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Total Synthesis of Chalaniline B: An Antibiotic Aminoxanthone from Vorinostat-Treated Fungus *Chalara* sp. 6661

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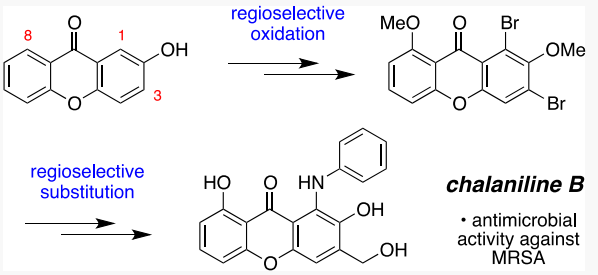
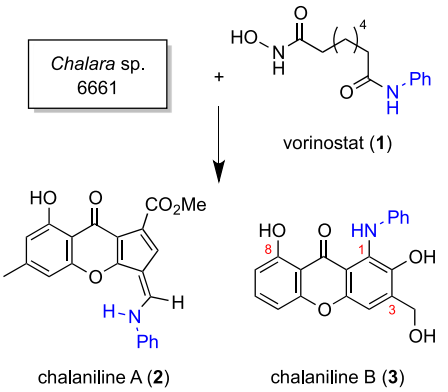
ABSTRACT: Chalaniline B [1-anilino-2,8-dihydroxy-3-(hydroxymethyl)xanthone], an antibiotic previously isolated from vorinostat-treated *Chalara* sp., was prepared in 7 steps from 2-hydroxyxanthone by a route incorporating regioselective oxidative transformations (bromination at C1/C3, ketone directed Pd(II)-catalyzed hydroxylation at C8), installation of the C1-anilino moiety by a regioselective Buchwald-Hartwig amination reaction from 1,3-dibromo-2,8-dimethoxyxanthone, and late-stage hydroxymethylation at C3 using a Stille cross-coupling. Biological evaluation of deshydroxymethylchalaniline B (1-anilino-2,8-dihydroxyxanthone) revealed MIC values of 8 μg mL^{-1} (25 μM) against both methicillin resistant *S. aureus* and *B. subtilis*.



Xanthones of natural origin exhibit a broad range of important biological activities and synthetic constructs based on the same 9*H*-xanthen-9-one heterocyclic template are versatile pharmacophores in medicinal chemistry efforts.[1] A majority of the xanthones that have been evaluated in the search for new therapeutic agents are oxygenated examples; however, aminoxanthones are increasingly emerging as lead compounds for drug development in a variety of disease areas, including cancer,[2a−c] malaria,[2d] and hypertension.[2e] Notwithstanding these welcome advances, the types of aminoxanthones examined to date are limited to only a few different classes, with *N*-sulfonyl[2a,b] or *N*-alkyl[2c−e] derivatives being typical. As such, it is expected that an exploration of more structurally diverse aminoxanthones will afford further revelations. In this regard, Loesgen and co-workers' discovery of chalaniline B (**3**),[3] an unusual 1-arylaminoxanthone[4] with promising antibiotic activity, is significant.

Chalaniline B (**3**) was identified from an antimicrobial-bioassay guided fractionation of a culture of the endophytic ascomycete *Chalara* sp. 6661 that had been treated with the HDAC inhibitor vorinostat (SAHA, **1**)[5] (Scheme 1).[3] Whatever its role in eliciting the production of xanthone **3** on an epigenetic level, the perturbation agent **1** is itself biotransformed in this process and it provides the anilino moiety found both within **3** and in another 'unnatural natural product,' chalaniline A (**2**), that was also discovered. Although arguably less intriguing than its coproduced aminofulvene partner **2** from a structural standpoint, preliminary findings indicate that 1-arylaminoxanthone **3** possesses a more profound biological activity profile than **2**. Chalaniline B (**3**) was determined to exhibit micromolar antimicrobial activity against a multidrug resistant *S. aureus* strain (ATCC# BAA-44) in a diffusion disk assay;[3] however, the limited quantity of material originally isolated (0.7 mg) prevented a more thorough and accurate assessment of its biological potential. Given its rare chemotype and the need to access more material for further biological studies, we elected to explore a *de novo* chemical synthesis of chalaniline B (**3**) that could be readily adapted to analog synthesis. The successful realization of this endeavor is described herein.

Scheme 1. Chalanilines A and B from Vorinostat-Treated *Chalara* sp. 6661



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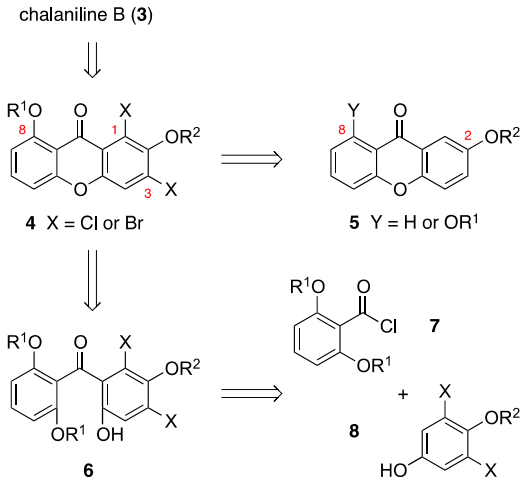
A key consideration for the design of our synthetic plan to secure chalaniline B was for the target to emerge from a fully oxidized xanthone (**4**) with halides at C1 and C3 (Scheme 2). It

Scheme 2. Retrosynthetic Analyses of Chalaniline B (3)

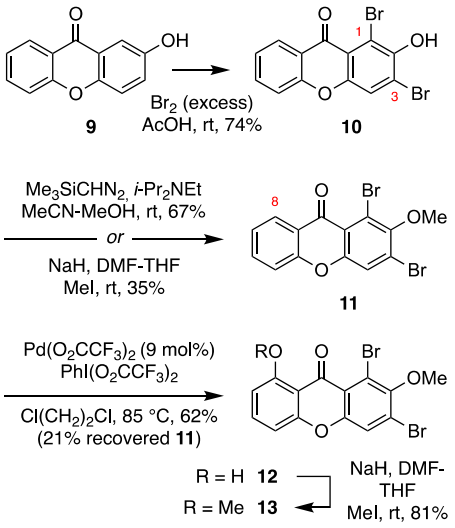


was anticipated that intrinsic differences in the reactivities of nucleofugal residues X would allow for the regioselective installation of C1-anilino and C3-hydroxymethyl moieties by applying an appropriate order of introduction. Furthermore, an intermediate such as **4** would provide a versatile platform from which to later generate chalaniline B analogs for the exploration of structure−activity relationships and biological mode-of-action studies. The pivotal intermediate **4** was itself envisioned to arise either via a standard xanthone synthesis from prefunctionalized fragments **7** and **8** or via functionalization of a preformed xanthone core of a lower oxidation state (**5**). The second strategy commencing from a minimally oxidized xanthone **5** (Y = H) was found to be optimal (*vide infra*).

Obtaining a suitable 1,3-dihaloxanthone **4** via assembly of prefunctionalized intermediates was precluded when it proved impossible to generate ketone **6** via Friedel−Crafts acylation of 3,5-dihalo-4-methoxyphenols **8** (X = Cl or Br) with 2,6-dimethoxybenzoyl chloride **7** (R^1 = Me).[6] Attempts to access the required ketone instead via Fries rearrangement of esters derived from the same starting materials, also failed. Presumably, the steric hindrance present in both coupling partners is responsible for the difficulty of engaging an acylium cation derived from **7** with a phenol **8**. It is noted, however, that Friedel−Crafts acylation of 3,4,5-trimethoxyphenol derivatives with 2,6-dimethoxybenzoic acid is successful.[7] Given the difficulties encountered in realizing intermediate **4** using the first approach, the oxidation based strategy was explored next. In initial findings that conform to classical principles of regiocontrol in electrophilic aromatic substitution reactions, it was established that NBS mediated bromination of '2,8-dihydroxyxanthone' derivatives (e.g., **5**, Y = OMe, R^2 = Me)[8] occurs exclusively at the unwanted C5 and C7 positions (chalaniline B numbering). To rectify this regioselectivity problem, it was decided to postpone introduction of C8 oxygenation until after halides had been installed at C1 and C3 from a less oxidized xanthone starting material **5** (Y = H) (Scheme 3).

In putting this plan into practice, 2-hydroxyxanthone (**9**)[9] was converted to dibromophenol **10** using reaction conditions adapted from the work of Trivedi et al.[10] It was found that **10**

Scheme 3. Synthesis of 1,3-Dibromo-2,8-dimethoxyxanthone (13) by Sequential Oxidations



readily disproportionates,[11] particularly in the presence acids or bases, and that it has limited stability during TLC analysis or preparative chromatographic purification on silica gel. Reaction conditions to achieve a direct conversion of **10** to 1,3-dibromo-2,8-dihydroxyxanthone could not be identified and so C8 oxidation was explored instead from the stable and well-behaved methyl ether **11**. Due to the instability of **10**, obtaining this simple ether in a high yield was not so straightforward (e.g., MeI, NaH, DMF-THF, gives **11** in 35% yield); nonetheless, phenol methylation mediated by trimethylsilyldiazomethane gave an acceptable outcome.[12] Carbonyl-group-directed Pd(II) catalyzed trifluoroacetoxylation of **11** according to the modified Sanford oxidation conditions of Dong and co-workers[13] performed admirably to give phenol **12**, albeit the reaction could not be pushed to completion.[14] Methylation of the newly installed phenol in **12** under standard conditions proceeded uneventfully to give 1,3-dibromo-2,8-dimethoxy-xanthone (**13**) representing the pivotal intermediate **4**.

With a reliable and concise route to **13** established, its further conversion to chalaniline B (**3**) was pursued. Transition-metal-catalyzed cross-coupling of nonsymmetrical poly-homohalogenated aromatic compounds has emerged as a powerful strategy for the regioselective synthesis of complex substituted arenes and heteroarenes.[15] With this approach, it is anticipated that a desired sense of regiocontrol will be achievable through judicious selection and survey of all reaction variables (including metal ligand) that may affect the rates of reaction at the different C−X bonds. In the case of the advancement of **13** to **3**, we were confident that installation of requisite anilino and hydroxymethyl moieties with the correct orientation could be realized by exploring different reaction conditions and varying the order of introduction of the two groups. Hydroxymethylation followed by amination was evaluated first (Scheme 4).

Application of Migita's hydroxymethylation method[16] to **13** using stannane **14** and the illustrated (unoptimized) Stille reaction conditions gave only the undesired C1 cross-coupled product **15**. The regiochemical outcome of this transformation was ascertained by conversion of **15** to the C1/C3 transposed chalaniline B triether derivative **16** using the amination procedure of Buchwald.[17] The fact that the signal for the NH proton of **16** appears at δ 6.74 ppm (rather than δ 9−11 ppm) in

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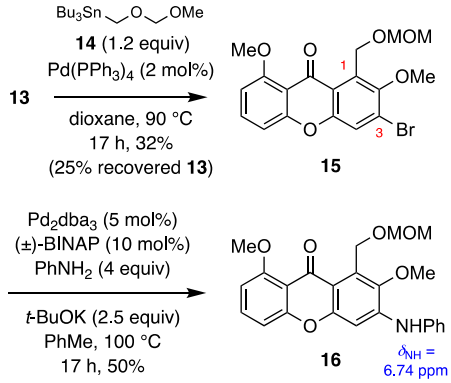
J. Org. Chem. XXXX, XXX, XXX−XXX

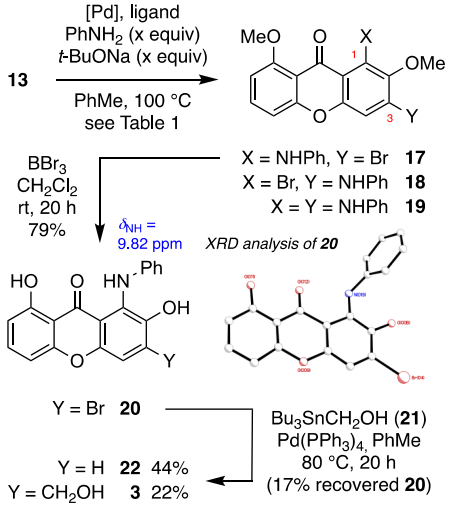
Scheme 4. C1-Selective Hydroxymethylation of 1,3-Dibromoxanthone 13 via Stille Coupling with Migita's Reagent



its ^{1}H NMR spectrum clearly indicates that the anilino moiety is not *ortho* to the xanthone carbonyl group (note: this regiochemical assignment was later confirmed by converting 1-bromo-3-anilinoxanthone **18** to **16** via Stille coupling with **14**). Different protocols were surveyed in an attempt to alter the regiochemical outcome of hydroxymethylation of **13**, but to no avail. For example, Cho et al. reported that use of $Pd(PPh_3)_4$ with CuI in DMF solvent effectively reverses the usual regioselectivity for Stille couplings of 3,5-dibromo-2-pyrone;[15f] however, in the case of substrate **13** and stannane **14**, the Cho protocol resulted only in protodehalogenation at C1 and no **15** nor the desired C3 hydroxymethyl regioisomer was formed. Examination of different ligands and Pd sources to favorably influence cross-coupling with **13** was also unsuccessful. Thus, a combination of Pd_2dba_3/BINAP gave again **15** in 37% yield plus a trace of the double Stille adduct, while use of $Pd(OAc)_2$/cataCXium A yielded 27% of **15** and 34% of a C1-butylated product.[18] Finally, the 'ligandless' Stille reaction conditions developed by Williams and co-workers [Pd_2dba_3/*i*-Pr_2NEt/LiCl/DMF] resulted in a complex mixture of reduced and butylated products.[19]

The failure to achieve a C3-selective hydroxymethylation of dibromide **13** was of limited consequence with the subsequent realization of a C1-selective amination; however, initial results toward this end were not encouraging (Scheme 5 and Table 1). Thus, given that Pd-catalyzed Stille cross-coupling of **13** gave exclusively C1 products, it was perplexing to find that amination under Buchwald's standard conditions (with BINAP as ligand and *t*-BuONa as base)[17] favored reaction at C3 (Table 1, entries 1−3).[20] With excess aniline and longer reaction times, 1,3-bisaniline **19** was the major product but formation of this unwanted adduct could be suppressed by limiting the quantity of the nucleophile. Reasoning that reaction at the more encumbered C1 site might be hampered by use of the bulky BINAP ligand, amination was conducted instead using Pd-$(PPh_3)_4$ in the absence of any additional ligand. This simple change had the desired effect; now aniline **17** was the major product, and only traces of **18** and **19** were formed (entry 4). However, upon protracted heating and a full examination of the resulting product distribution, it was found that hydrolysis, *tert*-butoxylation, and reduction (all also at C1) accompanied anilination (entry 5). Interestingly, intrinsic S_NAr reactivity (i.e., omission of Pd catalyst) was also found to favor C1 (entry 6), but this process was sluggish and likewise accompanied by formation of unwanted side products. Finally, use of Cs_2CO_3

Scheme 5. Amination of 1,3-Dibromoxanthone 13 and Completion of the Synthesis of Chalaniline B (3)



instead of *t*-BuONa (to avoid *tert*-butoxylation and hydroxylation by adventitious NaOH) and a greater quantity of aniline afforded an optimal result (entry 7).

With the 1-anilinoxanthone **17** in hand, we elected to deprotect the methylated phenols before executing hydroxymethylation. The order of events was chosen because it had been previously observed that attempted dealkylation of **16** resulted in decomposition. Boron tribromide mediated removal of methyl ethers from **17** proceeded cleanly and gave bromodiol **20** in a remarkably high yield. This enigmatic compound is yellow in solution but deposits small red-orange prisms in the solid state. Its identity, and unexpected axial chirality, was established by a single-crystal X-ray diffraction analysis.[21] Conversion of **20** directly to chalaniline B (**3**) was achieved by a Pd-catalyzed cross-coupling with the unprotected variant of Migita's reagent (**21**).[16] Even though unwanted reduction competed against the desired hydroxymethylation to give a significant quantity of simplified chalaniline B analog **22**, this transformation, in which successful C−C bond formation occurs in the presence of three acidic X−H residues in the substrate and one in the reagent, highlights the remarkable functional group tolerance of the Stille reaction.[22] The spectral and mass spectrometric signatures of the synthetic chalaniline B (**3**) so obtained agreed in all respects with the data reported earlier by Loesgen and co-workers.[3]

The quantity of materials provided by this effort enabled an accurate determination of the bioactivity of chalaniline B (**3**) and its truncated analog **22**. Both compounds were tested for cytotoxicity in mammalian cancer cells and antimicrobial activity in a panel of Gram-positive and Gram-negative bacteria and the pathogenic yeast *Candida albicans*.[23] Against Gram-positive bacteria, chalaniline B (**3**) exhibited weak antimicrobial activity when tested at a single dose of 128 μg mL^{-1}, but its deshydroxymethyl analog **22** showed potent activity against both methicillin-resistant *S. aureus* (ATCC# BAA-41) and the spore-forming bacterium *Bacillus subtilis* (ATCC# 49343), a laboratory surrogate for *Bacillus anthracis*, with MIC values of 8 μg mL^{-1} (25 μM) in each case (Table 2). No cytotoxicity was observed in single dose assays for **3** or **22** against human colon carcinoma at 10 μM (HCT-116), *C. albicans*, or two Gram-negative bacteria (at 128 μg mL^{-1}).[24]

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J. Org. Chem. XXXX, XXX, XXX−XXX

Table 1. Reaction Conditions and Outcome for the Amination of Dibromide 13 with Aniline[a]

[Pd]	additional ligand	x (equiv)	time (h)	**13** (%)[b]	**17** (%)[b]	**18** (%)[b]	**19** (%)[b]
$Pd_2(dba)_3$ (5 mol %)	BINAP (10 mol %)	1.50	7	<5	<5	19	30
$Pd(dba)_2$ (10 mol %)	BINAP (10 mol %)	1.25	20	8	10	18	21
$Pd(dba)_2$ (5 mol %)	BINAP (5 mol %)	0.65	2	54	8	15	<2
$Pd(PPh_3)_4$ (5 mol %)	none	1.00	2	45	21	<2	<2
$Pd(PPh_3)_4$ (5 mol %)	none	1.50	18	<2	21[c]	<2	<2
none	none	1.00	18	52	8	<1	<1
$Pd(PPh_3)_4$ (5 mol %)	none	2.00	16	8	48[d]	15	5

[a]See Scheme 5 for a depiction of the transformation and other reaction conditions. [b]Isolated yield. [c]**17** with X = OH (18%), *t*-BuO (11%), and H (7%) also generated. [d]Cs_2CO_3 used in place of *t*-BuONa.

Table 2. Antimicrobial Activity of Chalaniline B (3), 22, and Reference Antibiotics[a]

antibiotic agent	SA	MRSA	MDRSA	BS
chalaniline B (**3**)[b]	64 ± 14	57 ± 8	40 ± 2	67 ± 17
22[b]	75 ± 10	16 ± 3	51 ± 6	15 ± 1
22 MIC[c]	–	8 μg mL^{-1}	–	8 μg mL^{-1}
kanamycin[d]	1 ± 1	–	77 ± 3	–
vancomycin[d]	–	−1 ± 1	0 ± 0	–
chloramphenicol[d]	–	–	–	0 ± 0

[a]Percent growth of treated bacteria in the presence of agent vs vehicle control. [b]**3** and **22** dosed at 128 μg mL^{-1} (in triplicate). [c]Minimal inhibitory concentration (MIC) determined by variable concentration experiments.[24] [d]Reference antibiotics dosed at 100 μg mL^{-1} (in triplicate). SA = *S. aureus*, MRSA = methicillin-resistant *S. aureus*, MDRSA = multidrug-resistant *S. aureus*, BS = *B. subtilis*.

In summary, chalaniline B (**3**) was prepared in 7 steps and 2% overall yield from 2-hydroxyxanthone via a route devised with synthetic flexibility in mind and employing 1,3-dibromo-2,8-dimethoxyxanthone (**13**) as a key intermediate. A reevaluation of the biological activity of **3** confirmed its antibiotic character, and deshydroxymethyl chalaniline B (**22**) was discovered to exhibit even greater potency against MRSA. On the basis of these findings, additional studies of compounds analogous to **3**, and related 1-arylaminoxanthones, are warranted. Variations to how dibromoxanthone **13** is advanced synthetically will allow for the straightforward generation of different chalaniline B analogs for SAR studies and to probe the origin of bioactivity. The results of this work, which hopefully will further illuminate the therapeutic potential of hitherto little known arylaminoxanthones, will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Conditions. Preparative chromatographic separations were performed on silica gel 60 (35−75 μm), and reactions were followed by TLC analysis using silica gel 60 plates (2−25 μm) with fluorescent indicator (254 nm) and visualized by UV or phosphomolybdic acid (PMA). All commercially available reagents were used as received. Anhydrous solvents were obtained from a Pure Process Technologies solvent purification system and dispensed under Ar. Melting points were recorded on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a PerkinElmer Spectrum II FT-IR using an ATR probe for solids or a thin film between NaCl plates for oils (neat). NMR spectra were recorded on Bruker Avance spectrometers at the field strength specified from 5 mm diameter tubes, and carbon spectra were collected in the proton-decoupled mode [$^{13}C\{^1H\}$]. Chemical shift in ppm is quoted relative to solvent signals calibrated as follows, $CDCl_3$: δ_H ($CHCl_3$) = 7.26 ppm, δ_C($CDCl_3$) = 77.2 ppm; d_6-DMSO: δ_H ($D_3CSOCHD_2$) = 2.50 ppm, δ_C (D_3CSOCD_3) = 39.5 ppm; CD_3OD: δ_H (CHD_2OD) = 3.31 ppm, δ_C(CD_3OD) = 49.0 ppm. Numbers in parentheses following carbon atom chemical shifts refer to the number of attached hydrogen atoms as revealed by the DEPT spectral editing technique. Low (MS) and high resolution (HRMS) mass spectra were obtained using electrospray ionization (ESI) in positive ion mode. Ion mass/charge (m/z) ratios are reported as values in atomic mass units, and all high resolution measurements were obtained using a TOF mass analyzer.

*1,3-Dibromo-3-hydroxyxanthone (**10**).* A suspension of 2-hydroxyxanthone (**9**, 9.46 g, 44.6 mmol)[9] in AcOH (300 mL) at rt was treated with neat liquid Br_2 (7.80 mL, d = 3.12, 24.3 g, 152 mmol, 3.4 equiv), and the mixture stirred for 24 h. After this time, a further portion of neat liquid Br_2 (3.00 mL, d = 3.12, 9.36 g, 58.5 mmol, 1.3 equiv) was added and stirring was continued for another 24 h. The entire reaction mixture was then poured into H_2O (500 mL), and the resulting precipitate was removed by filtration through a glass fritted funnel. The filter cake was washed with H_2O (200 mL) and the solid sucked dry and then finely divided and allowed for 12 h to air-dry to afford 1,3-dibromo-2-hydroxy-xanthone (**10**, 12.24 g, 33.1 mmol, 74%) as a light brown solid. NMR spectral analysis indicated excellent purity and any further purification was unnecessary. Data for **10**: mp 192−193 °C; IR (neat) 3352, 2949,1649, 1611, 1584, 1466, 1444, 1414, 1333, 1287, 1230, 1206, 1172, 1142, 1036, 1021, 945, 879, 801, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, dd, J = 8.0, 1.2 Hz), 7.77 (1H, s), 7.71 (1H, ddd, J = 8.5, 7.1, 1.6 Hz), 7.41 (1H, d, J = 8.4 Hz), 7.38 (1H, tm, J = 7.2 Hz), 6.56 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.6 (0), 155.1 (0), 151.1 (0), 147.4 (0), 135.2 (1), 127.2 (1), 124.6 (1), 122.5 (1), 121.7 (0), 118.5 (0), 117.7 (1), 116.8 (0), 106.8 (0) ppm; ^1H NMR (400 MHz, d_6-DMSO) δ 8.14 (1H, dd, J = 8.1, 1.6 Hz), 8.04 (1H, s), 7.84 (1H, ddd, J = 8.7, 7.1, 1.7 Hz), 7.57 (1H, d, J = 8.0 Hz), 7.46 (1H, ddd, J = 8.1, 7.1, 0.9 Hz); $^{13}C\{^1H\}$ NMR (175 MHz, d_6-DMSO) δ 174.2 (0), 153.5 (0), 153.0 (0), 151.1 (0), 137.8 (1), 128.3 (1), 122.6 (0), 120.5 (1), 119.9 (1), 119.1 (0), 118.8 (1), 116.2 (0), 108.2 (0) ppm; MS (ESI) m/z 373 [($^{81}Br_2$)M + H]$^+$, 371 [(^{79}Br,^{81}Br)M + H]$^+$, 369 [($^{79}Br_2$)M + H]$^+$; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_7{}^{79}Br_2O_3$ 368.8762, found 368.8746.

*1,3-Dibromo-2-methoxyxanthone (**11**).* A stirred suspension of dibromoxanthanol **10** (1.40 g, 3.78 mmol) and iPr$_2$NEt (1.00 mL, d = 0.74, 740 mg, 5.73 mmol, 1.5 equiv) in MeCN−MeOH (9:1, 20 mL) at rt was treated with $TMSCHN_2$ (6.0 mL, 2.0 M in hexanes, 12.0 mmol, 3.2 equiv). The resulting mixture was stirred for 30 min and then filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with CH_2Cl_2) to afford the desired methyl ether **11** (968 mg, 2.52 mmol, 67%) as a colorless solid: mp 170−171 °C (EtOAc); IR (ATR) 3074, 2971, 2938, 1670, 1615, 1578, 1541, 1449, 1398, 1293, 1223, 1046, 967, 869, 849, 788 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (1H, dd, J = 7.9, 1.4 Hz), 7.77 (1H, s), 7.72 (1H, ddd, J = 8.6, 7.4, 1.6 Hz), 7.42 (1H, d, J = 8.2 Hz), 7.40 (1H, tm, J = 7.9 Hz), 3.95 (3H, s); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 175.7 (0), 154.8 (0), 153.7 (0), 151.8 (0), 135.2 (1), 127.3 (1), 124.9 (0), 124.7 (1), 122.5 (1), 121.8 (0), 119.7 (0), 117.6 (1), 117.5 (0), 60.9 (3); MS (ESI) m/z 409 [($^{81}Br_2$)M + Na]$^+$, 407 [(^{81}Br^{79}Br)M + Na]$^+$, 405 [($^{79}Br_2$)M + Na]$^+$, 387 [($^{81}Br_2$)M + H]$^+$, 385 [(^{81}Br^{79}Br)M + H]$^+$, 383 [($^{79}Br_2$)M + H]$^+$; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{14}H_8{}^{79}Br_2NaO_3$ 404.8738, found 404.8729.

*1,3-Dibromo-8-hydroxy-2-methoxyxanthone (**12**).* A 25 mL screw-cap vial was charged with a stir bar, 1,3-dibromo-2-methoxyxanthone (**11**, 734 mg, 1.91 mmol), $Pd(O_2CCF_3)_2$ (57 mg, 0.171 mmol,

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J. Org. Chem. XXXX, XXX, XXX−XXX

9 mol %), and $PhI(O_2CCF_3)_2$ (944 mg, 2.20 mmol, 1.2 equiv). 1,2-Dichloroethane (10 mL) was added, the cap was fitted, and the contents of the sealed vial were stirred at 85 °C (oil bath temp) for 18 h. After this time, the reaction mixture was allowed to cool and the cap was cautiously removed. The reaction mixture was loaded directly onto a SiO_2 chromatography column and eluted with CH_2Cl_2 to afford, in order of elution, the desired phenol product (**12**, 471 mg, 1.18 mmol, 62%) as a yellow solid and unreacted starting material (**11**, 154 mg, 0.401 mmol, 21%) as a pale yellow solid. Data for phenol **12**: mp 198−201 °C (EtOAc); IR (ATR) 3080, 2941, 1644, 1616, 1575, 1452, 1405, 1330, 1225, 1151, 1038, 968, 809, 755, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.53 (1H, s), 7.74 (1H, s), 7.59 (1H, t, J = 8.4 Hz), 6.85 (1H, d, J = 8.5 Hz), 6.81 (1H, d, J = 8.2 Hz), 3.95 (3H, s); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 181.3 (0), 162.1 (0), 155.1 (0), 153.7 (0), 152.1 (0), 137.3 (1), 126.0 (0), 122.4 (1), 118.5 (0), 117.1 (0), 111.5 (1), 108.9 (0), 106.7 (1), 60.9 (3); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_9{}^{79}Br_2O_4$ 398.8868, found 398.8883.

*1,3-Dibromo-2,8-dimethoxyxanthone (**13**).* A stirred suspension of phenol **12** (330 mg, 0.825 mmol) and NaH (40 mg, 60 wt % in mineral oil, 1.00 mmol, 1.2 equiv) in DMF−THF (3:1, 8 mL) at rt under Ar was treated with neat MeI (0.25 mL, d = 2.28, 570 mg, 4.01 mmol, 4.9 equiv). Progress of the transformation was monitored by TLC analysis, and further portions of NaH/MeI were added after 1.33 h (20 mg/0.10 mL) and 24 h (40 mg/0.20 mL). After the last addition, the reaction mixture was stirred for a final period of 24 h during which time the strong yellow color indicative of the presence of **12** (and its alkoxide anion) had fully dissipated. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (SiO_2, eluting with 30% EtOAc in hexanes) to afford diether **13** (276 mg, 0.667 mmol, 81%) as a colorless solid (note: **13** is considerably *more* polar than **12**): mp 172−176 °C (EtOAc); IR (ATR) 2940, 1672, 1610, 1574, 1472, 1448, 1399, 1291, 1253, 1198, 1081, 1034, 961, 926, 841, 804, 773, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, s), 7.57 (1H, t, J = 8.4 Hz), 6.95 (1H, dd, J = 8.4, 0.8 Hz), 6.80 (1H, dm, J = 8.4 Hz), 4.01 (3H, s), 3.92 (3H, s); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 175.1 (0), 160.8 (0), 156.8 (0), 152.6 (0), 151.8 (0), 135.2 (1), 123.9 (0), 121.6 (1), 121.1 (0), 117.3 (0), 112.6 (1), 109.4 (1), 106.2 (1), 60.9 (3), 56.6 (3); MS (ESI) m/z 417 $[(^{81}Br_2)M + H]^+$, 415 $[(^{81}Br^{79}Br)M + H]^+$, 413 $[(^{79}Br_2)M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{11}{}^{79}Br_2O_4$ 412.9024, found 412.9019.

*3-Bromo-2,8-dimethoxy-1-[(methoxymethyl)oxy]methylxanthone (**15**).* A 4 mL screw-cap vial provided with a magnetic stir bar was charged with dibromide **13** (51 mg, 0.123 mmol), stannane **14** (67 mg, 0.184 mmol, 1.5 equiv),[15] and $Pd(PPh_3)_4$ (3 mg, 0.0026 mmol, 2 mol %). 1,4-Dioxane (1.0 mL) was added, the cap was secured, and the contents of the vial were stirred with heating at 90 °C (oil bath temp.) for 16.5 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. The residue with purified by column chromatography (SiO_2, eluting with 30−55% EtOAc in hexanes) to afford in order of elution recovered starting material **13** (13 mg, 0.031 mmol, 25%) and C1-alkylated product **15** (16 mg, 0.039 mmol, 32%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (1H, s), 7.56 (1H, t, J = 8.4 Hz), 6.97 (1H, dm, J = 8.5 Hz), 6.78 (1H, dm, J = 8.3 Hz), 5.31 (2H, s), 4.91 (2H, s), 3.99 (3H, s), 3.94 (3H, s), 3.48 (3H, s); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 177.2 (0), 160.7 (0), 157.1 (0), 153.1 (0), 152.8 (0), 134.9 (1), 132.9 (0), 124.3 (0), 123.0 (1), 121.7 (0), 113.4 (0), 109.6 (1), 105.9 (1), 97.6 (2), 63.1 (3), 61.4 (2), 56.7 (3), 55.8 (3); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{18}{}^{79}BrO_6$ 409.0287, found 409.0307.

*3-Anilino-2,8-dimethoxy-1-[(methoxymethyl)oxy]methylxanthone (**16**).* A 4 mL screw-cap vial provided with a magnetic stir bar was charged with aryl bromide **15** (16 mg, 0.039 mmol), *t*-BuOK (10 mg, 0.089 mmol, 2.3 equiv), Pd_2dba_3 (2 mg, 0.0022 mmol, 5 mol %), and (±)-BINAP (2.5 mg, 0.0040 mmol, 10 mol %). A solution of $PhNH_2$ (0.80 mL, 0.2 M in PhMe, 0.160 mmol, 4.1 equiv) was added, the cap was secured, and the contents of the vial were stirred with heating at 100 °C (oil bath temp) for 17 h. The resulting red solution was allowed to cool to rt and then partitioned between EtOAc (10 mL) and H_2O (10 mL). The aqueous phase was extracted with EtOAc (5 mL), and the combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue with purified by column chromatography (SiO_2, eluting with 50−100% EtOAc in hexanes) to afford anilinoxanthone **16** (8.2 mg, 0.019 mmol, 50%) as a pale yellow oil: IR (neat) 3313, 2941, 1645, 1617, 1589, 1266, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, t, J = 8.3 Hz), 7.43 (2H, tm, J = 8.4 Hz), 7.28 (2H, dm, J = 8.6 Hz), 7.17 (1H, tt, J = 7.4, 0.9 Hz), 7.08 (1H, s), 6.90 (1H, dm, J = 8.4 Hz), 6.74 (1H, dm, J = 8.2 Hz), 6.74 (1H, br s, NH), 5.34 (2H, s), 4.96 (2H, s), 3.98 (3H, s), 3.95 (3H, s), 3.51 (3H, s); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 176.8 (0), 160.6 (0), 157.3 (0), 155.1 (0), 144.6 (0), 143.3 (0), 139.8 (0), 133.8 (1), 130.9 (0), 129.9 (2C, 1), 124.4 (1), 122.0 (2C, 1), 113,5 (0), 113.4 (0), 109.5 (1), 105.5 (1), 99.2 (1), 97.7 (2), 62.7 (3), 61.3 (2), 56.7 (3), 55.9 (3); MS (ESI) m/z 444 $[M + Na]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{24}NO_6$ 422.1604, found 422.1603.

*1-Anilino-3-bromo-2,8-dimethoxyxanthone (**17**).* A 4 mL screw-cap vial providedwith a magnetic stir bar was charged with dibromide **13** (55 mg, 0.132 mmol), $Pd(PPh_3)_4$ (8.0 mg, 0.007 mmol, 5 mol %), and Cs_2CO_3 (87 mg, 0.267 mmol, 2.0 equiv). A solution of freshly distilled aniline (25 mg, 0.269 mmol, 2.0 equiv) in anhydrous PhMe (1.30 mL) was added, and then the cap was fitted and the contents of the vial were stirred at 100 °C (oil bath temp) for 16 h. The reaction mixture was allowed to cool to rt, the vial was carefully opened, and the contents (a dark yellow suspension) were partitioned between EtOAc (10 mL) and H_2O (10 mL). The aqueous phase was extracted with EtOAc (5 mL), and the combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue (61 mg) was purified by column chromatography (SiO_2, eluting with 0−2% MeOH in CH_2Cl_2; CH_2Cl_2 only until **17** and **19** were collected) to afford, in order of elution, the deeply yellow colored 1-anilinoxanthone **17** (27.0 mg, 0.063 mmol, 48%), 1,3-bisanilinoxanthone **19** (2.9 mg, 0.0066 mmol, 5%), recovered starting material **13** (4.1 mg, 0.0099 mmol, 7.5%), and the quite polar 3-anilinoxanthone **18** (8.5 mg, 0.020 mmol, 15%).

Data for **17**: yellow semisolid; IR (neat) 3300, 2970, 1635, 1588, 1473, 1252, 1098, 814, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.09 (1H, s), 7.59 (1H, t, J = 8.4 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.10 (1H, s), 7.04−6.97 (4H, m), 6.80 (1H, d, J = 8.3 Hz), 4.02 (3H, s), 3.33 (3H, s); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 180.5 (0), 160.7 (0), 157.3 (0), 152.6 (0), 141.4 (0), 140.9 (0), 140.0 (0), 135.3 (1), 128.2 (2C, 1), 125.7 (0), 122.9 (1), 121.3 (2C, 1), 112.1 (0), 111.6 (0), 110.0 (1), 109.7 (1), 105.8 (1), 58.8 (3), 56.7 (3); MS (ESI) m/z 450 $[(^{81}Br)M + Na]^+$, 448 $[(^{79}Br)M + Na]^+$; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{16}{}^{79}BrNNaO_4$ 448.0160, found 448.0161.

Data for **18**: pale yellow oil; IR (neat) 3302, 2935, 1653, 1614, 1584, 1472, 1266, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, t, J = 8.3 Hz), 7.44 (2H, tm, J = 7.9 Hz), 7.29 (2H, dm, J = 7.6 Hz), 7.20 (1H, tm, J = 7.4 Hz), 7.02 (1H, s), 6.87 (1H, dd, J = 8.4, 0.8 Hz), 6.77 (1H, br s), 6.75 (1H, d, J = 8.4 Hz), 3.99 (3H, s), 3.96 (3H, s); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 174.9 (0), 160.7 (0), 157.0 (0), 154.8 (0), 143.5 (0), 143.0 (0), 139.4 (0), 134.1 (1), 130.0 (2C, 1), 124.9 (1), 122.5 (2C, 1), 115.8 (0), 112.8 (0), 112.6 (0), 109.3 (1), 105.8 (1), 98.1 (1), 60.3 (3), 56.5 (3); MS (ESI) m/z 428 $[(^{81}Br)M + H]^+$, 426 $[(^{79}Br)M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{17}{}^{79}BrNO_4$ 426.0341, found 426.0330.

Data for **19**: yellow oil; IR (neat) 3400, 2930, 1632, 1592, 1519, 1470, 1297, 1273, 1245, 1098, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.97 (1H, s), 7.50 (1H, t, J = 8.3 Hz), 7.41 (2H, tm, J = 7.3 Hz), 7.30 (2H, dm, J = 8.2 Hz), 7.25 (2H, tm, J = 7.4 Hz), 7.15 (1H, tm, J = 7.3 Hz), 7.04 (2H, d, J = 8.1 Hz), 6.97 (1H, tm, J = 7.4 Hz), 6.95 (1H, br s), 6.91 (1H, d, J = 8.4 Hz), 6.75 (1H, d, J = 8.3 Hz), 6.65 (1H, s), 4.00 (3H, s), 3.42 (3H, s); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 179.3 (0), 160.5 (0), 157.3 (0), 154.7 (0), 144.0 (0), 141.8 (0), 140.0 (0), 138.0 (0), 134.1 (1), 131.5 (0), 129.8 (2C, 1), 128.0 (2C, 1), 124.2 (1), 122.0 (2C, 1), 121.9 (1), 120.6 (2C, 1), 112.3 (0), 109.6 (1), 105.6 (0), 105.4 (1), 90.1 (1), 58.3 (3), 56.6 (3); MS (ESI) m/z 439 $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{23}N_2O_4$ 439.1658, found 439.1656.

*1-Anilino-3-bromo-2,8-dihydroxyxanthone (**20**).* A solution of diether **17** (133 mg, 0.312 mmol) in anhydrous CH_2Cl_2 (10 mL) at rt under Ar was treated with BBr_3 (3.5 mL, 1.0 M in CH_2Cl_2, 3.50 mmol, 11 equiv). The resulting dark red solution was stirred at rt for 20 h. After this time, sat. aq. sodium potassium tartrate (20 mL) was added and the

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J. Org. Chem. XXXX, XXX, XXX−XXX

biphasic mixture was stirred vigorously for 5 min. EtOAc (20 mL) was then added, and the layers were shaken and separated. The aqueous phase was extracted with EtOAc (2 × 15 mL), and the combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by column chromatography (SiO_2, eluting with 10−20% EtOAc in hexanes) to afford the desired diphenol **20** (98.2 mg, 0.247 mmol, 79%) as an orange powder: mp 197−200 °C (EtOAc); IR (neat) 3438, 3260, 2922, 1645, 1605, 1468, 1227, 1054, 765 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 12.34 (1H, s), 9.83 (1H, br s), 7.57 (1H, t, J = 8.3 Hz), 7.34 (1H, s), 7.32 (2H, dd, J = 8.4, 7.5 Hz), 7.07 (1H, tm, J = 7.4 Hz), 6.95 (2H, dm, J = 8.6 Hz), 6.86 (1H, dd, J = 8.4, 0.9 Hz), 6.76 (1H, dd, J = 8.2, 0.9 Hz), 5.31 (1H, s); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 184.9 (0), 161.8 (0), 155.7 (0), 150.9 (0), 141.3 (0), 140.2 (0), 137.2 (1), 132.4 (0), 129.4 (2C, 1), 123.2 (1), 119.5 (0), 119.3 (2C, 1), 113.2 (1), 111.1 (0), 110.8 (1), 108.6 (0), 106.8 (1); MS (ESI) m/z 400 $[(^{81}Br)M + H]^+$, 398 $[(^{79}Br)M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{13}{}^{79}BrNO_4$ 398.0028, found 398.0013.

*Chalaniline B (1-Anilino-3-(hydroxymethyl)-2,8-dihydroxyxanthone, **3**).* A 4 mL screw-cap vial provided with a magnetic stir bar was charged with bromide **20** (54 mg, 0.136 mmol) and $Pd(PPh_3)_4$ (16 mg, 0.0138 mmol, 10 mol %). A solution of stannane **21** (175 mg, 0.545 mmol, 4.0 equiv)[16] in PhMe (5.0 mL) was added, and the cap was fitted. The contents of the vial were stirred with heating at 80 °C (oil bath temp) for 24 h. The reaction mixture was cooled to rt and then subjected to two cycles of methanolysis (to facilitate protonation of any Bu_3Sn−OR bonds), as follows: MeOH (20 mL) was added, and the mixture was stirred for 5 min at rt and then concentrated *in vacuo*. The resulting residue was purified by column chromatography (SiO_2, eluting with 10−20% EtOAc in hexanes) to afford in order of elution recovered aryl bromide **20** (9.0 mg, 0.0226 mmol, 17%), the reduced side product **22** (19.2 mg, 0.0601 mmol, 44%), and chalaniline B (**3**) still associated with organotin residues. The impure chalaniline B was treated with 50% MeOH in CH_2Cl_2 (20 mL), stirred for 5 min, and again concentrated *in vacuo*. The residue was subjected sequentially to two further rounds of column chromatography (SiO_2, eluting with 25% EtOAc in hexanes, followed by SiO_2, eluting with 2% MeOH in CH_2Cl_2) to afford pure chalaniline B (**3**, 10.6 mg, 0.0303 mmol, 22%) as an amorphous yellow solid: IR (neat) 3322, 2922, 2855, 1645, 1599, 1466, 1233, 1057, 815, 746 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 12.47 (1H, s), 9.20 (1H, s), 7.56 (1H, t, J = 8.5 Hz), 7.30 (2H, t, J = 7.9 Hz), 7.21 (1H, s), 7.01 (1H, t, J = 6.9 Hz), 6.90−6.86 (3H, m), 6.75 (1H, d, J = 8.0 Hz), 5.62 (1H, s), 4.91 (2H, s); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 184.9 (0), 161.8 (0), 156.1 (0), 151.5 (0), 142.3 (0), 142.2 (0), 136.9 (0), 136.9 (1), 130.4 (0), 129.6 (2C, 1), 122.4 (1), 117.9 (2C, 1), 111.9 (0), 110.4 (1), 110.0 (1), 108.8 (0), 106.9 (1), 62.1 (2); ^1H NMR (700 MHz, CD_3OD) δ 7.61 (1H, t, J = 8.3 Hz), 7.31 (1H, s), 7.21 (2H, dd, J = 8.5, 7.5 Hz), 6.93 (1H, dd, J = 8.4, 0.7 Hz), 6.88 (1H, tt, J = 7.3, <1.0 Hz), 6.82 (2H, dd, J = 8.5, 0.9 Hz), 6.71 (1H, dd, J = 8.2, 0.7 Hz), 4.83 (2H, s); $^{13}C\{^1H\}$ NMR (175 MHz, CD_3OD) δ 186.2 (0), 162.8 (0), 157.4 (0), 152.7 (0), 144.6 (0), 143.7 (0), 141.4 (0), 137.8 (1), 132.2 (0), 129.6 (2C, 1), 121.8 (1), 118.5 (2C, 1), 112.5 (0), 110.9 (1), 109.7 (1), 109.6 (0), 107.7 (1), 60.8 (2); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{16}NO_5$ 350.1028, found 350.1032. ^1H and ^{13}C NMR spectral data for **3** (in $CDCl_3$) are in agreement with those previously reported by Loesgen and co-workers (see Supporting Information).[3]

Data for **22**: amorphous yellow solid; IR (neat) 2930, 1645, 1601, 1477, 1302, 1238, 819, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.45 (1H, s), 9.24 (1H, s), 4.32 (1H, t, J = 8.3 Hz), 7.40 (1H, d, J = 9.0 Hz), 7.30 (2H, t, J = 7.8 Hz), 7.15 (1H, d, J = 9.0 Hz), 7.02 (1H, t, J = 7.4 Hz), 6.91−6.86 (3H, m), 6.75 (1H, d, J = 8.2 Hz), 4.89 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 185.3 (0), 161.8 (0), 156.1 (0), 151.7 (0), 144.4 (0), 142.0 (0), 137.0 (1), 130.4 (0), 129.8 (2C, 1), 124.7 (1), 122.5 (1), 117.7 (2C, 1), 112.8 (0), 112.2 (1), 110.4 (1), 108.8 (0), 106.8 (1); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{14}NO_4$ 320.0923, found 320.0928.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00528.

Details for bioactivity assessments of **3** and **22**, the XRD analysis of **20**, and $^1H/^{13}C$ NMR spectra for all compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **3**, **9**−**13**, **15**−**20**, and **22** (ZIP)

Accession Codes

CCDC 2058688 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(7) For example, 1,2,3,8-tetramethoxyxanthone **4** (X = OMe, R^1/R^2 = Me) is available via acylation of 3,4,5-$(MeO)_3C_6H_2OBn$ with 2,6-$(MeO)_2C_6H_3CO_2H$ (TFAA, CH_2Cl_2, rt) followed by debenzylation and intramolecular S_NAr reaction (Me_4NOH). Multistep regioselective demethylation of this compound to diol **4** (X = OH, R^1/R^2 = Me) is also known, and we briefly considered using a corresponding bissulfonate ester **4** (e.g., X = OTf, R^1/R^2 = Me) as the key intermediate en route to chalaniline B. However, the length of the synthesis of the bissulfonate (seven steps) and discouraging early cross-coupling data meant that we abandoned this approach. For the synthesis of **4** (X = OH, R^1/R^2 = Me) as described above, see ref 2a and: Gil, S.; Palanca, P.; Sanz, V.; Tortajada, A. Synthesis of 1,2,3,8-Tetraoxygenated Xanthones. *J. Nat. Prod.* **1990**, *53*, 1198−1211.

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J. Org. Chem. XXXX, XXX, XXX−XXX

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(21) Interestingly, single crystals of anilinoxanthone **20** deposit as a conglomerate (i.e., homochiral) with diffraction intensities that fit the noncentrosymmetric space group *Fdd*2. The finding indicates that, in the solid state at least, **20** is a chiral compound due to restricted rotation about the congested C1−NHPh bond. Whether or not the enantiomorphic atropisomers of **20**, and related compounds such as chalaniline B (**3**), are configurationally stable in solution is an open question and one that could impact the potential utility of 2-substituted 1-anilinoxanthones in medicinal chemistry and drug development efforts.
(22) The conversion of **20** to **3** was also attempted with the Suzuki−Miyaura based hydroxymethylation method of Tanaka and coworkers using $AcOCH_2BF_3K$ as a cross-coupling partner. This newer procedure afforded only trace quantities of **3** (<5% yield), and reduction dominated (yield **22** > 60%). See: Murai, N.; Yonaga, M.; Tanaka, K. Palladium-Catalyzed Direct Hydroxymethylation of Aryl Halides and Triflates with Potassium Acetoxymethyltrifluoroborate. *Org. Lett.* **2012**, *14*, 1278−1281.
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J. Org. Chem. XXXX, XXX, XXX−XXX