Total Synthesis of *O*-Methylsterigmatocystin Using *N*-Alkylnitrilium Salts and Carbonyl−Alkene Interconversion in a New Xanthone Synthesis

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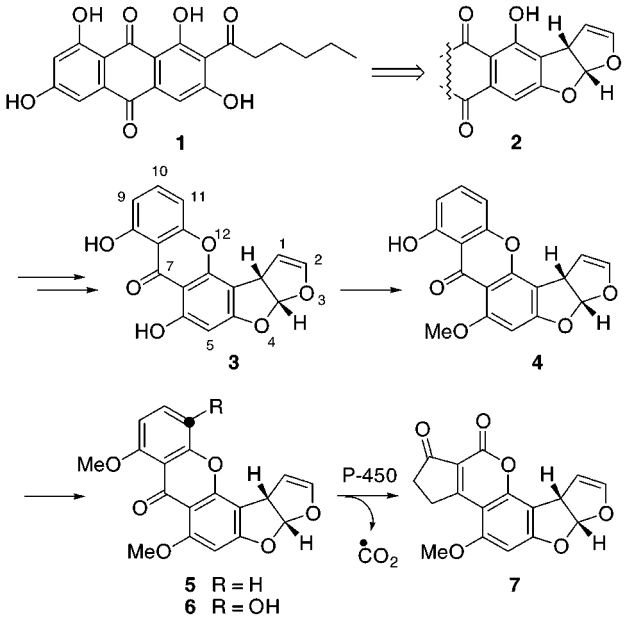
A general strategy is described for the preparation of substituted xanthones and embodied in the preparation of (±)-*O*-methylsterigmatocystin (OMST), the most advanced, known intermediate in the biosynthesis of aflatoxin. The essential features of this approach are the reaction of *N*-alkylnitrilium salts with activated aromatic rings, and protection of the derived xanthones as their corresponding alkenyl xanthenes. The latter are readily synthesized by reaction with *n*-butyllithium and dehydration. The resulting stabilization of the xanthone nucleus enables a wide range of chemical modification reactions to be carried out, and a facile and unusual cleavage of the alkene with peracid restores the desired xanthone. Compatibility of these operations with the preparation of the sensitive dihydrobisfuran is exemplified in the synthesis of OMST.

Introduction

Aflatoxin B_1 (**7**, AFB1) is an environmental carcinogen produced by certain species of the fungal genus *Aspergillus* and has worldwide consequences for human and animal health.[1] Its biosynthesis requires at least 15 steps from norsolorinic acid (**1**) and proceeds through formation of the characteristic dihydrobisfuran present in versicolorin A (**2**).[2] Oxidative cleavage and rearrangement of the anthraquinone nucleus of **2** gives demethylsterigmatocystin (**3**, DMST) which is sequentially *O*-methylated to sterigmatocystin (**4**, ST) and *O*-methylsterigmatocystin (**5**, OMST)[3−5] Recent biochemical and genetic evidence suggests that a *single* cytochrome P-450 converts **5** to AFB1 (**7**).[6] It is known that C-11 (•) in **5** is lost as CO_2, but the mechanism of this intriguing process is unknown.[7] To account for the oxidation state of this fragment and the required ring cleavage and skeletal rearrangement to aflatoxin, we have proposed a biogenetic hypothesis involving two cycles of oxidation.[2,7,8] The proposed product of the first oxidative cycle is 11-hydroxy-*O*-methylsterigmatocystin (**6**, Scheme 1), which putatively undergoes a second oxidation to lead on to ring cleavage, rearrangement, and decarboxylation to AFB1 (**7**).

11-Hydroxy-*O*-methylsterigmatocystin (**6**) is unknown as a natural product and may exist only transiently in the biosynthesis. To investigate its proposed intermediacy in the conversion of OMST (**5**) to AFB1 (**7**), syntheses of both **5** and **6** are required. It could be anticipated at the outset that a successful synthetic plan would provide a general route to the xanthone nucleus compatible with later elaboration of the sensitive dihydrobisfuran ring system (a masked dialdehyde), introduction of isotopic label, and maintence of the hydroquinone oxidation state of the A-ring in **6**. We describe a new synthesis of xanthones that meets these demands and takes advantage of the high electrophilicity of *N*-alkylnitrilium salts. In addition, a central tactic of xanthone protection was developed whereby the xanthone carbonyl is masked as a double bond to allow side chain elaboration under diverse reaction conditions. Scission of the olefin can be carried out subsequently in an especially facile manner to return the xanthone product in high yield. This strategy should prove useful in future syntheses of

Scheme 1



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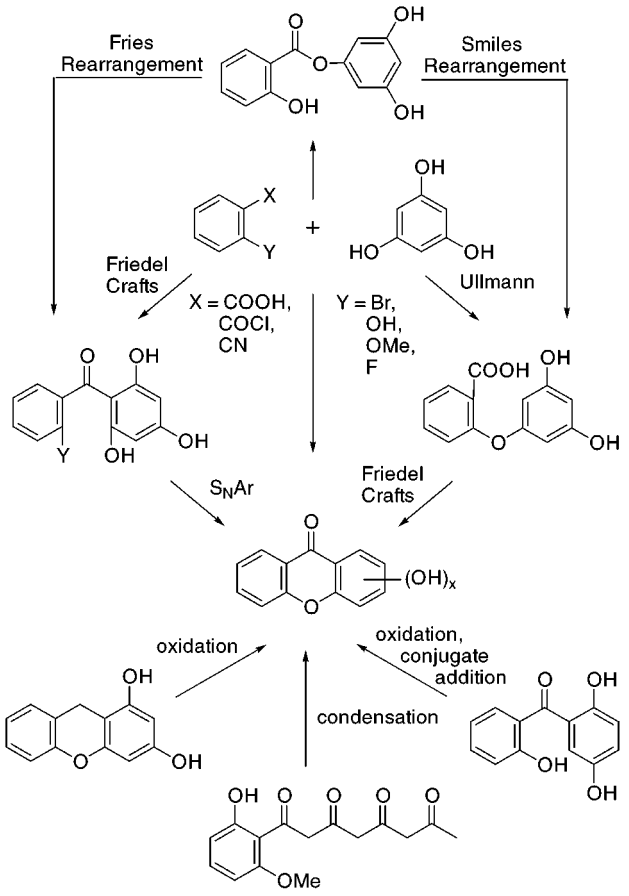
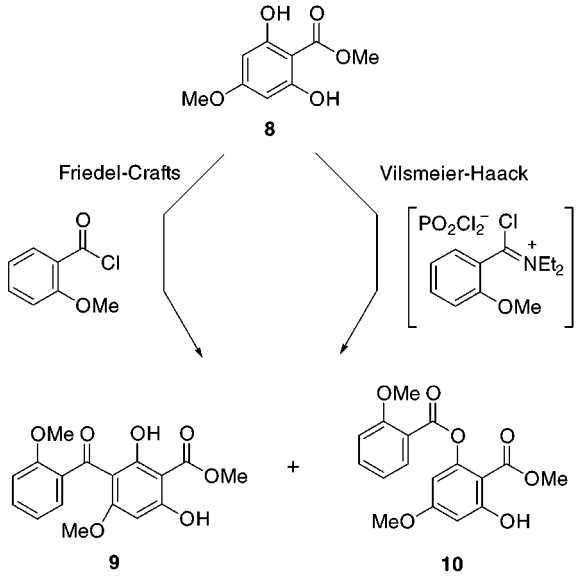
Scheme 2



complex xanthone-based natural products which are of broader importance for their demonstrated biological and pharmacological properties, e.g., antileukemic, anti-inflammatory, antimicrobial, tuberculostatic, and CNS activites.[9,10] We illustrate these developments in the synthesis of a representative group of benzophenone ketimines and in a total synthesis of (±)-*O*-methylsterigmatocystin (**5**).

Traditional xanthone syntheses involve the connection of two aryl fragments to form the internal pyranone ring (Scheme 2).[11,12] The carbonyl connection can be formed by three reaction types: (1) Friedel−Crafts acylation and variants;[13−15] (2) biaryl ester migration, such as the Fries rearrangement;[16,17] or (3) aryl anion addition to a benzoyl chloride.[18] The ether linkage can be formed intermolecularly by the Ullmann method,[10,19] or intramolecularly by an S_NAr mechanism[16,20] or Smiles rearrangement.[14,21] Because intermolecular acylation reactions are generally

Scheme 3



higher yielding than Ullmann ether syntheses, the most prevalent strategy for xanthone synthesis is acylation first followed by cyclization to form the biaryl ether. The xanthone skeleton can also be formed from two aryl components in one step by either a combined Friedel−Crafts/aryl condensation,[22,23] or by aryl anion addition to salicylaldehyde followed by reduction to the xanthene and eventual oxidation to the xanthone (Tanase method).[24] Some less conventional methods of xanthone synthesis are also known.[25,26] These generalized approaches are shown in Scheme 2.

At the outset of this project, we applied some of the standard methods of xanthone synthesis. Unfortunately, these proved to be inadequate for the preparation of xanthone precursors to **5** and **6**. For example, when methyl 2,6-dihydroxy-4-methoxybenzoate (**8**), a phloroglucinol-based nucleus, was subjected to Friedel−Crafts conditions ($AlCl_3$, $ZnCl_2$, Me_3SiCl) in the presence of a benzoyl chloride, a low yield of *O*-and *C*-acylated (**9**) products was isolated (Scheme 3), and the major product was the undesired ester **10**. Under Vilsmeier−Haack conditions, only the *O*-acylated product **10** was isolated. The standard Houben−Hoesch[27] procedure provided no product at all.[28] The presence of a methyl ester decreased the ring nucleophilicity to such an extent that standard acylating electrophiles were inefficient. For the acylation reaction to proceed, a more suitable electrophile was required. Ideally, we sought a simple procedure that

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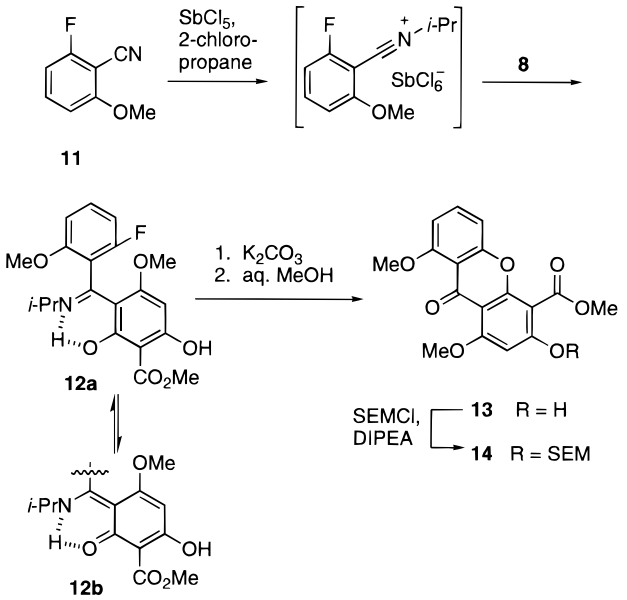
(28) Aryl anion addition to benzonitriles, benzamides, and Vilsmeier-type benzimidoyl chlorides were similarly unsuccessful.

Scheme 4



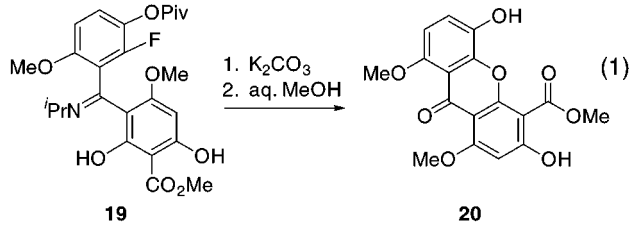
could be readily applied to the synthesis of various xanthone targets including xanthone **13** (Scheme 4) which was selected as a preliminary synthetic target in the preparation of OMST (**5**).

Meerwein demonstrated as early as 1955 that nitriles can be activated by *N*-alkylation in the presence of Lewis acids to become highly electrophilic nitrilium salts.[29] Most of the literature surrounding the application of these *N*-alkylnitrilium salts has focused on the use of amino and hydroxy nucleophiles in the synthesis of imidate esters and heterocycles. The reactions of *N*-alkylnitrilium salts with carbon nucleophiles has been limited to intramolecular reactions of electron rich aromatics to make quinazolines,[30] or intermolecular reactions with indole, pyrrole,[31] 1,3-dimethoxybenzene,[32] anisole,[33,34] and thiophene.[35]

The acylation reaction of alkylnitrilium salts surpasses the Houben−Hoesch acylation method owing to the enhanced electrophilicity of the intermediate. The protonated nitrile generated under Houben−Hoesch conditions exists in only low concentrations ($pK_a \sim -10$). In contrast, Meerwein's alkylated nitrilium ion is the principal reactive species in solution, and so it is a significantly more potent electrophile than the corresponding nitrile[36] or the related imidoyl chloride.[37]

Booth et al. reported the first intermolecular imino-acylation of 1,3-dimethoxybenzene, by *N*-methylnitrilium triflates in good yield (86%), although the reaction required excess reagents and several days to reach completion at room temperature.[32] Unfortunately, this method was not widely applicable because the *N*-methylnitrilium triflates were difficult to prepare and readily hydrolyzed on exposure to air, and, moreover, they could not be generated from benzonitriles containing electron-withdrawing groups. This work, however, did demonstrate the application of alkylnitrilium salts in intermolecular electrophilic aromatic acylation reactions.

Realizing the potential of this reaction among the limited known options for xanthone synthesis, we sought to develop this method for electophilic aromatic substitution reactions. By selecting a relatively stable and easily handled *N*-alkylnitrilium salt, the imino-acylation reaction was found to be widely applicable in the synthesis of various imines, some of which were subsequently converted to xanthones. We illustrate this method in the total synthesis of both OMST by way of xanthone **13**, and of xanthone **20** (eq 1), which can be similarly converted to 11-hydroxy-*O*-methylsterigmatocystin (**6**).



Results and Discussion

The synthesis of *O*-methylsterigmatocystin (**5**) was initiated by intermolecular imino-acylation of methyl 2,6-dihydroxy-4-methoxybenzoate **8**[38] by the *N*-isopropylnitrilium salt prepared from 2-fluoro-6-methoxy benzonitrile **11** and $SbCl_5$ in 2-chloropropane and methylene chloride. Benzophenone ketimine **12** was isolated in 92% yield (Scheme 4). Imine **12** was extraordinarily resistant to hydrolysis under both acidic and alkaline conditions, presumably due to the very strong hydrogen-bonding interaction between the imine and the *peri*-phenol. The ^1H NMR spectrum of this compound revealed the exceptional strength of this interaction by the appearance of the *peri*-phenolic hydrogen signal at approximately 18 ppm. In keeping with this observation, the ^{15}N NMR spectrum of **12** indicated an abberant hybridization for the supposed imine nitrogen. The ^{15}N signal resonates at 135 ppm relative to nitromethane as internal standard (380 ppm). This chemical shift, together with the N−H (isopropyl) coupling constant ($J_{NH} = 8$ Hz) suggests the existence of a significant tautomeric equilibrium between the phenol-imine (**12a**) and the keto-enamine (**12b**) form.[39,40] The predominance of the latter tautomer could explain the hydrolytic stability of this imine. However, the imine became susceptible to hydrolysis after intramolecular ether formation. In the presence of excess K_2CO_3 in dry refluxing acetonitrile,[41] the hydrogen-bonded phenol was freed to undergo nucleophilic substitution

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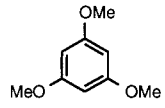
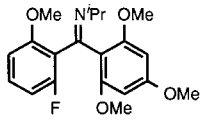
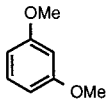
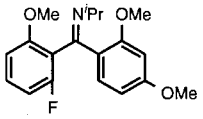
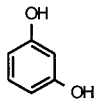
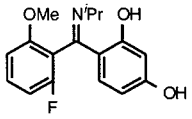
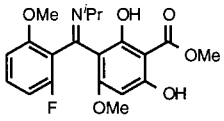
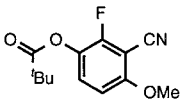
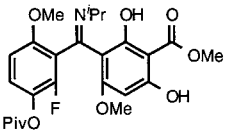
Table 1. Representative Nitrilium Acylation Reactions[a]

entry	arene	nitrile	time (h)	temp (°C)	Imine Product		yield (%)
1		**11**	0.25	0		**16**	99
2		**11**	2.5	20		**17**	92
3		**11**	3	20		**18**	82
4	**8**	**11**	60	40		**12**	92
5[b]	**8**	 **15**	6	20		**19**	85

[a] All reactions performed in dichloromethane using 1 equivalent each of arene and nitrile, 1 - 1.3 equivalents of $SbCl_5$, and 10 equivalents of isopropyl chloride. [b] 2.5 equivalents of arene used.

forming the corresponding xanthone imine. Addition of aqueous methanol and continued heating promoted hydrolysis of the imine to provide xanthone **13** in good yield.

Some model imino-acylations were performed to establish the scope of this reaction (Table 1). In general, the *N*-alkylnitrilium salts were formed in situ by reaction of the appropriate benzonitrile with $SbCl_5$ in the presence of excess 2-chloropropane in methylene chloride. Various aromatic nucleophiles were introduced, and imino acylation was carried out at the appropriate temperature (0 → 40 °C) depending on the nucleophilicity of the aromatic substrate. This procedure led to the formation of stable benzophenone ketimines.

The highly electron-rich aromatic rings, entries 1−3, proceeded very smoothly to the corresponding imines **16**, **17**, and **18** in 3 h or less at room temperature. In the case of trimethoxybenzene, the reaction was extremely rapid at 0 °C. This procedure was not found to be suitable for the acylations of phenol, anisole, or methylsalicylate in under 20 h. Entry 4 represents the key acylation step in this synthesis and highlights the relative reactivities of both the nucleophilic and the electrophilic partners in this reaction. Acylation of **8** requires considerably more time due to the electron-withdrawing nature of the ester substituent. Entry 5 demonstrates the enhanced electrophilicity of a benzonitrile **15**[42] bearing an electron-withdrawing pivaloate (Piv). The acylation of **8** occurs much faster and at room temperature as compared to the reaction between benzonitrile **11** and **8** (entry 4).[43] It can been seen that the alkylnitrilium acylation reaction tolerates a fairly wide range of steric hindrance as well as varying electronic properties of both the electrophile and the nucleophile. The imines **12** and **19** were then cyclized as described above and hydrolyzed to provide the corresponding xanthones **13** and **20** (Scheme 4 and eq 1, respectively).

Having secured a new and effective synthesis of xanthones, we proceeded to the elaboration of OMST (**5**) from **13**. In the synthesis of complex xanthones with functionalized aliphatic or aromatic side chains, the xanthone core is usually constructed relatively late in the synthesis. This strategy is exemplified in the syntheses of cervinomycin,[19] bikaverin,[44] *O*-methylsterigmatocystin,[45] and its saturated tetrahydrobisfuran analogue, dihydro-OMST,[16] and linear pyranoxanthones.[46] While the reasons for this strategy are unstated, delaying formation of the xanthone minimizes potential side reactions at the xanthone carbonyl, which is known to be susceptible to hydride reduction[24,47] and to nucleophilic attack by alkyl-[48] and aryllithium[49] reagents. In those

(42) The synthesis of **15** will be described in a future publication.

(43) *O*-Acylation of the nitrilium species blocks unwanted reactions and enhances electrophilicity. It should be noted that entry 5 was carried out with a 2.5-fold excess of the nucleophile to increase the rate of reaction and the net yield. At 1:1 stoichiometry we found that prolonged exposure of this nitrilium salt, and possibly the imine product **19**, to the acidic reaction conditions caused removal of the pivaloate ester and side reactions initiated by that unprotected phenol.

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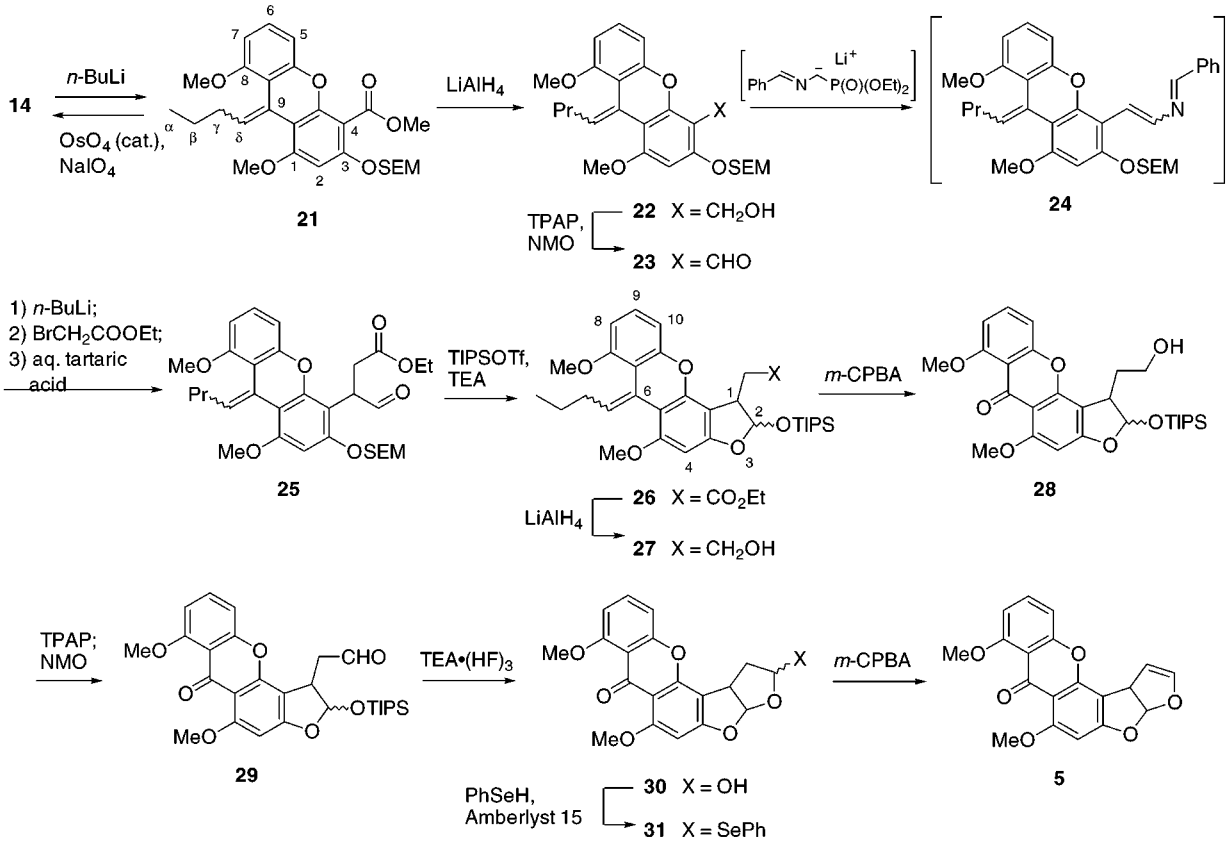
Scheme 5



cases when a hydride reductant ($LiAlH_4$[22] or diisoamylborane[45]) had been used in the presence of a functionalized xanthone, only low yields of desired product were obtained, presumably because of competitive reduction of the xanthone carbonyl.

A broadly applicable synthesis of xanthones, however, would construct the xanthone core first followed by completion of the desired structure. Vulnerability of side chains to the imino-acylation reaction conditions dictate such a plan of attack, particularly in the case of the sensitive dihydrobisfuran present in **5** and **6**. For biosynthetic experiments, the late introduction of label could be advantageously carried out in side chain positions. To achieve this order of synthesis, a method was needed to both protect the xanthone carbonyl and allow its efficient regeneration at a later stage.

Reduction of xanthones to the corresponding xanthenes proceeds readily, but the products are prone to autoxidation. Alternatively, ketalization was considered but never achieved. Finally, the ready reactivity of the xanthone carbonyl with alkyllithium reagents was turned to advantage.[49,48] Dehydration of the adduct of the SEM-protected xanthone **14** and *n*-BuLi was extremely facile during the course of silica gel chromatography forming butylene **21** (Scheme 5). Literature precedents for xanthone formation by oxidative cleavage of an alkyl xanthene derivative are limited[50,51] and involved hot, alkaline $KMnO_4$—conditions far too vigorous for the envisioned synthesis. Notwithstanding, treatment of **21** with $NaIO_4$ and catalytic OsO_4 in aqueous dioxane proceeded smoothly to regenerate the xanthone **14**.

With a xanthone carbonyl protection/deprotection method apparently in hand, the methyl ester of **21** was converted to the aldehyde **23** by a two-step $LiAlH_4$/TPAP[52] redox sequence and then subjected to the one-pot, multistep geminal disubstitution procedure of Martin[53] which has been further developed in this laboratory.[54,55] Aldehyde **23** was introduced into a solution of the lithium anion of diethyl 1-(*N*-benzylidenamino)-methylphosphonate. The resulting azadiene **24** was treated with *n*-butyllithium to generate an intermediate metalloenamine. Alkylation with ethyl bromoacetate followed by mild acid hydrolysis produced aldehyde **25**. Treatment of this aldehyde with TIPS triflate promoted rapid and specific cyclization with concomitant loss of the SEM protecting group to form the diastereomeric furanyl TIPS acetals, **26**.[56] The pendant ethyl ester was cleanly reduced to alcohol **27**. With all the necessary hydride reduction reactions having been carried out, the xanthone carbonyl could be reestablished by oxidative cleavage of the butylene group.

As before, $NaIO_4$/catalytic OsO_4 and, alternately, careful low-temperature ozonolysis were attempted to re-form the xanthone nucleus. In both cases, the starting material was readily consumed, but both the mass recovery and product yield were disappointingly low and variable. A milder strategy was envisioned in which the butylene

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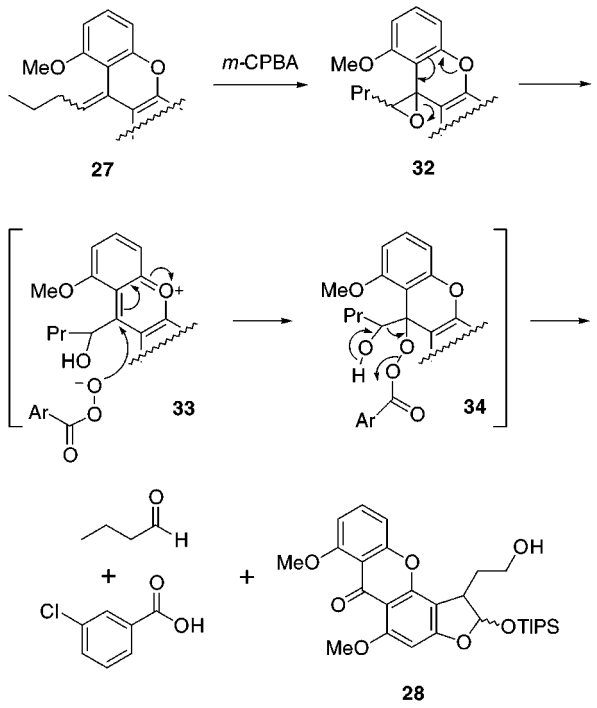
Scheme 6



group was to be oxidized to a xanthenyl spiroepoxide. After acid-catalyzed oxirane hydrolysis, it was hoped that the resultant diol could be cleaved with either $NaIO_4$ or $Pb(OAc)_4$. The reagent chosen to carry out the initial epoxidation was *m*-CPBA. Unexpectedly, the reaction of xanthene **27** with excess *m*-CPBA in the presence of 4 Å molecular sieves formed xanthone **28** rapidly and exclusively (Scheme 5). The product was easily recognizable owing to the strong blue fluorescence of the xanthone intermediates on TLC under long- and short-wave UV irradiation.

Mechanistically it is important to note that the olefin present in **27** is a multiply vinylogous enol ether. On the basis of ^{1}H NMR studies of a model xanthene−butylene cleavage reaction, we propose that the first equivalent of peracid forms the epoxide **32**, followed by an intramolecular oxirane opening with participation of the xanthene oxygen (Scheme 6). The resulting cationic intermediate **33** is quenched by remote addition of a second equivalent of *m*-CPBA. This *β*-hydroxy peracyl intermediate **34** can be cleaved to form the xanthone **28** and butyraldehyde with the concomitant loss of *m*-chlorobenzoate. When the model butylene−xanthene was treated with only 1 equiv of *m*-CPBA, the reaction was arrested at approximately 50% conversion. In fact, more than 2 equiv of oxidant are required to drive the reaction to completion due to competitive oxidation of butyraldehyde.

A mixture of the cis and trans xanthone alcohols **28** was efficiently oxidized to the diastereomeric aldehydes **29** with TPAP/NMO (Scheme 5). At this stage, the cis and trans aldehydes could be separated for characterization purposes, but, in general, they were carried on as a mixture through the next reaction. Treatment of the aldehydes **29** with TEA·$(HF)_3$ both removed the TIPS group and promoted cyclization to the furofuran *endo*- and *exo*-hemiacetals **30**. The hemiacetals exist in equilibrium with the phenolic dialdehyde.

Classically, the hemiactetals **30** have been dehydrated by flash vacuum pyrolysis of their corresponding acetates.[45,57−59] More recently, analogous phenyl sulfoxides have undergone thermal elimination to afford the dihydrobisfuran substructure.[54,55] We elected to examine selenoxide elimination and prepared the mixed phenylselenoacetals **31** using the method of Lallemand.[60] Oxidation with *m*-CPBA at 0 °C[61] proceeded in 15 min to give a single spot on TLC coincident with OMST (**5**). The ^{1}H NMR spectrum revealed that another product in addition to OMST had been formed with identical mobility on silica gel; the *m*-chlorobenzoyloxyacetal. This side reaction was also observed by Lallemand in the formation of a similar enol ether.[62] Notwithstanding, HPLC purification readily provided pure OMST (**5**), which was spectroscopically identical to an authentic sample.[63,64]

Conclusion

The use of *N*-alkylnitrilium salts as aromatic acylating reagents under relatively mild reaction conditions has been demonstrated. This method has been utilized to synthesize a variety of imines which can be converted to the corresponding xanthones. Application of this new approach has been demonstrated in the total synthesis of *O*-methylsterigmatocystin (**5**), a late intermediate in aflatoxin biosynthesis. In addition, a new carbonyl protecting group has been developed that greatly expands the tolerance of the xanthone nucleus to chemical modification. The protected alkenyl xanthene is easily formed by the addition of *n*-butyllithium and dehydration promoted by silica gel chromatography. The butylene group can be efficiently cleaved to restore the parent xanthone using *m*-CPBA in a mild, one-step deprotection reaction. Together, these construction and protection tactics provide a general strategy for the synthesis of complex xanthone natural products.

Experimental Procedures

Melting points were determined in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 400 MHz and are referenced to $CDCl_3$ (7.26 and 77.0 ppm), acetone-d_6 (2.04 and 29.9 ppm), or CD_2Cl_2 (5.32 and 54.0 ppm) as indicated by the individual experiments. High and low resolution mass spectra were recorded at 70 eV in EI^+, CI^+, or FAB operating modes. Combustion analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). Flash chromatography was performed on EM silica gel 60 (230−400 mesh). A ratio of 25−100:1 silica gel/crude product by weight and flow rates of 1−2 in/min were normally employed for flash columns. Thin-layer chromatography was performed on glass plates containing fluorescent indicator, visualized by UV and 20% ethanolic solution of phosphomolybdic acid reagent. Reagents were supplied by Aldrich Chemical Co. All nonaqueous reactions were performed in flame-dried glassware under a positive atmosphere of dry N_2 or Ar. All solvents were dried and

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distilled immediately prior to use (THF and Et_2O were distilled from sodium/benzophenone ketyl, and CH_2Cl_2 and CH_3CN were distilled from CaH_2).

2,4-Dihydroxy-6,6′-dimethoxy-2′-fluoro-3-(methoxycarbonyl)-benzophenone-*N*-(2-methylethyl)ketimine (12). To a solution of 2-fluoro-6-methoxybenzonitrile **11** (6.5 g, 0.043 mol) and 2-chloropropane (32 mL, 0.35 mol) in 90 mL of dry CH_2Cl_2 was added antimony(V) chloride ($SbCl_5$, 65 mL, 0.065 mol, 1 M in CH_2Cl_2). The yellow solution was stirred at room temperature for 2 h. A 0.5 M CH_2Cl_2 solution of ester **8** (9.4 g, 0.047 mol) was added via cannula, and the mixture was heated to reflux for 60 h. The reaction was cooled, quenched by the addition of 1 N NaOH, and extracted four times with 150 mL portions of $CHCl_3$. The organic extracts were concentrated to a red oil and redissolved in 400 mL of ethyl acetate from which all the imine was extracted into 500 mL of 10% HCl. The aqueous solution was then neutralized with solid NaOH and extracted four times with 100-mL portions of $CHCl_3$, which was dried over $MgSO_4$, filtered, and concentrated under vacuum to provide 15.5 g (92%) of pure **12** as a yellow solid. In smaller scale reactions (<2 g), the workup was modified such that the initial $CHCl_3$ extract was purified by flash chromatography (40% ethyl acetate/hexane). Vapor recrystallization from ethyl acetate and hexane produced yellow rods: mp 146−147°; R_f = 0.30 (5% CH_3CN/CH_2Cl_2); ^{1}H NMR (300 MHz, acetone-d_6) δ 17.87 (s, 1H), 13.0 (s, 1H), 7.47 (ddd, J = 8.4, 8.3, 6.9 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.86 (dd, J = 8.9, 8.4 Hz, 1H), 5.56 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.46 (m, 1H), 3.32 (s, 3H), 1.20 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 173.2, 172.2, 166.4, 161.8, 158.2 (d, J_{C-F} = 245 Hz), 156.3 (d, $^3J_{C-F}$ = 7.8 Hz), 130.4 (d, $^3J_{C-F}$ = 10.1 Hz), 113.1 (d, $^2J_{C-F}$ = 20.2 Hz), 107.5 (d, $^2J_{C-F}$ = 21.5 Hz), 106.0 (d, $^4J_{C-F}$ = 3 Hz), 101.5, 98.1, 87.6, 55.9, 55.1, 52.0, 48.0, 23.0, 22.9; IR ($CHCl_3$) 3001, 2966, 2860, 1630, 1617, 1572, 1548, 1090 cm^{-1}; MS (EI) *m/e* (rel inten) 391 (M^+, 75.7), 359 (100); HRMS (EI) calcd for $C_{20}H_{22}FNO_6$ (M^+): 391.1431, found 391.1435.

1,8-Dimethoxy-3-hydroxy-4-(methoxycarbonyl)-9*H*-xanthen-9-one (13). Imine **12** (13.85 g, 35.4 mmol) and K_2CO_3 (48.95 g, 354 mmol) were stirred at reflux in 1770 mL of dry CH_3CN for 19 h. Hydrolysis was accomplished by adding 600 mL of a 1:1 H_2O/MeOH solution and stirring at reflux for an additional 4 h. The reaction mixture was acidified to pH ∼ 6 with concentrated HCl, and the CH_3CN and CH_3OH were removed under vacuum. The residual aqueous layer was extracted repeatedly with $CHCl_3$. The organic layer was then washed with brine, dried over $MgSO_4$, filtered, and adsorbed onto 60 g of silica gel. The preadsorbed residue was purified by flash chromatography (5% CH_3OH/CH_2Cl_2) to afford 8 g (68%) of **13** as a white powder. Recrystallization from cold CH_2Cl_2 produced fine white needles: mp 227−229 °C; R_f = 0.45 (5% CH_3OH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.54 (s, 1H), 7.52 (t, J = 8.3 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.35 (s, 1H), 4.06 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (75 MHz, pyridine-d_5) δ 174.06, 170.14, 167.2, 165.4, 160.8, 158.2, 157.2, 134.5, 114.5, 110.2, 108.7, 107.4, 97.9, 96.5, 56.8, 56.7, 53.0; IR ($CHCl_3$) 3006, 2953, 1652, 1583, 1115, 1079 cm^{-1}; MS (EI) *m/e* (rel inten) 330 (M^+, 65.39), 298.1 (100); HRMS (EI) calcd for $C_{17}H_{14}O_7$ (M^+): 330.0740, found 330.0743; 330. Anal. calcd for $C_{17}H_{14}O_7$: C, 61.82; H, 4.27. Found: C, 61.82; H, 4.28.

General Procedure for Nitrilium Acylation Reaction: 2′-Fluoro-2,4,6,6′-tetramethoxybenzophenone-*N*-(2-methylethyl)ketimine (16). To a solution of **11** (0.11 g, 0.072 mmol) and 2-chloropropane (0.7 mL, 7.2 mmol) in 2 mL of dry CH_2Cl_2 was added antimony(V) chloride (0.9 mL, 0.9 mmol). The yellow solution was stirred at room temperature for 30 min. The mixture was then cooled to 0 °C, and solid 1,3,5-trimethoxybenzene (0.12 g, 0.72 mmol) was added. After 15 min, the reaction was quenched by the addition of 2 N NaOH and extracted three times with CH_2Cl_2. The organic portion was washed with 1.8 M Rochelle's salt and dried with brine followed by $MgSO_4$. The mixture was filtered and concentrated under vacuum to provide 0.26 g (99%) of pure **16** as a yellow sticky solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (ddd, J = 8.3, 8.3, 6.3 Hz, 1H), 6.62 (ddd, J = 8.4, 8.4, 0.9 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.08 (s, 2H), 3.78 (s, 3H), 3.68 (s, 6H), 3.61 (s, 3H), 3.54 (m, J = 6.2 Hz, 1H), 1.16 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 161.1 (d, J = 247 Hz), 158.7 (d, J = 6.8 Hz), 158.1, 153.0, 128.6 (d, J = 10.5 Hz), 120.8 (d, J = 15.0 Hz), 108.7, 108.2 (d, J = 23.2 Hz), 106.9 (d, J = 3 Hz), 90.2, 56.2, 55.5, 55.1, 53.9, 23.3; IR ($CHCl_3$) 3006, 2956, 1604, 1583, 1463 cm^{-1}; MS (EI) *m/e* (rel inten) 361 (M^+, 9), 318 (100), 303 (30); HRMS (EI) calcd for $C_{20}H_{24}FNO_4$ (M^+): 361.1689, found 361.1693.

2′-Fluoro-2,4,6′-trimethoxybenzophenone-*N*-(2-methylethyl)ketimine (17). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (ddd, J = 8.6, 8.5, 6.4 Hz, 1H), 7.08 (dd, J = 8.2, 0.6 Hz, 1H), 6.65 (dd, J = 8.5, 8.4 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.44 (m, 2H), 3.78 (s, 3H,), 3.76 (s, 3H), 3.70 (s, 3H), 3.61 (m, J = 6.5 Hz, 1H), 1.18 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 160.3 (d, J = 246 Hz), 158.2 (d, J = 7 Hz), 157.0, 156.3, 129.6 129.0 (d, J = 10 Hz), 120.8 (d, J = 18 Hz), 119.7, 108.3 (d, J = 22 Hz), 106.9 (d, J = 3 Hz), 104.0, 98.2, 56.1, 55.3, 55.2, 53.4, 23.4; IR ($CHCl_3$) 3008, 2966, 2933, 1607, 1466 cm^{-1}; MS (CI^+ (NH_3)) *m/e* (rel inten) 332 [($M + H)^+$], 100), 288 (5); HRMS (CI) calcd for $C_{19}H_{23}FNO_3$ [($M + H)^+$]: 332.1662, found 332.1656.

2,4-Dihydroxy-2′-fluoro-6′-methoxybenzophenone-*N*-(2-methylethyl)ketimine (18). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (ddd, J = 8.3, 8.3, 6.7 Hz, 1H), 6.81 (m, J = 8.3, 7.6 Hz, 2H), 6.56 (d, J = 8.8 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 6.13 (dd, J = 8.8, 2.4 Hz, 1H), 3.75 (s, 3H), 3.39 (m, J = 6.3 Hz, 1H), 1.21 (d, J = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 163.4, 162.6, 159.2 (d, J = 246 Hz), 157.3 (d, J = 7 Hz), 132.2, 131.6 (d, J = 10 Hz), 111.4, 109.8 (d, J = 24 Hz), 108.1 (d, J = 22 Hz), 106.6, 104.9, 56.1, 51.1, 23.5, 23.3; IR ($CHCl_3$) 3582, 3020, 2972, 1615, 1470 cm^{-1}; MS (EI) *m/e* (rel inten) 303 (M^+, 100), 288 (38), 272 (60), 230 (35); HRMS (EI) calcd for $C_{17}H_{18}FNO_3$ (M^+): 303.1271, found 303.1275.

2,4-Dihydroxy-6,6′-dimethoxy-2′-fluoro-3-(methoxycarbonyl)-3′-pivaloylbenzophenone-*N*-(2-methylethyl)-ketimine (19). R_f = 0.6 (2%MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 17.00 (brs, 1H), 13.21 (s, 1H), 7.08 (dd, J = 8.8, 8.4 Hz, 1H), 6.69 (dd, J = 9.2, 1.2 Hz, 1H), 5.54 (s, 1H), 4.00 (s, 3H), 3.75 (s, 3H), 3.46 (m, 1H), 3.36 (s, 3H), 1.35 (s, 9H), 1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 176.3, 173.3, 172.5, 166.5, 160.8, 153.5 (d, 6 Hz), 150.0 (d, J = 247 Hz), 132.3 (d, J = 14 Hz), 123.7, 114.5 (d, J = 18 Hz), 105.6 (d, J = 3 Hz), 101.6, 98.1, 88.0, 56.2, 55.4, 52.2, 48.3, 39.0, 27.0, 23.3, 23.0; IR ($CHCl_3$) 3032, 2984, 1752, 1630, 1571, 1550 cm^{-1}; MS (EI) *m/e* (rel inten) 491 (M^+, 40), 459 (100), 375 (15); HRMS (EI) calcd for $C_{25}H_{30}FNO_8$ (M^+): 491.1955, found 491.1960;

3,5-Dihydroxy-1,8-dimethoxy-4-(methoxycarbonyl)-9*H*-xanthen-9-one (20). A suspension of **19** (1 g, 2.04 mmol), K_2CO_3 (5.6 g, 40.36 mmol), KF•Al_2O_3[65] (0.33 g, 2.04 mmol), and 18-crown-6 (0.05 g, 0.2 mmol) in 200 mL of dry CH_3CN was heated to reflux and stirred for 6 h. A 1:1 mixture of CH_3OH/H_2O (200 mL) was added and the resulting solution stirred at reflux for 1 h then overnight at room temperature. The reaction mixture was concentrated to an orange residue, dissolved in 100 mL of 1 N HCl and 300 mL of CH_2Cl_2, and extracted three times with 100 mL portions of CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash chromatography (2.5% CH_3OH/10% CH_3CN/CH_2Cl_2) afforded 0.53 g (75%) of **20** as a white solid: mp 244−245° (dec); R_f = 0.2 (2% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.38 (s, 1H), 7.18 (d, J = 8.9 Hz, 1H), 6.70 (d, J = 8.9 Hz, 1H), 6.38 (s, 1H), 5.80 (brs, 1H), 4.10 (s, 3H), 3.99 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6/pyridine-d_5) δ 173.6, 168.1, 164.7, 163.7, 156.7, 151.6, 145.3, 139.8, 119.7, 114.4, 107.2, 106.7, 98.1, 95.3, 56.2, 55.8, 52.0; IR ($CHCl_3$) 3534, 3009, 1652, 1582, 1483 cm^{-1}; MS (EI) *m/e* (rel inten) 346 (M^+, 75), 314 (100), 299 (78); HRMS (EI) calcd for $C_{17}H_{14}O_8$ (M^+): 346.0689, found 346.0691. Anal. calcd for $C_{17}H_{14}O_8$: C, 58.96; H, 4.05. Found: C, 58.72; H, 4.08.

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1,8-Dimethoxy-4-(methoxycarbonyl)-3-[2-(trimethylsilyl)ethoxymethoxy]-9*H*-xanthen-9-one (14). Procedure 1: 2-(Trimethylsilyl)ethoxymethyl chloride (SEMCl, 4.3 mL, 24.1 mmol) was added dropwise to a 0 °C mixture of **13** (5.3 g, 16.1 mmol) and diisopropylethylamine (DIPEA, 5.3 g, 30.5 mmol) in 230 mL of dry CH_2Cl_2 and stirred for 2 h while warming to room temperature. Saturated aqueous NH_4Cl was added, and the resulting mixture was extracted with 50-mL portions of cold 5% HCl, 5% $NaHCO_3$, and brine. The organic portion was dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash chromatography (2.5% CH_3OH/10% CH_3CN/CH_2Cl_2) afforded 6.73 g (91%) of **14** as a yellow solid: mp 128−129 °C; $R_f = 0.6$ (2.5% CH_3OH/10% CH_3CN/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (t, $J = 8.4$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 6.71 (d, $J = 8.4$ Hz, 1H), 6.60 (s, 1H), 5.30 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 3.75 (t, $J = 8.3$ Hz, 2H), 0.91 (t, $J = 8.3$ Hz, 2H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 164.6, 162.3, 159.9, 158.8, 156.1, 154.4, 133.5, 112.9, 108.8, 108.1, 105.8, 104.5, 93.2, 92.8, 66.7, 56.1, 55.9, 55.1, 17.6, −1.7; IR ($CHCl_3$) 3012, 2950, 1726, 1652, 1471 cm^{-1}; MS (EI) *m/e* (rel inten) 460 (M^+, 28), 402 (100), 387 (62); HRMS (EI) calcd for $C_{23}H_{28}O_8Si$ (M^+) 460.1553, found 460.1554. Anal. calcd for $C_{23}H_{28}O_8Si$: C, 60.0; H, 6.09. Found: C, 59.98; H, 6.18.

Procedure 2: To a 7 mL solution of **21** (72 mg, 0.144 mmol) in dioxane/H_2O (1:1) were added a 2.5 wt % solution of OsO_4 in 2-methyl-2-propanol (0.1 mL, 0.01 mmol) and $NaIO_4$ (46 mg, 0.216 mmol). After stirring for 24 h, another 20 mg (0.95 mmol) of $NaIO_4$ and 1 mL of pyridine were added. The reaction was quenched after 48 h by the addition of 5 mL of 10% Na_2SO_3, and the mixture was diluted with 10 mL of CH_2Cl_2. After extracting with 5-mL portions of 10% Na_2SO_3 and brine, the organic portion was dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash chromatography (10% CH_3CN/CH_2Cl_2) afforded 52 mg (79%) of **14**.

1,8-Dimethoxy-4-(methoxycarbonyl)-3-[2-(trimethylsilyl)ethoxymethoxy]-9*H*-xanthene-$\Delta^{9,\delta}$-butane (21). To a cooled (−78 °C) solution of ester **14** (86 mg, 0.187 mmol) in 4 mL of THF was added *n*-butyllithium (0.35 mL, 0.7 M solution in hexanes). After 10 min, tartaric acid (0.5 mL of 1 M soln) and ethyl acetate (3 mL) were added, and the reaction mixture was warmed to room temperature. The mixture was extracted with saturated NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (10% acetone/1% acetic acid/$CHCl_3$) to provide **21** as a roughly 1:1 mixture of *E*/*Z* olefins (0.072 g, 77%). Trituration with hexanes afforded a white solid. *All the butylene-masked xanthone compounds that follow exist as inseparable mixtures of E/Z isomers which have been arbitrarily designated as A and B in the ^{1}H NMR spectra*: mp 107−108.5°; $R_f = 0.56$ (20% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, $J = 8.2$ Hz, 1H, B), 7.08 (t, $J = 8.2$ Hz, 1H, A), 6.71 (m, 4H, A/B), 6.59 (s, 1H, B), 6.57 (s, 1H, A), 6.23 (dd, $J = 7.3$. 7.0 Hz, 1H, A), 6.15 (dd, $J = 7.3$, 7.2 Hz, 1H, A), 5.26 (s, 2H, A), 5.24 (s, 2H, B), 3.97 (s, 3H, A), 3.95 (s, 3H, B), 3.86 (s, 6H, A), 3.86 (s, 6H, B), 3.78 (m, 4H, A/B), 2.26 (m, 2H, A/B), 1.83 (m, 2H, A/B), 1.41 (m, 4H, A/B), 0.94 (t, $J = 8.3$ Hz, 4H, A/B), 0.89 (t, $J = 7.3$ Hz, 3H, A), 0.87 (t, $J = 7.3$ Hz, 3H, B), 0.01 (s, 18H, A/B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 157.4, 157.2, 155.8, 155.7, 155.3, 154.9, 154.1, 153.3, 153.0, 151.4, 133.8, 133.7, 128.1, 126.8, 117.9, 116.9, 114.3, 111.4, 109.2, 108.9, 108.6, 106.5, 106.3, 106.1, 94.7, 94.3, 93.9, 93.7, 93.5, 66.6, 66.5, 55.9, 55.8, 55.4, 55.3, 52.3, 33.3, 22.7, 18.0, 14.0, −1.4; IR ($CHCl_3$) 3013, 2953, 1724, 1613 cm^{-1}; MS (EI) *m/e* (rel inten) 500 (M^+, 28), 442 (12), 427 (31), 411 (68), 385 (100); HRMS (EI) calcd for $C_{27}H_{36}O_7Si$ (M^+) 500.2230, found 500.2237. Anal. calcd for $C_{27}H_{36}O_7Si$: C, 64.80; H, 7.20. Found: C, 64.80; H, 7.35.

1,8-Dimethoxy-4-(hydroxymethyl)-3-[2-(trimethylsilyl)-ethoxymethoxy]-9*H*-xanthene-$\Delta^{9,\delta}$-butane (22). To a 0 °C solution of ester **21** (254 mg, 0.51 mmol) in 15 mL of Et_2O was added $LiAlH_4$ (20 mg, 0.558 mmol). After 20 min, the reaction was quenched by cautious addition of $NaSO_4 \cdot 10H_2O$. The mixture was diluted with Et_2O and ethyl acetate and stirred overnight at room temperature. The resulting white precipitate was filtered, and the filtrate was concentrated to afford 0.24 g (>99%) of **22** as a mixture of *E*/*Z* isomers as a light yellow oil, which needed no further purification: $R_f = 0.33$ (20% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, $J = 8.2$ Hz, 1H, B), 7.10 (t, $J = 8.2$ Hz, 1H, A), 6.80 (dd, $J = 8.5$, 8.3 Hz, 2H, A/B), 6.69 (d, $J = 8.3$ Hz, 2H, A/B), 6.59 (s, 1H, B), 6.58 (s, 1H, A), 6.23 (dd, $J = 7.1$ Hz, 1H, A), 6.16 (dd, $J = 7.3$, 7.0 Hz, 1H, B), 5.29 (d, $J = 2.4$ Hz, 2H, A), 5.26 (s, 2H, B), 4.88 (s, 1H, A), 4.86 (s, 1H, B), 3.86 (s, 6H, A/B), 3.85 (s, 12H, A/B), 3.78 (m, 4H, A/B), 2.28 (m, 4H, A/B), 1.85 (m, 2H, A/B), 1.41 (m, 4H, A/B), 0.97 (t, $J = 8.3$ Hz, 4H A/B), 0.89 (t, $J = 7.3$ Hz, 3H, A), 0.87 (t, $J = 7.3$ Hz, 3H, B), 0.01 (s, 18H, A/B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 155.9, 155.8, 155.7, 155.69, 155.0, 154.9, 153.7, 153.5, 152.2, 133.3, 133.1, 127.9, 126.7, 118.3, 117.2, 114.5, 111.4, 110.6, 110.2, 108.9, 108.6, 108.5, 106.4, 105.9, 94.9, 94.0, 93.8, 93.6, 66.5, 55.7, 55.2, 54.3, 33.2, 22.6, 17.9, 14.0, 13.9, −1.5; IR ($CHCl_3$) 3600, 3010, 2946, 1615, 1061 cm^{-1}; MS (EI) *m/e* (rel inten) 472 (M^+, 47), 399 (18), 357 (17), 324 (85); HRMS (EI) calcd for $C_{26}H_{36}O_6Si$ (M^+) 472.2281, found 472.2286. Anal. calcd for $C_{26}H_{36}O_6Si$: C, 66.07; H, 7.63. Found: C, 66.09; H, 7.75.

1,8-Dimethoxy-4-formyl-3-[2-(trimethylsilyl)ethoxymethoxy]-9*H*-xanthene-$\Delta^{9,\delta}$-butane (23). To a room temperature solution of alcohol **22** (240 mg, 0.513 mmol) in 25 mL of CH_2Cl_2 were added 4 Å molecular sieves (480 mg, 2 g/g) and *N*-methylmorpholine *N*-oxide (96 mg, 0.82 mmol). After 20 min, TPAP (11 mg, 0.0308 mmol) was added, and the mixture stirred for 30 min. The mixture was concentrated under vacuum. Purification by flash chromatography provided 230 mg of *E* and *Z* **23** (96%) as a yellow oil: $R_f = 0.42$ (20% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.55 (s, 1H, A), 10.54 (s, 1H, B), 7.23 (t, $J = 8.3$ Hz, 1H, B), 7.13 (t, $J = 8.2$ Hz, 1H, A), 6.85 (dd, $J = 8.9$, 7.3 Hz, 2H, A/B), 6.72 (d, $J = 8.2$ Hz, 2H, A/B), 6.61 (s, 1H, B), 6.59 (s, 1H, A), 6.25 (dd, $J = 7.2$, 7.1 Hz, 1H, A), 6.13 (dd, $J = 7.3$, 7.1 Hz, 1H, B), 5.36 (s, 2H, A), 5.33 (s, 2H, B), 3.92 (s, 6H, A/B), 3.88 (s, 6H, A/B), 3.83 (m, 4H, A/B), 2.28 (m, 2H, A/B), 1.80 (m, 2H, A/B), 1.39 (m, 4H, A/B), 0.96 (dt, $J = 9.4$, 6.8 Hz, 4H, A/B), 0.88 (t, $J = 7.4$ Hz, 3H, A), 0.87 (t, $J = 7.3$ Hz, 3H, B), 0.004 (s, 18H, A/B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 187.0, 160.7, 160.6, 160.1, 159.0, 157.7, 156.0, 155.6, 155.5, 154.6, 153.0, 134.0, 133.8, 128.3, 127.0, 117.3, 116.7, 114.2, 111.1, 109.3, 108.9, 108.7, 108.6, 108.2, 106.7, 106.3, 94.2, 93.6, 93.5, 93.4, 66.9, 66.8, 55.9, 55.7, 55.5, 55.4, 55.3, 33.3, 33.1, 22.6, 22.5, 17.9, 13.9, −1.5; IR ($CHCl_3$) 3010, 2950, 1674, 1590, 1065, cm^{-1}; MS (EI) *m/e* (rel inten) 470 (M^+, 20), 412 (18), 397 (46), 381 (77), 355 (100); HRMS (EI) calcd for $C_{26}H_{34}O_6Si$ (M^+) 470.2125, found 470.2117. Anal. calcd for $C_{26}H_{34}O_6Si$: C, 66.38; H, 7.23. Found: C, 65.70; H, 7.28.

1,8-Dimethoxy-4-(ethyl-3′-formylpropanoate)-3-[2-(trimethylsilyl)ethoxymethoxy]-9*H*-xanthene-$\Delta^{9,\delta}$-butane (25). To a cooled (−78 °C) solution of diethyl 1-(*N*-benzylidenamino)-methylphosphonate[66,67] (1.02 g, 4.5 mmol) in 23 mL of dry THF was added *n*-butyllithium (3.2 mL, 1.4 M in hexanes, 4.5 mmol) over 12 min. This solution stirred at −65 °C for 1 h. After the resulting lithium benzylidenaminomethylphosphonate was cooled to −78 °C, a solution of aldehyde **23** (1.7 g, 3.77 mmol) in 10 mL of dry THF was added via cannula over 3 min. After 50 min, the mixture was allowed to stir at room temperature for 1.5 h. The reaction mixture was then cooled to −78 °C, and *n*BuLi (3.8 mL, 1.4 M) was added over 4 min. After 2.5 h, ethyl bromoacetate (2.5 mL, 22.62 mmol) was added to the −78 °C mixture, which was then allowed to warm to room temperature over 1.5 h. The reaction was quenched by the addition of 10 mL of 1 M aqueous tartaric acid and stirred for 1 h. The mixture was extracted with 10-mL portions of cold 5% HCl (2×), 5% $NaHCO_3$ (2×), and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (10% ethyl acetate/hexane) to give 1.23 g (57%) of **25**, a yellow oil, as a mixture of *E* and

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Z isomers: $R_f = 0.48$ (20% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (m, 2H, A/B), 7.25−7.13 (m, 1H, B), 7.13−7.0 (m, 1H, A), 6.8−6.7 (m, 4H, A/B), 6.64 (s, 1H, B), 6.61 (s, 1H, A), 6.25−6.12 (m, 2H, A/B), 5.30 (s, 2H, A), 5.29 (s, 2H, B), 4.65−4.58 (m, 2H, A/B), 4.25−4.05 (m, 4H, A/B), 3.86 (s, 6H, A/B), 3.7−3.8 (m, 4H, A/B), 3.3−3.1 (m, 2H, A/B), 2.55−2.35 (m, 2H, A/B), 2.35−2.25 (m, 2H, A/B), 1.9−1.75 (m, 2H, A/B), 1.5−1.3 (m, 4H, A/B), 1.2 (m, 6H, A/B), 0.98−0.86 (m, 10H, A/B), 0.004 (s, 18H, A/B); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 199.7, 172.3, 156.1, 155.9, 155.9, 155.7, 154.9, 154.8, 153.4, 133.7, 133.5, 128.4, 128.2, 126.9, 118.2, 117.1, 114.4, 111.4, 109.1, 108.9, 108.8, 108.6, 106.6, 1061, 105.6, 105.3, 105.2, 94.3, 93.5, 93.3, 93.1, 66.6, 66.5, 60.4, 55.8, 55.3, 44.5, 44.4, 33.4, 33.3, 22.7, 18.0, 17.9, 14.1, 14.0, −1.4; IR ($CHCl_3$) 3012, 2958, 1723, 1465, 1058, cm^{-1}; MS (EI) *m/e* (rel inten) 570 (M^+, 49), 512 (15), 483 (75), 481 (67), 455 (100); HRMS (EI) calcd for $C_{31}H_{42}O_8Si$ (M^+) 570.2649, found 570.2660. Anal. calcd for $C_{31}H_{42}O_8Si$: C, 65.26; H, 7.37. Found: C, 65.06; H, 7.41.

5,7-Dimethoxy-1-(ethoxycarbonylmethyl)-2-[tris(1-methylethyl)silyloxy)]-6*H*-furo[2,3-*c*]xanthene-$\Delta^{6,\delta}$-butane (26). Aldehyde **25** (1 g, 1.88 mmol) and triethylamine (0.4 mL, 3 mmol) were combined in 25 mL of dry THF and cooled to 0 °C. Triisopropylsilyl trifluoromethylsulfonate (TIPSOTf, 2.3 mL, 2.25 mmol) was added dropwise and the mixture stirred for 4 h while warming to room temperature. The reaction was quenched by the addition of *N*,*N*-dimethylethanolamine (0.6 mL, 5.63 mmol) and extracted with 10-mL portions of cold 5% HCl, 5% $NaHCO_3$, and brine, and dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (5% ethyl acetate/hexane) to provide 0.97 g (86%) of a colorless oil, **26**, as a mixture of 4 isomers: *E* and *Z*, and cis and trans acetals: $R_f = 0.57$ (10% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, $J = 8.2$ Hz, 1H, B), 7.10 (t, $J = 8.2$ Hz, 1H, A), 6.80−6.75 (m, 2H, A/B), 6.68 (d, $J = 8.2$ Hz, 2H, A/B), 6.27 (s, 1H, B), 6.25 (s, 1H, A), 6.18−6.12 (m, 2H, A/B), 5.97−5.89 (m, 2H, A/B), 4.2−4.05 (m, 4H, A/B), 3.86 (s, 3H, A/B), 3.83 (s, 3H, OC*H*$_3$, A/B), 3.75−3.6 (m, 2H, *H*-1, A/B), 2.9−2.75 (m, 2H, (HC*H*CO_2), A/B), 2.6−2.4 (m, 2H, A/B), 2.4−2.2 (m, 2H, A/B), 1.9−1.8 (m, 2H, A/B), 1.55−1.3 (m, 4H, A/B), 1.3−1.0 (m, 48H, A/B), 0.90 (t, $J = 7.4$ Hz, 3H, A), 0.89 (t, $J = 7.2$ Hz, 3H, B); ^{13}C NMR (100 MHz, acetone-d_6) δ 171.7, 160.4, 159.0, 158.1, 157.9, 156.9, 156.8, 155.8, 154.3, 152.5, 151.0, 133.3, 133.0, 129.2, 127.9, 119.6, 118.4, 115.4, 111.3, 109.7, 109.4, 109.1, 108.3, 107.8, 107.4, 107.2, 106.9, 91.4, 91.3, 90.8, 90.6, 61.0, 56.4, 56.1, 55.8, 55.6, 47.2, 47.1, 36.9, 36.5, 34.0, 23.4, 18.2, 18.1, 14.4, 14.3, 13.0, 12.8, 12.7; IR ($CHCl_3$) 3007, 2930, 1730, 1635, 1091 cm^{-1}; MS (FAB) *m/e* (rel inten) 596 (M^+, 54), 565 (16), 539 (21), 479 (22); HRMS (EI) calcd for $C_{34}H_{48}O_7Si$ (M^+) 596.3169, found 596.3177. Anal. calcd for $C_{34}H_{48}O_7Si$: C, 68.46; H, 8.05. Found: C, 67.99; H, 8.42.

5,7-Dimethoxy-1-(hydroxyethyl)-2-[tris(1-methylethyl)silyloxy)]-6*H*-furo[2,3-*c*]xanthene-$\Delta^{6,\delta}$-butane (27). $LiAlH_4$ (8.4 mg, 0.22 mmol) was added to a 0 °C solution of ester **26** (80 mg, 0.138 mmol) in 7 mL of dry Et_2O. After warming to room temperature over 1 h, $NaSO_4 \cdot 10H_2O$ was added cautiously, and the suspension stirred for 1 h. The mixture was filtered, and the filtrate was concentrated under vacuum to afford 76 mg (99%) of **27** as a mixture of *E*/*Z* and cis/trans isomers as a faint yellow oil requiring no further purification: $R_f = 0.49$ (20% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, $J = 8.2$ Hz, 1H, B), 7.10 (t, $J = 8.2$ Hz, 1H, A), 6.83−6.74 (m, 2H, A/B), 6.69 (d, $J = 8.2$ Hz, 2H, A/B), 6.30 (s, 1H, B), 6.28 (s, 1H, A), 6.21−6.13 (m, 2H, A/B), 5.85−5.82 (m, 2H, A/B), 3.86 (s, 6H, B), 3.83 (s, 6H, A), 3.75−3.65 (m, 4H, A/B), 3.6−3.35 (m, 2H, A/B), 2.4−2.0 (m, 4H, A/B), 2.0−1.75 (m, 4H, A/B), 1.5−1.28 (m, 4H, A/B), 1.1−1.05 (m, 42H, A/B), 0.89 (t, $J = 7.3$ Hz, 6H, A/B); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.6, 159.3, 159.2, 157.8, 157.7, 157.6, 157.5, 157.3, 157.1, 156.9, 156.0, 154.5, 152.6, 151.2, 133.0, 132.9, 129.2, 127.9, 120.1, 118.7, 115.7, 111.5, 109.9, 109.5, 109.2, 108.9, 108.4, 107.8, 107.2, 105.4, 104.6, 104.3, 104.1, 101.7, 91.5, 90.8, 90.7, 89.7, 61.5, 60.7, 60.3, 56.5, 56.3, 55.9, 55.7, 48.3, 43.5, 43.2, 43.1, 36.1, 35.9, 34.2, 34.1, 23.5, 18.4, 18.3, 18.2, 14.4, 13.1, 12.9; IR ($CHCl_3$) 3615, 3005, 2946, 2868, 1633, 1486, 1088 cm^{-1}; MS (EI) *m/e* (rel inten) 554 (M^+, 14), 380 (45), 349 (68), 323 (100); HRMS (EI) calcd for $C_{32}H_{46}O_6Si$ (M^+) 554.3064, found 554.3068. Anal. calcd for $C_{32}H_{46}O_6Si$: C, 69.31; H, 8.30. Found: C, 69.12; H, 8.29.

5,7-Dimethoxy-1-(acetaldehyde)-2-[tris(1-methylethyl)silyloxy)]-6*H*-furo[2,3-*c*]xanthen-6-one (28). To a 10 mL CH_2Cl_2 solution of alcohol **27** (30 mg, 0.054 mmol) were added 4 Å molecular sieves (250 mg) and *m*-CPBA (57−86%, 125 mg, 0.72 mmol). The reaction was quenched after 30 min by the addition of 2 N NaOH. The mixture was extracted three times with CH_2Cl_2, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography (2−5% CH_3OH/CH_2Cl_2) to afford 20 mg (68%) of xanthone **28**: $R_f = 0.26$ (2.5% CH_3OH/10% CH_3CN/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 (t, $J = 8.3$ Hz, 1H), 6.9 (d, $J = 8.2$ Hz, 1H), 6.73 (d, $J = 8.3$ Hz, 1H), 6.3 (s, 1H), 5.99 (d, $J = 1.3$ Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.79 (m, 2H), 3.55 (t, $J = 6.4$ Hz, 1H), 2.0 (m, 2H), 1.1−1.05 (m, 21H). Without further purification, the crude alcohol **28** (25 mg, 0.044 mmol) was dissolved in 2.2 mL of CH_2Cl_2 and treated with *N*-methylmorpholine *N*-oxide (8.4 mg, 0.072 mmol) and 4 Å molecular sieves (50 mg). After 15 min, TPAP (0.95 mg, 0.0027 mol) was added to the reaction. After 30 min, the reaction was concentrated under vacuum and purified by flash chromatography (2% CH_3OH/CH_2Cl_2) to afford 21 mg of the cis and trans aldehydes **29** (92%):

Cis furan: $R_f = 0.73$ (5% CH_3OH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.48 (t, $J = 8.3$ Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 6.76 (d, $J = 8.4$ Hz, 1H), 6.35 (d, $J = 6.3$ Hz, 1H), 6.31 (s, 1H), 4.13 (m, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.25−3.4 (m, 1H), 3.1−3.2 (m, 1H), 1.07 (m, 21H). trans furan: $R_f = 0.62$ (5% CH_3OH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.50 (t, $J = 8.2$ Hz, 1H), 6.90 (d, $J = 8.0$ Hz, 1H), 6.76 (d, $J = 8.6$ Hz, 1H), 6.33 (s, 1H), 5.89 (s, 1H), 3.94 (m, 7H), 2.9−3.1 (m, 1H), 2.6−2.75 (m, 1H), 1.08 (m, 21H). ^{13}C NMR (100 MHz, acetone-d_6) δ 201.2, 173.9, 164.1, 163.7, 161.2, 157.5, 154.4, 134.5, 114.7, 109.9, 109.5, 108.5, 107.5, 106.7, 91.6, 56.8, 45.7, 44.6, 18.23, 18.16, 12.9; IR ($CHCl_3$) 3014, 2948, 2863, 2723, 1593, 1470, 1097 cm^{-1}. MS (EI) *m/e* (rel inten) 512 (M^+, 21), 441 (43), 310 (100); HRMS (EI) calcd for $C_{28}H_{36}O_7Si$ (M^+) 512.2230, found 512.2235. Anal. calcd for $C_{28}H_{36}O_7Si$: C, 65.63; H, 7.03. Found: C, 64.82; H, 7.35.

6,8-Dihydroxy-2-hydroxy-7*H*-1,2-dihydrofuro[3′,2′:4,5]-furo[2,3-*c*]xanthen-7-one; *O*-Methylsterigmatocystin Hydrate (30). To a 4 mL CH_3CN/CH_2Cl_2 solution (1:1) of cis and trans aldehydes **29** (25 mg, 0.048 mmol) was added 5 drops of TEA·$(HF)_3$. After 8.5 h, the reaction mixture was purified by flash chromatography (1−5% CH_3OH/CH_2Cl_2) to provide 15 mg (88%) of **30** as a mixture of *endo* and *exo* hemiacetals and open-form aldehydes in the form of a white solid: mp 238−239 °C (dec); $R_f = 0.38$ (5% CH_3OH/CH_2Cl_2); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.61 (s, 1H), 7.55 (t), 7.53 (t, $J = 8.4$ Hz, 1H), 7.0 (d), 6.96 (d, $J = 8.4$ Hz, 1H), 6.95 (d), 6.80 (d, $J = 8.8$ Hz, 1H), 6.45 (d, $J = 6$ Hz, 1H), 6.42 (d), 6.38 (s), 6.35 (s, 1H), 6.30 (s), 6.26 (s), 5.90 (d), 5.59 (d, $J = 4.4$ Hz, 1H), 5.40 (s, 1H), 4.15 (m), 3.86 (s, 3H), 3.82 (s, 3H), 3.61 (d, $J = 4$ Hz, 1H), 2.6−1.9 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 200.5, 173.8, 173.6, 173.5, 163.1, 163.0, 162.0, 161.8, 160.0, 159.8, 159.5, 156.2, 156.0, 152.7, 152.6, 152.4, 133.7, 133.6, 133.5, 113.2, 112.9, 112.7, 110.4, 108.8, 108.7, 107.7, 107.4, 107.1, 106.2, 106.1, 105.5, 104.4, 99.8, 99.7, 98.8, 95.9, 95.3, 89.9, 89.8, 56.0, 55.8, 42.5, 42.1, 37.4, 35.0, 28.5; IR ($CHCl_3$) 3684, 3599, 3023, 2928, 1705, 1598 cm^{-1}. MS (EI) *m/e* (rel inten) 356 (M^+, 100), 338 (44); HRMS (EI) calcd for $C_{19}H_{16}O_7$ (M^+) 356.0896, found 356.0899. Anal. calcd for $C_{19}H_{16}O_7$: C, 64.04; H, 4.49. Found: C, 62.31; H, 4.67. Second trial, found: C, 64.26; H, 5.55.

6,8-Dimethoxy-7*H*-furo[3′,2′:4,5]furo[2,3-*c*]xanthen-7-one; *O*-Methylsterigmatocystin (5). To 5 mL of CH_3CN were added hemiacetal **30** (15 mg, 0.042 mmol), PhSeH (0.02 mL, 0.188 mmol), 4 Å molecular sieves (30 mg), and trace Amberlyst 15 resin (about 10 beads). This suspension was stirred at room temperature for 72 h. A small amount of the hemiacetal **30** was still present, as observed by TLC, but this is due to gradual hydrolysis of the selenoacetal on SiO_2. The

reaction mixture was quickly filtered through a column of silica gel (eluted with 5% CH_3OH/CH_2Cl_2) providing 13 mg (62%) of pure selenoacetal **31** ($R_f = 0.8$, 5% CH_3OH/CH_2Cl_2) along with approximately 7 mg of product **31** mixed with hemiacetal **30**. To minimize the rapid product decomposition, **31** was carried to the next reaction without characterization. A 0 °C solution of **31** (10 mg, 0.02 mmol) in 2.6 mL of CH_2Cl_2 was treated with 4 Å molecular sieves (22 mg) and *m*-CPBA (57−86%, 11 mg, 0.065 mmol) in 0.8 mL CH_2Cl_2 (dried over sieves). After 20 min, the reaction was compared to an authentic sample of OMST **5** by TLC and deemed complete. The mixture was purified by flash chromatography (2−5% CH_3OH/CH_2Cl_2) to provide 3 mg (44%) of crude **5**. Further purification was carried out by HPLC to provide pure OMST **5** which was identical to an authentic sample in all respects:[63] HPLC: retention time = 13.7 min on a Spherex 5 C18 column (Phenomenex, 250 × 4.6 mm) eluted with 50% H_2O (0.1% TFA)/CH_3CN, 1 mL/min flow rate; coinjection with authentic sample confirmed identity; $R_f = 0.8$ (5% CH_3OH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, $J = 8.4$ Hz, 1H, *H*-10), 7.00 (d, $J = 8.4$ Hz, 1H, *H*-11), 6.81 (d, $J = 7.2$ Hz, 1H, *H*-3a), 6.80 (d, $J = 8$ Hz, 1H, *H*-9), 6.50 (t, $J = 2.4$ Hz, 1H, *H*-2), 6.41 (s, 1H, *H*-5), 5.48 (t, $J = 2.4$ Hz, 1H, *H*-1), 4.82 (dt, $J = 7,2$, 1.6 Hz, 1H, *H*-12c), 3.94 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3); UV λ_{max} (CH_3OH) nm: 236, 310; IR ($CHCl_3$) 3020, 2927, 2853, 1598, 1473 cm^{-1}. MS (EI) *m/e* (rel inten) 338 (M^+, 100), 323 (24), 309 (40); HRMS (EI) calcd for $C_{19}H_{14}O_6$ (M^+) 338.0790, found 338.0794.

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Supporting Information Available: Reproductions of ^{1}H and ^{13}C NMR spectra for compounds **12**, **16**-**19**, **23**, **26**, **28**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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