.76 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 3.78 (s, 3H), 3.40 (s, 3H), 3.25 (dd, *J* = 11.6, 4.2 Hz, 1H), 2.61 (s, 1H), 2.59 (s, 1H), 2.08 (dt, *J* = 12.8, 3.4 Hz, 1H), 1.96 (ddd, *J* = 13.2, 7.6, 3.7 Hz, 1H), 1.77 (td, *J* = 13.4, 3.2 Hz, 1H), 1.69 (dd, *J* = 10.0, 8.1 Hz, 1H), 1.63 – 1.49 (m, 1H), 1.21 (s, 3H), 1.06 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4, 139.0, 135.7, 123.3, 107.4, 99.0, 96.3, 84.3, 76.1, 56.0, 55.7, 47.3, 38.3, 37.8, 27.5, 25.4, 23.4, 19.7, 15.2; HRMS (TOF MS ES+) *m/z* calculated for $C_{19}H_{30}NO_4$ $(M + H)^+$ 336.2175, found 336.2182.

4-((*E*)-3,7-Dimethylocta-2,6-dienyl)-*N*-((2R,4aR,9aR)-5-methoxy-2-(methoxymethoxy)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-7-yl)-3,5-bis(methoxymethoxy)benzamide (27)

To a stirred solution of carboxylic acid **21** (42 mg, 0.11 mmol) and amine **26** (31 mg, 92 μmol) in anhydrous CH_2Cl_2 (1 mL) was added EDC (53 mg, 0.28 mmol) and 4-(dimethylamino)pyridine (2.3 mg, 18 μmol). The solution was stirred at rt for 20 hours and then washed with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered, and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 60% EtOAc in hexanes) afforded amide **27** (32 mg, 51%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.27 (s, 2H), 7.19 (d, *J* = 2.1 Hz, 1H), 6.91 (d, *J* = 2.2 Hz, 1H), 5.26 (s, 4H), 5.24 – 5.18 (m, 1H), 5.12 – 5.04 (m, 1H), 4.79 (d, *J* = 6.8 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 3.86 (s, 3H), 3.50 (s, 6H), 3.46 (d, *J* = 7.2 Hz, 2H), 3.43 (s, 3H), 3.28 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.72 (s, 1H), 2.70 (s, 1H), 2.13 (dt, *J* = 12.7, 3.3 Hz, 1H), 2.09 – 2.03 (m, 2H), 2.01 – 1.95 (m, 3H), 1.85 – 1.77 (m, 4H), 1.73 (t, *J* = 9.1 Hz, 1H), 1.66 (s, 3H), 1.63 – 1.55 (m, 4H), 1.26 (s, 3H), 1.09 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 155.9 (2C), 148.9, 139.8, 135.5, 134.2, 131.5, 130.2, 127.2, 124.4, 122.8, 121.9, 113.4, 106.7 (2C), 103.4, 96.3, 94.7 (2C), 84.2, 76.8, 56.3 (2C), 56.2, 55.8, 47.2, 39.9, 38.4, 37.7, 27.5, 26.8, 25.8, 25.4, 23.4, 23.0, 19.8, 17.8, 16.3, 15.2. HRMS (TOF MS ES+) *m/z* calculated for $C_{40}H_{58}NO_9$ $(M + H)^+$ 696.4112, found 696.4122.

Methyl 4-methoxy-1-methyl-1H-indole-6-carboxylate (29)

An oven-dried flask was charged with commercial methyl 4-hydroxyindole-6-carboxylate (50 mg, 0.26 mmol) in anhydrous DMF (1 mL) at 0 °C. To this solution was added NaH (60% in mineral oil, 31 mg, 0.79 mmol) and the solution was stirred for 30 minutes at 0 °C. After CH_3I (40 μL, 0.63 mmol) was added dropwise to the solution via syringe, the solution was allowed to equilibrate to rt overnight. The reaction was quenched with the addition of H_2O (3 mL) and the mixture was extracted with EtOAc (5x). The organic extracts were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 20% EtOAc in hexanes) afforded the dimethylated compound **29** (47.8 mg, 83%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.20 (s, 1H), 7.11 (d, *J* = 3.0 Hz, 1H), 6.61 (d, *J* = 2.7 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.84 (s, 3H).[30]

4-Methoxy-1-methyl-1H-indole-6-carboxylic acid (30)

To a stirred solution of indole **29** (47.8 mg, 0.22 mmol) in THF (1 mL) and H_2O (1 mL) was added $LiOH{\cdot}H_2O$ (18 mg, 0.44 mmol). The flask was stirred at rt overnight and then the solution was washed with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered, and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 40% EtOAc in hexanes) afforded the carboxylic acid **30** (42.4 mg, 95%) as a white powder: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.27 (s, 1H), 7.15 (d, *J* = 2.9 Hz, 1H), 6.64 (d, *J* = 2.9 Hz, 1H),

4.03 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 153.1, 137.4, 131.0, 123.7, 123.3, 107.0, 100.2, 99.2, 55.7, 33.4. HRMS (TOF MS ES-) *m/z* calculated for $C_{11}H_{10}NO_3$ $(M - H)^-$ 204.0661, found 204.0669.

4-Methoxy-1-methyl-1H-indol-6-amine (31)

An oven-dried flask was charged with carboxylic acid **30** (31 mg, 0.15 mmol) in anhydrous benzene (15 mL). To this stirred solution was added triethylamine (210 μL, 1.50 mmol) followed by the dropwise addition of DPPA (326 μL, 1.50 mmol) via syringe. The solution was stirred at rt for 15 minutes, and then the flask was fitted with a reflux condenser and heated at reflux overnight. The benzene was removed under reduced pressure and the residue was dissolved in THF (1.5 mL). To this solution was added aqueous 4N LiOH (755 μL, 3.00 mmol) and the resulting mixture was stirred vigorously at rt for 2 hours. After the mixture was diluted with H_2O, the layers were separated. The aqueous layer was extracted with EtOAc (3x) and the combined organic extracts were washed with brine, and dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 80% EtOAc in hexanes) afforded amine **31** (24.7 mg, 93%) as a brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (d, *J* = 3.1 Hz, 1H), 6.43 (d, *J* = 3.1 Hz, 1H), 6.24 (s, 1H), 6.01 (s, 1H), 3.90 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 143.1, 139.3, 125.4, 112.7, 98.3, 91.8, 88.2, 55.4, 33.0. HRMS (TOF MS ES+) *m/z* calculated for $C_{10}H_{13}N_2O$ $(M + H)^+$ 177.1028, found 177.1033.

(2R,4aR,9aR)-5-Methoxy-*N*-(4-methoxy-1-methyl-1H-indol-6-yl)-2-(methoxymethoxy)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene-7-carboxamide (32)

To a stirred solution of carboxylic acid **24** (20 mg, 57 μmol) and amine **31** (12 mg, 68 μmol) in anhydrous CH_2Cl_2 (1 mL) was added EDC (33 mg, 0.17 mmol) and 4-(dimethylamino)pyridine (1.4 mg, 11 μmol). The solution was stirred at rt for 24 hours and then washed with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered, and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 80% EtOAc in hexanes) afforded **32** (20.4 mg, 99%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.61 (s, 1H), 7.36 (d, *J* = 1.4 Hz, 1H), 7.25 (s, 1H), 6.93 (d, *J* = 3.1 Hz, 1H), 6.63 (s, 1H), 6.53 (d, *J* = 3.0 Hz, 1H), 4.77 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 6.9 Hz, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 3.74 (s, 3H), 3.41 (s, 3H), 3.27 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.78 – 2.69 (m, 2H), 2.15 (dt, *J* = 12.7, 3.2 Hz, 1H), 2.03 – 1.97 (m, 1H), 1.81 (td, *J* = 13.8, 3.2 Hz, 1H), 1.71 (dd, *J* = 11.1, 6.9 Hz, 1H), 1.59 (d, *J* = 14.0 Hz, 1H), 1.26 (s, 3H), 1.09 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 153.4, 149.3, 146.1, 138.2, 133.8, 127.6, 126.6, 122.5, 120.4, 116.3, 108.9, 98.5, 96.4, 95.0, 94.3, 84.1, 77.8, 56.4, 55.8, 55.6, 47.1, 38.4, 37.7, 33.2, 27.6, 25.4, 23.4, 20.0, 15.3. HRMS (TOF MS ES+) *m/z* calculated for $C_{30}H_{39}N_2O_6$ $(M + H)^+$ 523.2808, found 523.2812.

(2R,4aR,9aR)-2-Hydroxy-5-methoxy-*N*-(4-methoxy-1-methyl-1H-indol-6-yl)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthene-7-carboxamide (33), NSC#795315

To a stirred solution of amide **32** (15 mg, 29 μmol) in MeOH (3 mL) was added *p*-TsOH·H_2O (11 mg, 29 μmol). The flask was sealed and stirred for 2 days at rt. The solution was diluted with EtOAc and then washed with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic extracts were dried over Na_2SO_4 and filtered, and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 80% EtOAc in hexanes) afforded **33** (9 mg, 65%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.60 (s, 1H), 7.35 (s, 1H), 7.26 (s, 1H), 6.93 (d, *J* = 1.1 Hz, 1H), 6.62 (s, 1H), 6.53 (s, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.74 (s, 3H), 3.43 (d, *J* = 8.8 Hz, 1H), 2.80 – 2.73 (m, 2H), 2.15 (d, *J* = 14.3 Hz, 1H), 1.93 – 1.82 (m, 2H), 1.73 – 1.66 (m, 1H), 1.64 – 1.56 (m, 2H), 1.26 (s, 3H), 1.11 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 152.4, 148.3, 145.1, 137.2, 132.8, 126.6, 125.6, 121.5, 119.4, 115.3, 107.9, 97.5, 94.0, 93.3, 77.1, 76.9, 55.4, 54.6, 45.8, 37.6, 36.8, 32.3, 27.5, 26.5, 22.5, 19.1, 13.5. HRMS (TOF MS ES+) *m/z* calculated for $C_{28}H_{35}N_2O_5$ $(M + H)^+$ 479.2546, found 479.2541.

4-Methoxy-*N*-((2R,4aR,9aR)-5-methoxy-2-(methoxymethoxy)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-7-yl)-1-methyl-1H-indole-6-carboxamide (34)

To a stirred solution of amine **26** (11.5 mg, 34 μmol) and carboxylic acid **30** (16.5 mg, 80 μmol) in anhydrous CH_2Cl_2 (1 mL) was added EDC (26 mg, 0.14 mmol) and 4-(dimethylamino)pyridine (1 mg, 7 μmol). The solution was stirred at rt for 24 hours and then washed with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered, and the filtrate was concentrated *in vacuo*. Final purification using an ISCO Combiflash Rf chromatography gradient (0 to 100% EtOAc in hexanes) afforded amide **34** (8 mg, 45%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.51 (s, 1H), 7.23 (d, *J* = 2.3 Hz, 1H), 7.10 (d, *J* = 3.1 Hz, 1H), 6.99 (d, *J* = 1.0 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.62 (d, *J* = 2.6 Hz, 1H), 4.77 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.02 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.41 (s, 3H), 3.28 (dd, *J* = 11.5, 4.1 Hz, 1H), 2.71 (s, 1H), 2.68 (s, 1H), 2.13 (dt, *J* = 12.7, 3.3 Hz, 1H), 1.99 (ddd, *J* = 11.4, 7.5, 3.5 Hz, 1H), 1.80 (td, *J* = 13.8, 3.3 Hz, 1H), 1.64 – 1.57 (m, 1H), 1.26 (s, 3H), 1.08 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 153.5, 149.0, 139.7, 137.6, 130.6, 130.1, 129.7, 122.9, 121.9, 113.3, 103.3, 102.7, 99.0, 98.1, 96.3, 84.2, 67.2, 56.2, 55.8, 55.7, 47.2, 38.4, 37.7, 33.4, 27.5, 25.5, 23.4, 19.9, 15.2. HRMS (TOF MS ES+) *m/z* calculated for $C_{30}H_{39}N_2O_6$ $(M + H)^+$ 523.2808, found 523.2818.

N-((2R,4aR,9aR)-2-Hydroxy-5-methoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-7-yl)-4-methoxy-1-methyl-1H-indole-6-carboxamide (35), NSC#795316

To a stirred solution of amide **34** (8.6 mg, 16 μmol) in MeOH (1.6 mL) was added *p*-TsOH·H_2O (6 mg, 31 μmol). The flask was sealed and stirred for 2 days at rt. The solution was diluted with EtOAc and then washed with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic extracts were dried over Na_2SO_4 and filtered, and the filtrate was concentrated *in vacuo*.

Final purification using an an ISCO Combiflash Rf chromatography gradient (0 to 100% EtOAc in hexanes) afforded amide **35** (4.7 mg, 60%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.52 (s, 1H), 7.23 (d, *J* = 2.1 Hz, 1H), 7.09 (d, *J* = 3.0 Hz, 1H), 7.00 (s, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.62 (d, *J* = 3.1 Hz, 1H), 4.02 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.42 (dd, *J* = 11.1, 2.8 Hz, 1H), 2.71 (s, 1H), 2.68 (s, 1H), 2.16 – 2.09 (m, 1H), 1.91 – 1.79 (m, 2H), 1.71 (t, *J* = 9.0 Hz, 1H), 1.65 – 1.56 (m, 2H), 1.25 (s, 3H), 1.09 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 153.5, 149.0, 139.7, 137.6, 130.7, 130.1, 129.8, 122.8, 122.0, 113.3, 103.5, 102.7, 99.0, 98.2, 78.2, 56.2, 55.7, 47.0, 38.5, 37.9, 33.4, 28.5, 27.5, 23.5, 19.9, 14.4. One carbon signal was obscured by the chloroform resonance; when the spectrum was recorded in C_6D_6 this was observed at 76.4 ppm. HRMS (ESI) m/z calcd for $C_{28}H_{35}N_2O_5$ $(M + H)^+$ 479.2546, found 479.2540.

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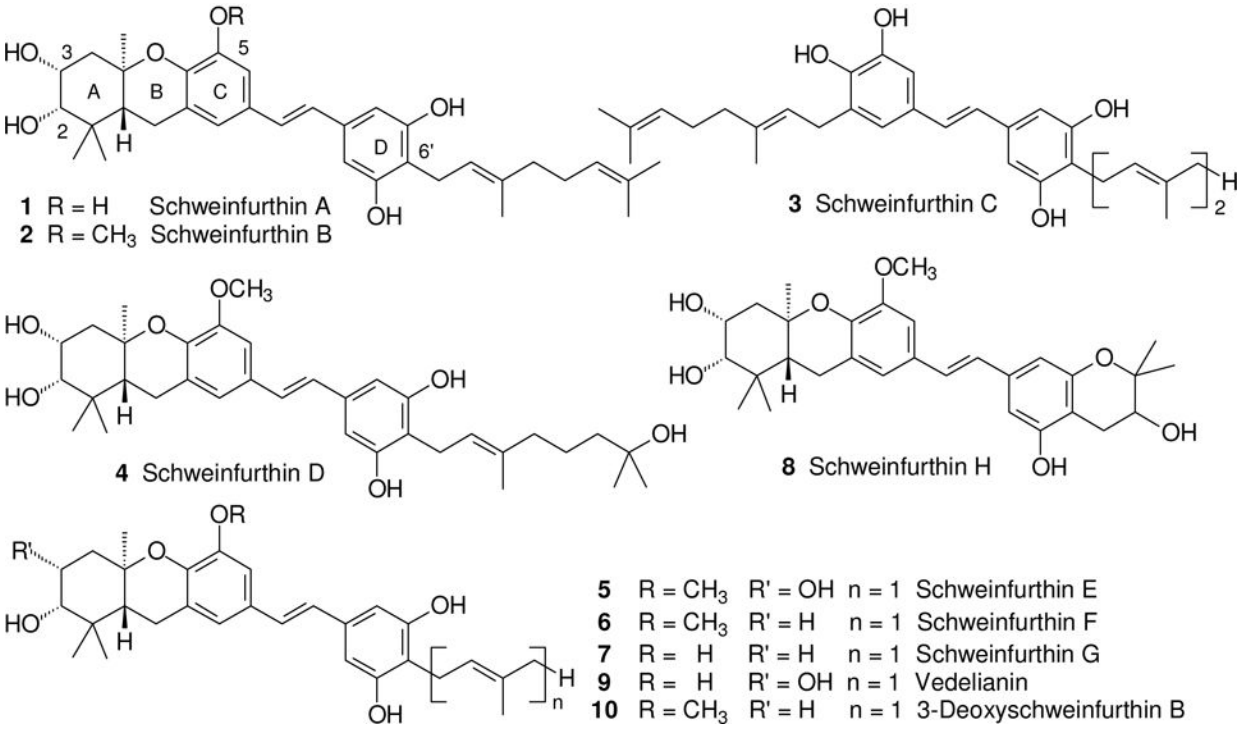
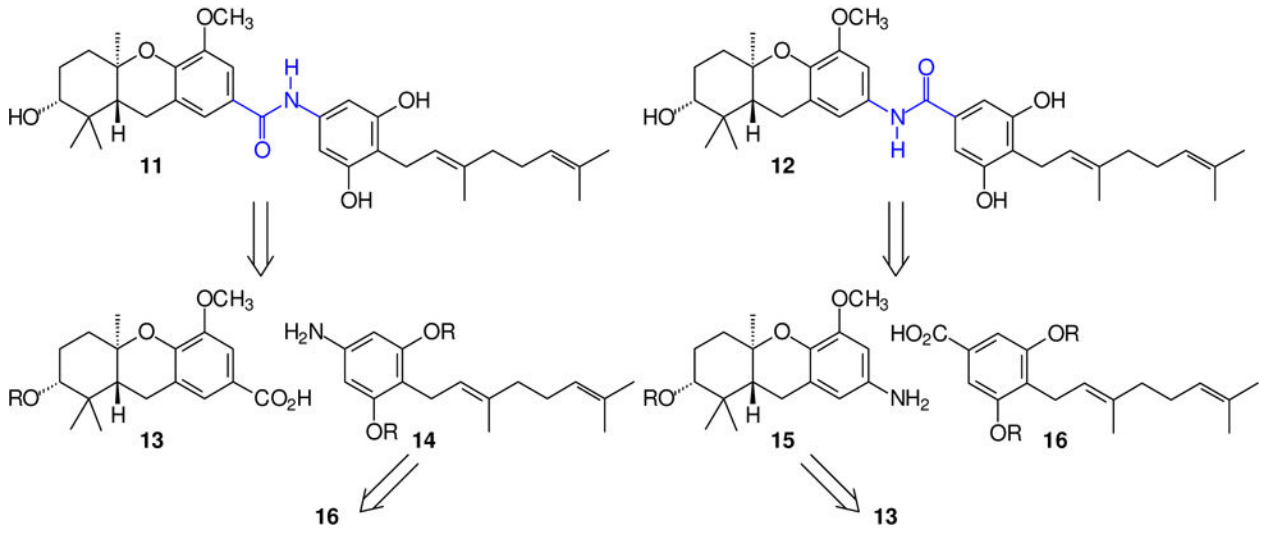
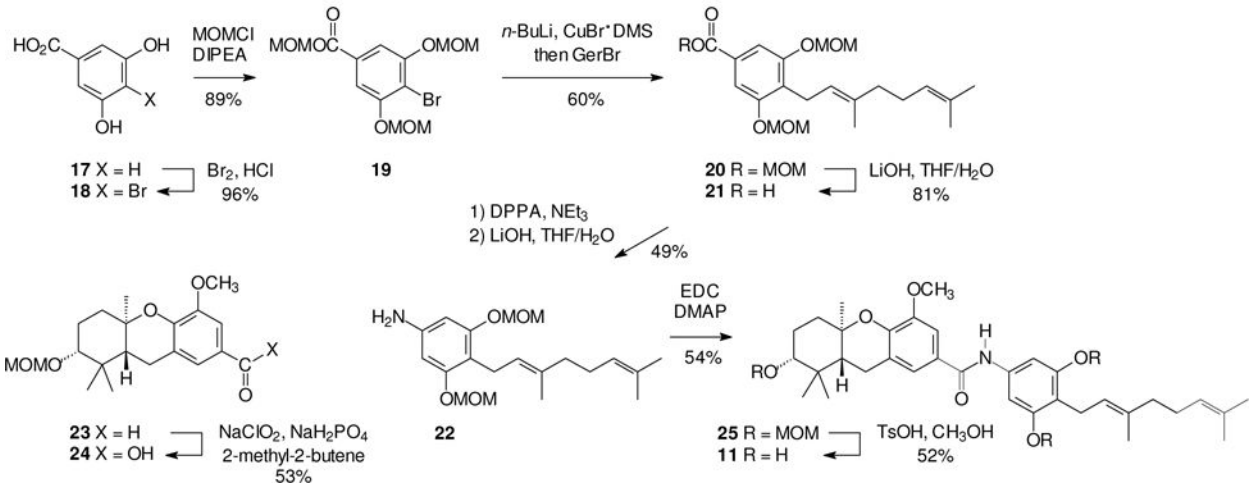


Figure 1.
Some natural schweinfurthins (**1–9**) and a lead analogue (**10**).

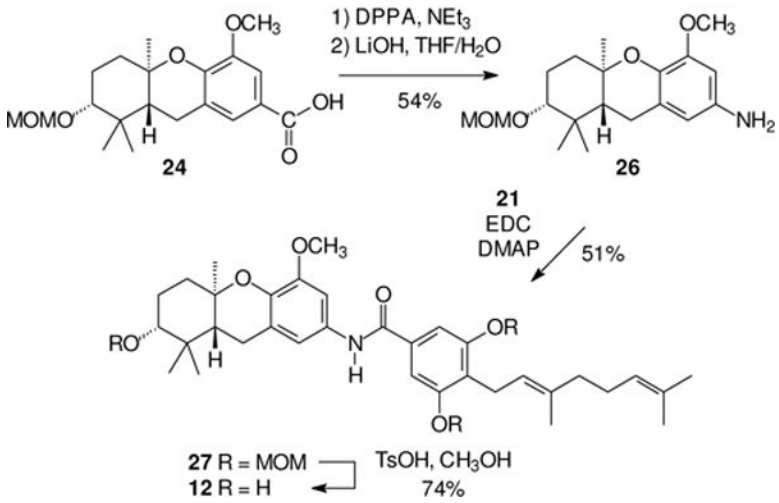


Scheme 1.
Retrosynthesis of a representative schweinfurthin amide.



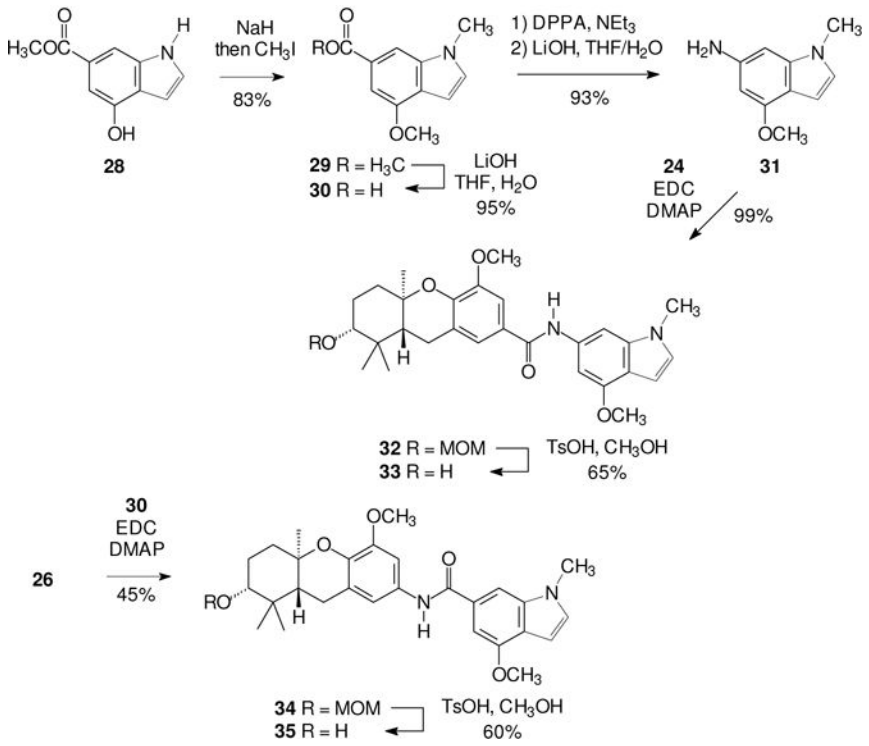
Scheme 2.

Synthesis of the first amide analogue of a schweinfurthin.



Scheme 3.

Synthesis of an isomeric schweinfurthin amide.



Scheme 4.

Synthesis of schweinfurthin-indole amides.

Table 1

NCI 60 Data Summary

Compound	Mean GI_{50} (μM)	Differential at GI_{50} (log_{10})	Pearson Correlation Coefficient to **1** at GI_{50}	LogP (calculated)[a]
1	0.36	3.11	1.00	8.29
10	0.87	3.25	0.77	8.94
11	0.21	2.73	0.78	7.89
12	1.1	1.50	0.65	7.89
33	0.66	2.41	0.78	4.61
35	6.6	2.12	0.70	4.61

[a]Values were determined using the calculator at http://www.molinspiration.com/services/properties.html