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Enantioselective Total Synthesis and Biological Evaluation of (+)-Kibdelone A and a Tetrahydroxanthone Analogue

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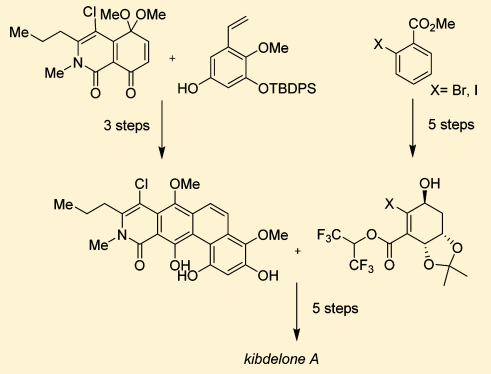
Supporting Information

ABSTRACT: The total synthesis of kibdelone A has been accomplished via In(III)-catalyzed arylation of a heterocyclic quinone monoketal and iodine-mediated oxidative photochemical electrocyclization for construction of the ABCD ring moiety. Enzymatic dihydroxylation of methyl 2-halobenzoate substrates was employed for synthesis of activated 2-halo-cyclohexene F-ring fragments. A one pot *oxa*-Michael/Friedel–Crafts process allowed access to the first simplified DEF ring analogues of the kibdelones.



INTRODUCTION

In the past decade, the polycyclic xanthone natural products have attracted significant attention from the scientific community because of the potential of several members of the family, including kibdelones A–C (**1**, **3**, **4**, Figure 1),[1] as antiproliferative agents. Although the exact mode of action of these natural products has yet to be determined, it is likely that their potent anticancer activity may be related to the presence of the C-7 substituted tetrahydroxanthone pharmacophore (Figure 1 highlighted in red).[2] In particular, kibdelones A–C (**1**, **3**, **4**) are active at low nanomolar concentrations against tumor cell lines, while the congener isokibdelone A (**2**) was found to be 10–200 fold less potent.[3] Both natural products possess a common ABCD core and diverge in their respective connectivity of the E/F rings (cf. **1** and **2**, Figure 1) and therefore substitution of the tetrahydroxanthone core.

Recently, we reported an approach to (+)-kibdelone C (**4**) utilizing Pt(IV)-mediated arylation of a quinone monoketal to construct the ABCD ring system, which was then further reacted with a chiral, nonracemic iodocyclohexene carboxylate EF ring synthon via site selective *oxa*-Michael reaction followed by Friedel–Crafts cyclization to construct the hexacyclic core.[4] Although our synthesis established one of the first routes to a nonfully aromatic polycyclic xanthone,[5] there was still room for improved synthetic access to this family of natural products to enable mode of action studies. In this paper, we report the total synthesis of kibdelone A employing In(III)-catalyzed arylation of a heterocyclic quinone monoketal for construction of the

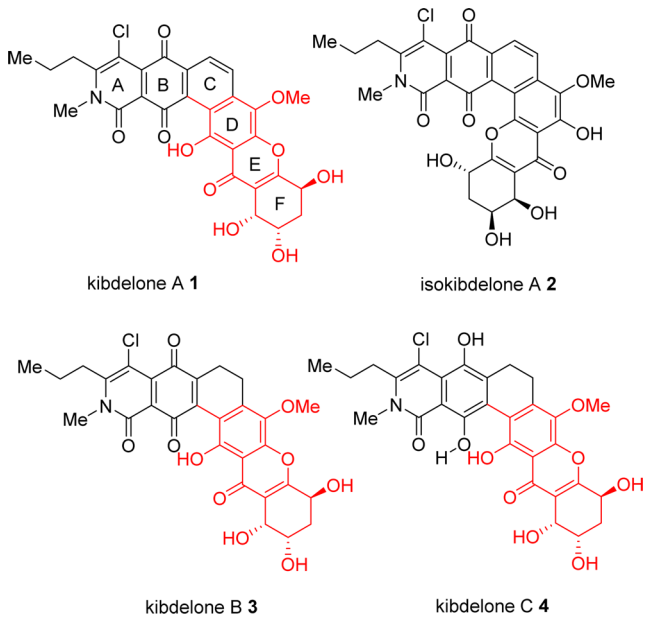


Figure 1. Structures of isolated polycyclic xanthone natural products.

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ABCD ring system. Enzymatic dihydroxylation of methyl 2-halobenzoate substrates was also successfully employed for synthesis of activated halo-cyclohexene F-ring fragments.

RESULTS AND DISCUSSION

Kibdelone A (**1**)[3] is known to be stable upon exposure to air or standing in solution in contrast to kibdelones B (**3**) and C (**4**), which have been shown to interconvert in alcoholic solvents to an equilibrium mixture of kibdelones A/B/C. Learning from our previous synthetic endeavors,[4] we wished to access the more stable congener kibdelone A **1** using a one pot *oxa*-Michael/Friedel−Crafts cyclization between phenanthrenetriol **5** and activated halocyclohexene ester synthon **6** to form the structurally challenging tetrahydroxanthone pharmacophore (Figure 2)

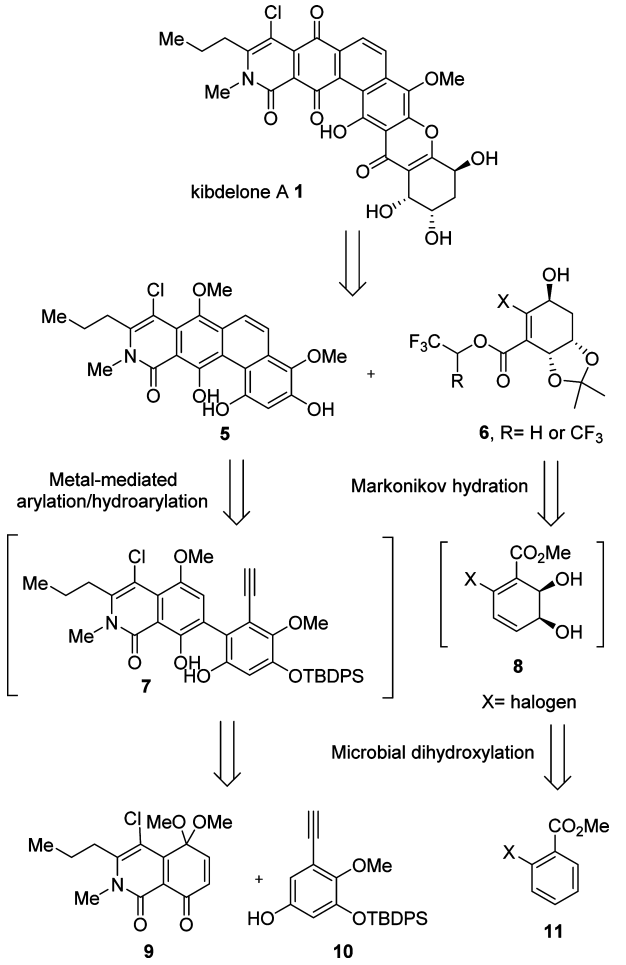
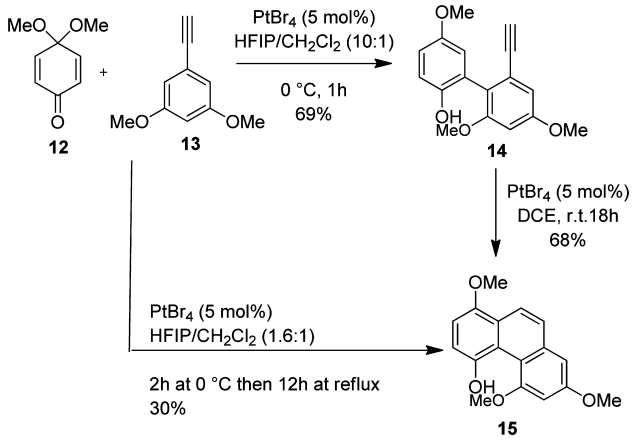


Figure 2. Retrosynthetic analysis for kibdelone A (**1**).

Activated chiral F-ring synthon **6** may be accessed via microbial dihydroxylation of methyl 2-halobenzoate **11** followed by acetonide formation and Markovnikov hydration of diol **8**.[6] As an initial synthetic approach, we envisioned that ABCD core structure **5** could be accessed utilizing a metal-mediated Friedel−Crafts/hydroarylation cascade between quinone monoketal **9** and aryl alkyne **10**.

We first studied the possibility for phenanthrene formation by a metal-mediated Friedel−Crafts/hydroarylation cascade of model quinone monoketal **12** and the commercially available aryl alkyne, 1-ethynyl-3,5-dimethoxybenzene **13** (Scheme 1).[7]

Scheme 1. Model Studies for Phenanthrene Formation



This study revealed that formation of biaryl **14** and hydroarylation to phenanthrene **15** could be achieved using $PtBr_4$ in a one- or two-pot process and that highly ionizing solvents such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)[8] and 2,2,2-trifluoroethanol (TFE) were critical for the biaryl formation; <30% yield of **14** and longer reaction times (12 h) were observed in the absence of fluorinated solvents. Other metals such as $InCl_3$ and $AuCl_3$ were found to catalyze the initial biaryl formation in high yield, but further hydroarylation was not observed.

In order to evaluate the Friedel−Crafts/hydroarylation cascade on the natural product system, alkyne **10** was synthesized in two steps from bromide **16**. Under optimized reaction conditions, we were able to construct alkynyl biaryl **7** in 62% yield by treatment of quinone monoketal **9**[4a] with aryl alkyne **10** using a catalytic amount of $AuCl_3$ in HFIP/DCE (10:1). However, further hydroarylation to the desired product **5** was not observed in any one- or two-pot processes attempted. Metals known to catalyze alkyne hydroarylation[9] with electron-rich, -neutral, or -poor systems including $PtBr_4$, $PtCl_2$, $PtCl_2(PhCN)_2/AgSbF_6$, $Au(PPh_3)Cl/AgSbF_6$, $AuCl_3$, $Fe(OTf)_3$, $FeCl_3$, $InCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, $RuCl_3$, $RhCl_3$, $ZrCl_4$, $Bi(OTf)_3$, and $GaCl_3$ were evaluated but afforded only the starting material (**7**) or the derived methyl ketone (**18**). Furthermore, metals known to generate metal vinylidenes[10] including $[RuCl_2(CO)_3]_2$, $RuClCp(PPh_3)_2NH_4PF_6$, $W(CO_5)\cdot THF$ and $Mo(CO)_6$ and $W(CO)_6$ were also evaluated but failed to generate the desired phenanthrene ring system via hydroarylation. We believe that the hydration of the alkyne was promoted by the B ring phenol rather than by water in the reaction. The latter was demonstrated by pretreatment of biaryl **7** to form the corresponding metal phenolate complexes ($Ti(iOPr)_4$, toluene; $B(OMe)_3$, benzene, reflux) and submitting these intermediates to hydroarylation conditions ($InCl_3$, toluene, 100 °C) which did not afford ketone product **18** (Scheme 2). The difference in reactivity between model substrate **14** and biaryl **7** to proceed in further hydroarylation may be explained in part by the net electron-withdrawing properties of the quinolinone ring of **7** relative to biaryl alkyne **14**.

As an alternative route, we considered access to the ABCD ring system through oxidative photochemical cyclization utilizing biaryl styrene **20** employed in our (+)-kibdelone C synthesis (Scheme 3). Treatment of quinone monoketal **9** with styrene **19** and $InCl_3$ (15 mol %) in 1:1 CH_3CN/HFIP led to the production of biaryl **20** in 70% yield. The current In(III)

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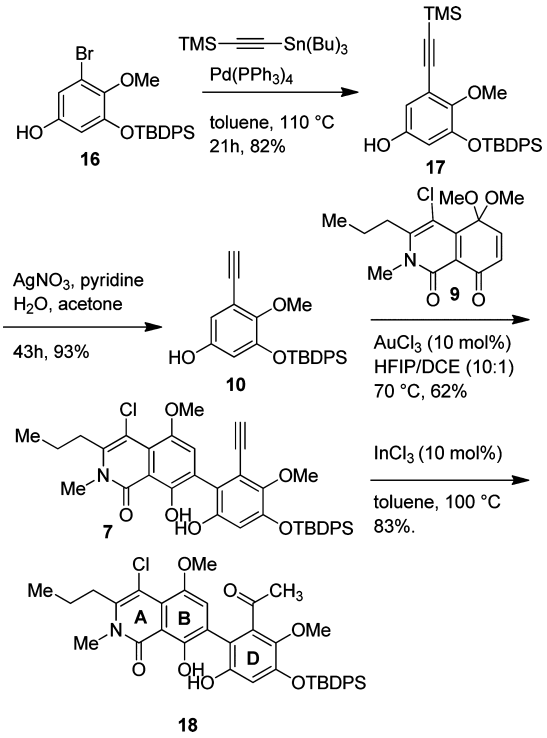
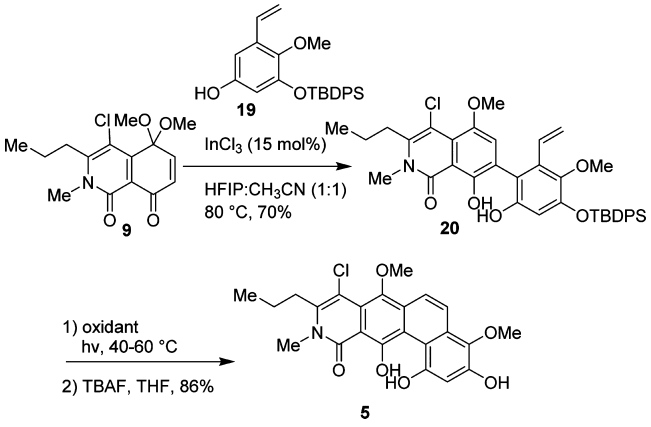
Scheme 2. First Approach to the ABCD Fragment of Kibdelone A and Isokibdelone A via a Friedel–Crafts/ Hydroarylation Cascade



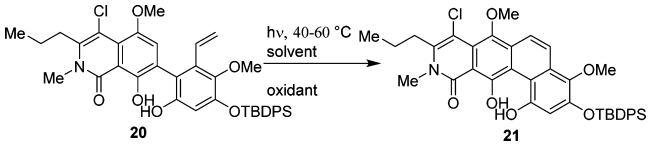
Scheme 3. Second-Generation Approach to ABCD triol 5 via Oxidative Photochemical Electrocyclization



conditions provide an alternative and robust catalyst system to the previously reported Pt(IV) methodology.[4a]

With biaryl **20** in hand, we evaluated construction of the C-ring of the ABCD core of kibdelone A (Table 1). Historically, air and iodine have been used as oxidants in photochemical, oxidative electrocyclization of stilbenes en route to various natural product systems.[11] For example, both the Kelly[12] and Mehta[13] groups employed oxidative photochemical cyclization in ambient air to construct the C-ring of cervinomycin A_2, although in both cases low yields were observed. Initial photochemical cyclization of substrate **20** with oxidants including oxygen and PIDA were unsuccessful. However, use of catalytic iodine gave the desired product **21** in 38% yield (entry 3, Table 1).

Table 1. Oxidative Photochemical Cyclization



entry	oxidant (equiv)	solvent	additive	yield[a] (%)
1	O_2	cyclohexane	none	0
2	PIDA (1.2)	cyclohexane	none	0
3	I_2 (0.1)	cyclohexane	none	38
4	I_2 (0.5)	cyclohexane	none	20
5	I_2 (1.0)	cyclohexane	none	10
6	I_2 (1.1)	toluene	THF (20 equiv)	73
7	I_2 (1.1)	THF	solvent	70

[a]Isolated yield of phenanthrene **21**.

In an attempt to optimize the photochemical cyclization, we increased the amount of iodine, which instead was found to decrease yield (entries 4 and 5, Table 1), likely because of product degradation by the generated hydrogen iodide.[11] Use of tetrahydrofuran as HI scavenger[11a] (entry 6, Table 1) was found to be effective and yielded the desired ABCD ring system (**21**) in 73% yield. Use of THF as solvent[14] (entry 7) was also found to give similar yields and enable more concentrated reaction conditions. The TBDPS protecting group of the ABCD ring system **21** was then removed with TBAF to afford the desired phenanthrene triol **5**[4a] in 86% yield (Scheme 3).

Our next goal was to establish whether the one pot *oxa*-Michael/Friedel–Crafts cyclization (Figure 2) between phenanthrenetriol **5** and activated halocyclohexene ester synthon **6** was a viable route to access the challenging tetrahydroxanthone core of kibdelone A (**1**). Such a route was attempted to circumvent use of an acid and heat sensitive vinylogous carbonate intermediate as employed in our (+)-kibdelone C[4b] synthesis. Furthermore, use of an activated ester (cf. Figure 2, **6**, R = H, CF_3) was deemed beneficial for the *oxa*-Michael reaction by lowering the LUMO of the Michael acceptor[15] and to provide a more active leaving group for Friedel–Crafts acylation.

For this study, the activated chiral F-ring synthons[4] (**25**–**27**, Scheme 4) were synthesized from diols **8a**/**8b** obtained by microbial dihydroxylation of methyl 2-halobenzoate substrates (**11a**,**b**) with toluene dioxygenase overexpressed in *E. coli* JM109 (pDTG601A).[16] Dihydroxylation of methyl 2-halobenzoate **11a**,**b** by whole-cell fermentation with *E. coli* JM 109 (pDTG601A) afforded a mixture of the corresponding diols **22a**,**b** and the desired diols **8a**,**b** in a 4:1 mixture if the halogen was iodine and in an improved ratio of 1:3.5 if the halogen was bromine.

Selectivity for diol formation can be explained by Boyd's rule,[17] which stipulates that the larger group directs the enzymatic dihydroxylation. In the case where X is iodine (**11a**), the halogen and not the methyl ester directs the enzymatic process and therefore provides the desired diol (**8a**) as the minor product.[6] Furthermore, the orientation of the benzoate during docking of the active site of the enzyme can also be influenced by the positive charge (δ+) of iodine.[6b] This is not the case when X is bromine (**11b**), and therefore better ratios for the desired diol (**8b**) are observed. The desired diols **8a**,**b** were then protected as acetonides followed by Markovnikov hydration[6a] using $Co(acac)_2$ to afford the methyl-ester F-ring synthons **23** and **24** in three steps.

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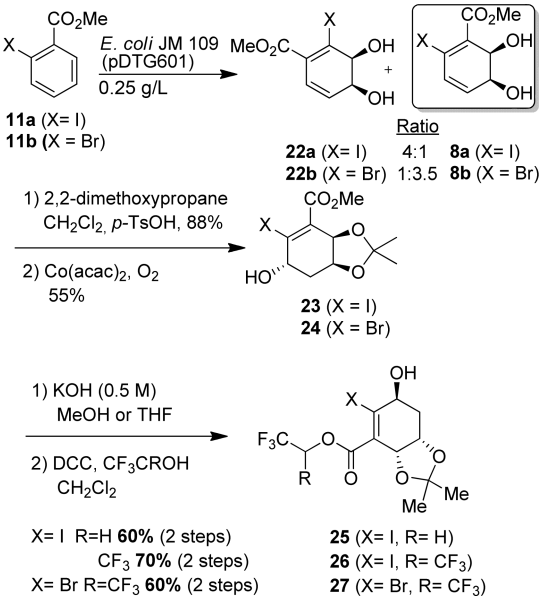
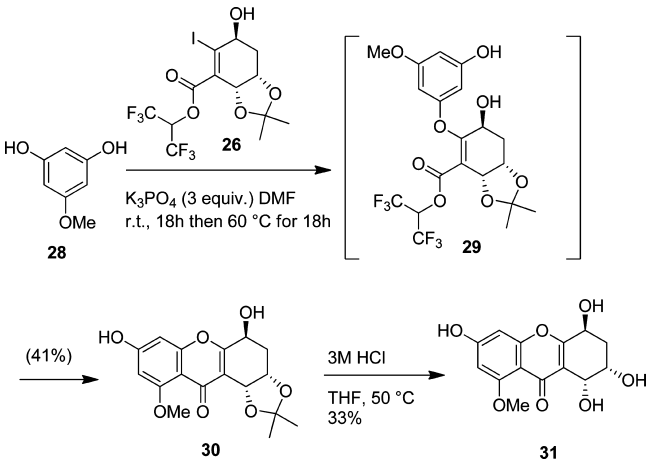
Scheme 4. Synthesis of Activated F-Ring Ester Intermediates by Microbial Dihydroxylation



Methyl esters (**23** and **24**) were subsequently transformed to the activated F-ring synthons (**25**–**27**) through a saponification/DCC coupling sequence with the corresponding fluorinated alcohols. A one pot *oxa*-Michael/Friedel–Crafts procedure was then attempted with the known monomethoxy phloroglucinol **28**[18] (Scheme 5). To our delight, careful

Scheme 5. One-Pot *oxa*-Michael/Intramolecular Friedel–Crafts Cyclization for Tetrahydroxanthone Formation



optimization utilizing the highly activated HFIP ester **26** led to the finding that tetrahydroxanthone formation under basic conditions was possible in a one pot process allowing us to avoid isolation of the acid and heat sensitive vinylogous carbonate (**29**). In addition, the *oxa*-Michael reaction proceeded in a site selective manner at room temperature, while the Friedel–Crafts cyclization required heating to 60 °C in the presence of K_3PO_4 to yield tetrahydroxanthone **30** in 41% yield. The requirement of base for the Friedel–Crafts cyclization was supported by the isolation of vinylogous carbonate **29** and its subsequent thermolysis in DMF (60 °C) which proved to be unfruitful.

Both one and two pot processes were also attempted with trifluoroethyl ester **25** but were found to be lower yielding for both the *oxa*-Michael and the Friedel–Crafts steps. Final deprotection of **30** was done under standard acetonide deprotection conditions to afford the simplified kibdelone tetrahydroxanthone analogue[2] **31**. The low yield for this transformation may be explained by the propensity of the chiral ring of the tetrahydroxanthone to eliminate water and rearomatize once deprotected.[5b]

We next evaluated use of the new activated F-ring synthons with the ABCD ring core triol of kibdelone A (**5**, Scheme 6). We found that iodo HFIP ester **26** displayed improved reactivity in the *oxa*-Michael fragment coupling with the ABCD ring core in comparison with our first generation F-ring methyl-ester (**23**) synthon, although a one pot process for tetrahydroxanthone formation was not observed. For example, treatment of **5** with **26** using K_3PO_4 in DMA at room temperature cleanly afforded adduct **34** in 61% yield, while reaction of methyl ester **23** under previously developed conditions for (+)-kibdelone C (DMSO, 60 °C)[4b] with methyl ester synthon **23** showed no reactivity. Both trifluoro and HFIP intermediates (**25**–**27**) proved to be quite reactive at room temperature using polar solvents with few differences observed between iodo and bromo derivatives. Further Friedel–Crafts cyclization was attempted using a one- or two-pot process with the natural product precursors (**33** and **34**) under thermal, Lewis acid-catalyzed, and *N*-methylimidazole-promoted conditions, but in these cases only starting material, aromatized F-ring, or retro-Michael products were observed. Accordingly, cyclization was performed using a two-step sequence via saponification/cyanuric chloride activation of vinylogous carbonates **33** and **34** in 52 and 42% yield over two steps, respectively. A three-step process bypassing isolation of the vinylogous carbonate from **5** and **25** or **26** was attempted but was found to be less effective (22 and 29% yields, respectively). Final deprotection of the acetonide moiety of the F-ring and oxidation of the B-ring using CAN in water/CH_3CN afforded kibdelone A (**1**) in good yield. A careful study of the pH of the final CAN oxidation revealed that acidic conditions such as AcOH in CH_3CN or CAN impregnated on silica in CH_2Cl_2, which were successful for the synthesis of (+)-kibelone C,[4b] were unfavorable because of the increased propensity for oxidation of the D ring.

Kibdelone A methyl ether **35** and simplified analogues (**30**, **31**, Scheme 5) were submitted to the NCI 60 cell-line panel for evaluation of the relevance of C-7 substituted tetrahydroxanthone pharmacophore to the anticancer activity of these natural products. Kibdelone A (**1**) had been previously tested as the natural product. Compound **35** (OMe-kibdelone A) was approximately equipotent with **1** with a mean GI_{50} value of 3.2 nM. Simplified analogues **30** and **31**, however, were found to be inactive at 10 μM. Coupled with the inactivity of tetracycle **5** and weak activity of C19–C20 saturated tetracyclic analogues **36** and **37** (Figure 3), both with a mean GI_{50} of 4.5 μM,[4a] it appears at this stage that the complete hexacyclic scaffold of the kibdelones may be required for optimum cell growth inhibition.

■ CONCLUSION

We have developed a new sequence for the construction of the ABCD rings systems of both kibdelone A and isokibdelone A using In(III)-catalyzed arylation of a heterocyclic quinone monoketal followed by iodine-mediated oxidative photochemical electrocyclization. Construction of the tetrahydrox-

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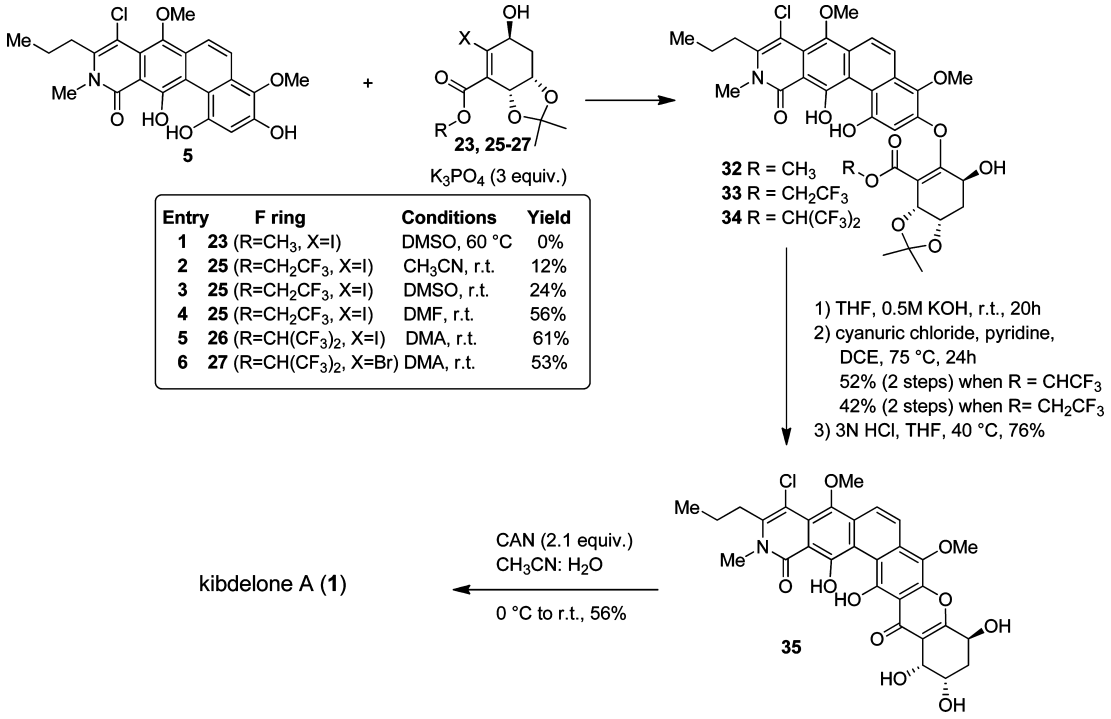
Scheme 6. Completion of the Synthesis of Kibdelone A (1)



Entry	F ring	Conditions	Yield
1	**23** (R=CH_3, X=I)	DMSO, 60 °C	0%
2	**25** (R=CH_2CF_3, X=I)	CH_3CN, r.t.	12%
3	**25** (R=CH_2CF_3, X=I)	DMSO, r.t.	24%
4	**25** (R=CH_2CF_3, X=I)	DMF, r.t.	56%
5	**26** (R=$CH(CF_3)_2$, X=I)	DMA, r.t.	61%
6	**27** (R=$CH(CF_3)_2$, X=Br)	DMA, r.t.	53%

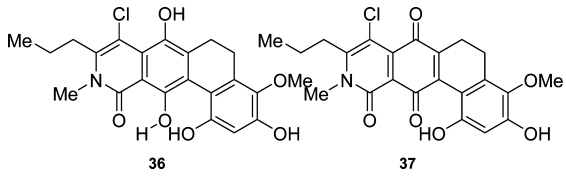


Figure 3. ABCD ring fragments of kibdelone and isokibdelone submitted to NCI 60-cell line screening.[4a]

anthone ring system for both kibdelone A and a simplified analogue has been accomplished utilizing trifluoro- and HFIP-ester activated iodo-cyclohexene derivatives formed from methyl 2-halobenzoates by enzymatic dihydroxylation. A one-pot *oxa*-Michael/Friedel–Crafts cyclization cascade process for tetrahydroxanthone formation was possible with simple phenols but was not viable with a kibdelone A ABCD ring fragment. Further studies on the synthesis of the kibdelones and analogues as well as additional biological studies are currently in progress and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were recorded at 400, 500, or 600 MHz at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded at 100, 125, or 151 MHz at ambient temperature with complete proton decoupling using $CDCl_3$ as the solvent unless otherwise stated. Infrared spectra were recorded on a FT-IR spectrophotometer. High-resolution mass spectra (HRMS) was carried out by electronic impact (EI) using a Q-TOF mass spectrometer. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200–400 mesh silica gel. Melting points were recorded on a Mel-temp apparatus. HPLC grade tetrahydrofuran, methylene chloride, diethyl ether, toluene, acetonitrile, and benzene were purchased and dried by passing through a PURE SOLV solvent purification system. Photochemistry experiments were performed using a Hanovia 450 W medium pressure mercury lamp housed in quartz immersion cooler with a system circulator. Analytical LC–MS was performed on an ultra performance liquid chromatography (UPLC) with a Binary solvent manager, SQ mass spectrometer, PhotoDiode Array detector, and evaporative light scattering detector (ELSD). An Acquity UPLC BEH C18 1.7 μm column was used for analytical UPLC–MS. Preparative HPLC separations were carried out on a Personal Purification System using a C18 column. Optical rotations were determined on an automatic digital polarimeter.

2′-Ethynyl-4′,5,6′-trimethoxy-[1,1′-biphenyl′]-2-ol (14). $PtBr_4$ (7.8 mg, 0.015 mmol) was added to a stirred solution of quinone monoketal **12**[19] (47 mg, 0.30 mmol) and 1-ethynyl-3,5-dimethoxybenzene **13** (148 mg, 0.915 mmol) in CH_2Cl_2 (0.27 mL)/HFIP (3.1 mL) at 0 °C for 1 h. The reaction mixture was concentrated under reduced pressure to a brown oil. The oil was purified on flash silica column using 0–50% EtOAc in hexanes to yield compound **14** as a yellow solid (60 mg, 69% yield): mp 110–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.94 (d, 1H, J = 8.8 Hz), 6.85 (dd, 1H, J = 8.8, 3.2 Hz), 6.82 (dd, 1H, J = 3.2 Hz), 6.80 (d, 1H, J = 2.4 Hz), 6.60 (d, 1H, J = 2.4 Hz), 4.82 (s, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 2.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.2, 157.7, 153.0, 147.5, 124.4, 123.7, 121.5, 117.0, 116.9, 115.1, 109.6, 100.6, 82.1, 80.7, 56.1, 55.7, 55.6; IR (film) ν_{max} 3462 (br), 3279, 2940, 2838, 1596, 1464, 1152, 1037; HRMS m/z calcd. for $C_{17}H_{17}O_4$ $(MH)^+$ 285.1127, found 285.1126.

1,5,7-Trimethoxyphenanthren-4-ol (15). Method from biaryl **14**: $PtBr_4$ (1.0 mg, 0.0019 mmol) was added to a stirred solution of biaryl **14** (10 mg, 0.035 mmol) in dichloroethane (3 mL) at room temperature. The resulting mixture was then stirred at this temperature for 18 h. The reaction mixture was concentrated under reduced pressure to a brown oil. The oil was taken up in CH_2Cl_2 and purified on a flash silica column using 0–25% EtOAc/hexanes to afford compound **15** as a bright orange oil (6.8 mg, 68% yield).

Method from quinone monoketal **12**: $PtBr_4$ (5.5 mg, 0.011 mmol) was added to a solution of quinone monoketal **12**[19] (330 mg, 2.14 mmol) and 1-ethynyl-3,5-dimethoxybenzene **13** (104 mg, 0.638 mmol) in CH_2Cl_2 (1 mL)/HFIP (1.7 mL) at 0 °C. The resulting solution was allowed to stir at room temperature for 2 h and was then heated under reflux for 12 h. The solution was concentrated under reduced pressure to afford a brown oil, which was purified on a flash silica column using a 0–25% EtOAc in hexanes to yield compound **15** as a bright orange oil (18.1 mg, 30% yield): ^{1}H NMR (400 MHz,

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$CDCl_3$) δ (ppm) 9.11 (s, 1H), 8.21 (d, 1H, J = 9.2 Hz), 7.54 (d, 1H, J = 9.2 Hz), 7.15 (d, 1H, J = 9.0 Hz), 7.01 (d, 1H, J = 2.5 Hz), 7.00 (d, 1H, J = 9.0 Hz), 6.85 (d, 1H, J = 2.5 Hz), 4.06 (s, 3H), 3,99 (s, 3H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ (ppm) 158.3, 155.5, 149.2, 147.6, 136.2, 125.7, 124.1, 122.4, 119.8, 115.6, 114.4, 107.6, 103.5, 101.7, 58.2, 56.4, 55.6; IR (film) ν_{max} 3301 (br), 3004, 2939, 2833, 1611, 1420, 1265, 1095, 740; HRMS m/z calcd. for $C_{17}H_{17}O_4$ $(MH)^+$ 285.1127, found 285.1128.

3-((*tert*-Butyldiphenylsilyl)oxy)-4-methoxy-5-((trimethylsilyl)ethynyl)phenol (17). A solution of bromide **16**[4a] (3.38g, 7.40 mmol) and trimethyl (tributylstannyl)ethynyl)silane[20] (8.27 mL, 22.2 mmol) in toluene (125 mL) was degassed for 5 min. $Pd(PPh_3)_4$ (0.651 g, 0.563 mmol) was added, and the solution was heated at reflux for 22 h. Water (300 mL) was added to the reaction mixture, and the product extracted with EtOAc (3 × 300 mL). The organics were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated to a brown oil. The oil was then purified on a flash silica column (0−10% EtOAc in hexanes) to afford compound **17** as a light orange oil/foam (2.89 g, 82% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.73−7.71 (m, 4H), 7.44−7.35 (m, 6H), 6.39 (d, 1H, J = 3.8 Hz), 6.01 (d, 1H, J = 3.8 Hz), 4.35 (s, 1H), 3.88 (s, 3H), 1.11 (s, 9H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 152.0, 149.2, 146.5, 135.5, 132.4, 130.1, 127.9, 118.2, 111.8, 109.5, 100.9, 98.5, 60.9, 26.5, 19.6, −0.04; IR (film) ν_{max} 3550−3200, 2958, 2896, 1592, 1461, 1426, 1062, 843; HRMS m/z calcd. for $C_{28}H_{35}O_3Si_2$ $(MH)^+$ 475.2125, found 475.2112

3-((*tert*-Butyldiphenylsilyl)oxy)-5-ethynyl-4-methoxyphenol (10). Silver nitrate (8.4 mg, 0.0493 mmol), H_2O (0.53 μL, 0.0294 mmol) and pyridine (1.6 μL, 0.0197 mmol) were added to a stirring solution of **17** (234 mg, 0.493 mmol) in acetone (5 mL), and the mixture was heated in the dark at 40 °C for 43 h. The resulting solution was concentrated under reduced pressure, diluted with EtOAc (50 mL) and washed with brine (25 mL). The aqueous phase was extracted twice more with EtOAc (50 mL). The organics were combined and dried over Na_2SO_4, filtered and concentrated to a light brown oil. The oil was purified on flash silica column using 10% EtOAc in hexanes to afford compound **10** as a beige foam (184 mg, 93% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.74−7.72 (m, 4H), 7.45−7.36 (m, 6H), 6.43 (d, 1H, J = 2.8 Hz), 6.03 (d, 1H, J = 2.8 Hz), 4.41 (br s, 1H), 3.91 (s, 3H), 3.22 (s, 1H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.9, 149.3, 146.9, 135.5, 132.3, 130.1, 127.9, 117.2, 111.9, 109.7, 80.9, 79.6, 61.2, 26.4, 19.5; IR (film) ν_{max} 3301 (broad), 3075, 3015, 2961, 2933, 2859, 1572, 1461, 1429, 1218, 751; HRMS m/z calcd. for $C_{25}H_{27}O_3Si$ $(MH)^+$ 403.1729, found 403.1721.

TBDPS Biaryl Alkyne 7. $AuCl_3$ (5.4 mg, 0.0176 mmol) was added to a stirring solution of quinone monoketal **9**[4a] (55.0 mg, 0.180 mmol) and phenol **10** in HFIP (7.6 mL)/DCE (0.8 mL). The resulting solution was degassed for 15 min and was then heated at 70 °C for 39 h. The resulting solution was then concentrated under reduced pressure to afford a brown oil. The oil was purified on a flash silica column using 0−20% EtOAc in hexanes to yield **7** as an orange oil (75 mg, 62% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 14.86 (s, 1H), 7.80−7.76 (m, 4H), 7.53 (s, 1H), 7.44−7.38 (m, 6H), 6.58 (s, 1H), 6.34 (s, 1H), 3.98 (s, 3H), 3.87 (s, 3H), 3.64 (s, 3H), 3.20 (s, 1H), 2.97−2.94 (m, 2H), 1.69−1.65 (m, 2H), 1.15 (s, 9H), 1.10 (t, 3H, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.6, 151.3, 150.4, 149.3, 148.3, 146.3, 140.9, 135.6, 135.5, 132.4, 132.1, 130.1, 130.1, 127.9, 127.9, 126.4, 125.5, 120.8, 120.8, 116.8, 112.2, 111.1, 110.5, 84.3, 79.5, 61.1, 58.5, 32.6, 31.9, 26.5, 20.8, 19.6, 14.1; IR (film) ν_{max} 3301 (broad), 3017, 2961, 2933, 2860, 1573, 1461, 1428, 1219, 753; HRMS m/z calcd. for $C_{39}H_{40}ClNO_6SiNa$ $(M + Na)^+$ 704.2211, found 704.2198.

Biaryl Methyl Ketone 18. $InCl_3$ (0.47 mg, 0.00212 mmol) was added to a stirring solution of biaryl alkyne **7** (14.5 mg, 0.0213 mmol) in toluene (1.5 mL). The resulting mixture was stirred for 30 min at room temperature and subsequently heated at 80 °C for 1.5 h and then at 100 °C for 16 h. The solution was concentrated under reduced pressure to afford a brown oil, which was purified on a flash silica column (0−20% EtOAc in hexanes) to afford compound **18** as a light yellow foam (12.3 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 14.60 (s, 1H), 7.80−7.74 (m, 4H), 7.46−7.38 (m, 6H), 7.09 (s, 1H), 6.29 (s, 1H), 6.15 (s, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.65 (s, 3H), 2.98−2.93 (m, 2H), 2.15 (s, 3H), 1.72−1.63 (m, 2H), 1.14 (s, 9H), 1.10 (t, 3H, J = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.1, 165.4, 151.4, 150.3, 149.6, 146.7, 141.1, 141.0, 138.1, 135.5, 135.5, 132.1, 132.1, 130.1, 130.1, 127.9, 127.9, 125.3, 124.2, 119.8, 114.0, 111.2, 110.8, 110.5, 62.4, 58.1, 32.6, 32.2, 32.0, 26.6, 20.8, 19.5, 14.1; IR (film) ν_{max} 3004, 2959, 2932, 2860, 1700, 1630, 1572, 1460, 1428, 1237, 1220, 753; HRMS m/z calcd. for $C_{39}H_{43}ClNO_7Si$ $(MH)^+$ 700.2497, found 700.2478.

Biaryl Styrene 20. $InCl_3$ (54.0 mg, 0.244 mmol) was added to a stirring solution of quinone monoketal **9**[4a] (0.508 g, 1.63 mmol) and styrene **19**[4a] (16.3 mmol) in a 1:1 HFIP (50 mL)/ CH_3CN (50 mL) previously degassed with argon for 30 min. The reaction mixture was then heated at 80 °C for 45 h. The solution was allowed to cool to room temperature and was then concentrated to afford a brown foam. The foam was purified on a flash silica column using 0−20% EtOAc in hexanes to afford compound **20**[4a] as an orange foam (0.783 g, 70% yield).

Phenanthrene 21. Biaryl styrene **20** (111 mg, 0.162 mmol) in THF (32 mL) was placed in a Pyrex tube and degassed for 15 min. I_2 (46.0 mg, 0.180 mmol) was added to the mixture, and the reaction was stirred for 5 min. The resulting solution was irradiated with Hanovia mercury lamp (hot water changed every hour) for 5 h. The solution was quenched with a saturated solution of sodium thiosulfate (25 mL) and extracted into EtOAc (3 × 50 mL). The organics were then dried over Na_2SO_4, filtered, and concentrated to afford a yellow brown oil. The oil was purified on a flash silica column using 0−30% EtOAc in hexanes to afford compound **21**[4a] as a bright yellow solid.

For toluene/THF preparation (Table 1, entry 6): Biaryl styrene **20** (199 mg, 0.291 mmol) was separated into 2 Pyrex tubes and then dissolved in toluene (55 mL each tube) and degassed for 30 min. THF (0.25 mL, 6.2 mmol) and I_2 (41 mg each, 82 mg total, 0.32 mmol) were added, and the reaction stirred for 5 min. The resulting solution was irradiated with Hanovia mercury lamp (hot water changed every hour) for 6 h. The reaction mixture was then dissolved with toluene, washed with an aqueous saturated sodium thiosulfate solution (50 mL) and dried over Na_2SO_4, filtered, and concentrated to afford a brown yellow oil. The oil was purified on flash silica column using a 0−20% EtOAc in hexanes solvent system to yield **21**[4a] as a bright yellow solid.

Phenanthrene 5. TBAF (0.25 mL, 1.0M, 0.25 mmol) was added to a stirring solution of phenanthrene **21** (144 mg, 0.211 mmol) in THF (7 mL) at 0 °C. The resulting solution was stirred for 1.5 h at this temperature. A saturated aqueous ammonium chloride solution was then added, and the reaction mixture was extracted with EtOAc (2 × 25 mL). The organics were then dried over Na_2SO_4, filtered, and concentrated to a yellow oil. The oil was purified on flash silica column using 0−20% EtOAc in CH_2Cl_2 as solvent to afford compound **5**[4a] as a bright yellow solid.

(3*S*,4*S*)-Methyl 3,4-dihydroxy-2-iodocyclohexa-1,5-dienecarboxylate (22a), (5*S*,6*R*)-Methyl 5,6-dihydroxy-2-iodocyclohexa-1,3-dienecarboxylate (8a). In a 12-L fermentation culture of grown *E. coli* JM109 (pDTG601) cells was added 15 g of methyl 2-iodobenzoate (**11a**) in 1 g portions over 3 h.[16c] At the end of addition, the cells were separated from the broth by centrifugation at 7000 rpm for 20 min. The cell-free broth was extracted three times with a total of 8 L of base-washed. Evaporation of the EtOAc extract afforded 3.5 g of diols **22a** and **8a**, in a 4:1 ratio, as determined by ^{1}H NMR analysis. These diols were separated by column chromatography on water deactivated silica gel (10% w/w) using 3:2 EtOAc/hexanes as eluent to afford 2.4 g of **22a** (8.1 mmol, 14.3% yield) as a yellow oil and 0.6 g of **8a** (2.0 mmol, 3.5% yield). Attempts to completely remove the solvent from **8a** resulted in aromatization, and thus the material was taken on directly to the next step. The amount of **8a** used in the acetonide formation was estimated from the amount of **22a** recovered using the 4:1 ratio obtained previously.

(3*S*,4*S*)-Methyl 3,4-dihydroxy-2-iodocyclohexa-1,5-dienecarboxylate (22a). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 6.19 (d, 1H, J = 9.8 Hz), 6.11 (dd, 1H, J = 9.8, 3.8 Hz), 4.42 (m, 1H), 4.36 (t,

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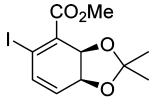
1H, J = 6.6 Hz), 3.83 (s, 3H), 3.12 (br d, 1H, J = 7.6 Hz), 2.59 (br d, 1H, J = 7.2 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 166.0, 134.3, 129.3, 123.9, 111.2, 75.88, 67.2, 52.4; IR (film) 3346, 2950, 2919, 1722, 1553, 1435, 1250 cm^{-1}; MS (EI) m/z (%) $[M]^+$ 296 (12), 278 (83), 264 (38), 247 (90), 231 (31), 137 (100), 109 (95), 92 (43), 81 (89), 63 (35), 59 (38), 53 (62); HRMS m/z calcd. for $C_8H_9IO_4$ 295.9546, found 295.9538; $[\alpha]_D^{20}$ +50 (c 1.7, CH_2Cl_2).

(3a*R*,7a*S*)-Methyl 5-iodo-2,2-dimethyl-3a,7a-dihydrobenzo-[*d*][1,3]dioxole-4-carboxylate (38).



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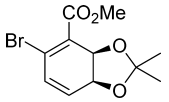
A catalytic amount of *p*-TsOH was added to a stirred solution of diol **8a** (20 mg, 0.07 mmol) and dimethoxypropane (1 mL) in CH_2Cl_2 (1 mL). The reaction was monitored by TLC analysis (1:1 EtOAc/hexanes). After consumption of starting material, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 1.0 M NaOH (1 mL), and dried over anhydrous $MgSO_4$. The filtrate was concentrated in vacuo and further purified by column chromatography on silica gel (1:1 EtOAc/hexanes) to afford acetonide **38** as an oil (20 mg, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.52 (d, 1H, J = 9.9 Hz), 5.79 (dd,1H, J = 9.9, 3.6 Hz), 4.98 (d, 1H, J = 8.1 Hz), 4.78 (dd, 1H, J = 8.1, 3.6 Hz), 3.87 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.4, 135.3, 131.5, 130.3, 106.6, 101.2, 71.5, 70.7, 52.3, 26.7, 25.4; IR (film) 3437, 2987, 1715, 1631, 1241, 1040 cm^{-1}; MS (EI) m/z (%) 335 (20), 279 (32), 278 (46), 247 (40), 246 (15), 152 (34); HRMS m/z calcd. for for $C_{11}H_{13}IO_4$ 335.9864, found 335.9859; $[\alpha]_D^{20}$ +71 (c 2.0, CH_2Cl_2).

(3a*R*,6*S*,7a*S*)-Methyl-6-hydroxy-5-iodo-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxole-4-carboxylate (23). To a stirred solution of acetonide **38** (20 mg, 0.06 mmol) in isopropanol (1 mL) was added cobalt acetylacetonate (3 mg, 0.01 mmol). The resulting solution was evacuated/refilled with oxygen gas three times and was stirred under an atmosphere of oxygen at 75 °C for 1 h. The mixture was allowed to cool to room temperature, the solvent was removed in vacuo, and the crude residue purified by chromatography on silica gel using mixture of hexane/EtOAc (2:1) as eluant to afford alcohol **23** as a white solid (13 mg, 62% yield), whose physical and spectroscopic properties were identical to those previously published:[4b] mp = 62−64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.86 (dd, 1H, J = 5.1, 1.8 Hz), 4.54 (m, 1H), 4.40 (m, 1H), 3.88 (s, 3H), 2.64 (dt, 1H, J = 14.4, 4.8 Hz), 2.46 (d, 1H, J = 4.8 Hz), 1.90 (m, 1H) 1.39 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 137.9, 115.2, 109.8, 74.1, 71.9, 68.3, 52.5, 33.1, 27.5, 26.4; $[\alpha]_D^{20}$ +170 (c 0.25, $CHCl_3$).

(5*S*,6*R*)-Methyl 5,6-dihydroxy-2-bromocyclohexa-1,3-dienecarboxylate (8b), and (3*S*,4*S*)-Methyl 3,4-dihydroxy-2-iodocyclohexa-1,5-dienecarboxylate (22b). Similarly, when 15 g of methyl 2-bromobenzoate **11b** was used as substrate, 4.0 g of diols **22b** and **8b** in a 1:3.5 ratio was obtained. These diols were separated by column chromatography on water deactivated silica gel (10% w/w) using 3:2 EtOAc/hexanes as eluent to afford 2.8 g of **22b**, as a yellow oil and 0.8 g of **8b**, which is unstable and hence converted directly to the acetonide. The amount of **8b** used in the acetonide formation was estimated from the amount of **22b** recovered using the 1:3.5 ratio obtained previously.

(5*S*,6*R*)-Methyl 2-bromo-5,6-dihydroxycyclohexa-1,3-dienecarboxylate (8b). mp 106−109 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 6.17 (dd, 1H, J = 10.0, 2.5 Hz), 6.04 (ddd, 1H, J = 10.0, 2.5, 1.3 Hz), 4.57 (m, 1H), 4.49 (m, 1H), 3.85 (s, 3H), 3.00 (br d, 1H, J = 7.9 Hz), 2.97 (br s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 166.6, 137.5, 130.0, 128.0, 127.3, 68.4, 68.1, 52.3; IR (KBr) 3402, 1703, 1437, 1314, 1234, 1048 cm^{-1}; MS (EI) m/z (%) 248 (9), 218 (38), 216 (47), 190 (82), 189 (53), 188 (85), 187 (48), 109 (71), 108 (31), 81 (100), 65 (79), 59 (45), 53 (54); HRMS m/z calcd. for $C_8H_9BrO_4$ 247.9684, found 247.9679; $[\alpha]_D^{20}$ = +29 (c 1.0, CH_2Cl_2).

(3a*R*,7a*S*)-Methyl 5-bromo-2,2-dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxole-4-carboxylate (39).



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^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.17 (d, J = 0.72 Hz, 1H), 5.94 (dd, 1H, J = 9.87, 3.36 Hz), 4.99 (d, 1H, J = 8.04 Hz), 4.75 (m, 1H), 3.82 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 165.8, 131.3, 129.9, 125.8, 125.7, 106.5, 72.1, 70.6, 52.2, 26.7, 25.2; IR (film) ν 2988, 2951, 1725, 1639, 1582, 1434 cm^{-1}; MS (EI) m/z (%) 275 (24), 273 (25), 233 (41), 231 (45), 201 (28), 199 (28), 108 (33); HRMS m/z calcd. for $C_{11}H_{13}BrO_4$ 287.9997, found 287.9994; $[\alpha]_D^{20}$ +286 (c 1.1, CH_2Cl_2).

(3a*R*,6*S*,7a*S*)-Methyl-5-bromo-6-hydroxy-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxole-4-carboxylate (24). To a stirred solution of acetonide **39** (50 mg, 0.17 mmol) (derived from diol **8b**) in isopropanol (2 mL) was added cobalt acetylacetonate (6 mg, 0.02 mmol). The resulting solution was evacuated/refilled with oxygen three times and was stirred under an atmosphere of oxygen at 75 °C for 1 h. The mixture was allowed to cool to room temperature, the solvent was removed in vacuo, and the crude residue purified by chromatography on silica gel using mixture of hexanes/EtOAc (2:1) as eluant to afford alcohol **24** as a viscous oil (37 mg, 70% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.89 (dd, 1H, J = 1.8, 5.1 Hz), 4.51 (m, 1H), 4.48 (m, 1H), 3.87 (s, 3H), 2.66 (m, 1H), 1.86−1.94 (m, 2H), 1.39 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 162.2, 132.9, 131.8, 109.8, 74.4, 71.7, 66.5, 52.4, 33.2, 27.6, 26.3; IR (film) ν_{max} 3432 (br), 2987, 2935, 1727, 1643, 1239, 1039, 731; HRMS m/z calcd. for $C_{10}H_{12}BrO_5$ (M − CH_3) 290.9868, found 290.9881 (4.4 ppm).

Iodocyclohexene Acetonide Trifluorocarboxylate 25. 0.5 M KOH (4.1 mL) was added to a stirring solution of methyl ester **23** (229 mg, 0.647 mmol) in MeOH (2.2 mL) at room temperature. The resulting solution was stirred for 20 h. The solution was then acidified to pH 2 using a 0.5 M HCl solution and extracted into EtOAc (3 × 50 mL). The organics were then dried over Na_2SO_4, filtered and concentrated to a yellow oil. DMAP (11.2 mg, 0.097 mmol) and 2,2,2-trifluoroethanol (0.24 mL, 3.30 mmol) were added to a stirring solution of the crude oil in dichloromethane (13 mL). The resulting solution was cooled to 0 °C, and DCC (147 mg, 0.712 mmol) was added. The reaction mixture was slowly allowed to warm up to rt and continued to stir for 40 h. The reaction mixture was then filtered through Celite and concentrated under reduced pressure to yield an orange oil. The solid was purified on a flash silica column using 0−15% EtOAc in CH_2Cl_2 to yield **25** as light yellow oil (0.423 g, 60%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.68 (dq, 1H, J = 12.7, 8.4 Hz), 4.60−4.49 (m, 1H), 4.43−4.34 (m, 2H), 2.66 (dt, 1H, J = 14.3, 4.8 Hz), 2.45 (d, 1H, J = 4.8 Hz), 1.91 (ddd, 1H, J = 14.2, 9.5, 2.5 Hz), 1.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.9, 136.9, 122.8 (J = 221 Hz), 116.8, 110.0, 74.0, 72.0, 68.3, 60.99 (J = 30 Hz), 32.9, 27.3, 26.3; ^{19}F (ppm) −73.2; IR (film) ν_{max} 3565−3339, 2986, 2936, 2874, 1744, 1285, 1226, 1167, 1073; HRMS m/z calcd. for $C_{12}H_{13}F_3IO_4$ ($MH^+ - H_2O$) 405.9889, found 405.9894; $[\alpha]_D^{23}$ = +47° (c = 0.1, $CHCl_3$).

Iodocyclohexene Acetonide Hexafluoro-carboxylate 26. A 0.5 M aqueous KOH solution (3.9 mL) was added to a stirring solution of methyl ester **23** (191 mg, 0.321 mmol) in MeOH (1.8 mL) at room temperature. The resulting solution was stirred for 2 h. The solution was then acidified to pH 2 using a 0.5 M HCl solution and extracted into EtOAc (3 × 50 mL). The organics were then dried over Na_2SO_4, filtered and concentrated to a light yellow oil. DMAP (6.6 mg, 0.054 mmol) and hexafluoroisopropanol (0.29 mL, 2.8 mmol) were added to a stirring solution of the crude oil in dichloromethane (11 mL). The resulting solution was cooled to 0 °C and DCC (122 mg, 0.592 mmol) was added. The reaction mixture was slowly allowed to warm up to rt and continued to stir for 14 h. The reaction mixture was then filtered through Celite and concentrated under reduced pressure to yield a white solid. The solid was purified on a flash silica

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column using a 0−10% EtOAc in CH_2Cl_2 solvent system to yield **26** as a yellow oil (0.184 g, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.81 (hept, 1H, J = 6.0 Hz), 4.75 (dd, 1H, J = 5.1, 1.8 Hz), 4.48 (td,1H, J = 4.6, 2.4 Hz), 4.34 (dtd,1H, J = 10.1, 5.1, 1.8 Hz), 2.62 (dt, 1H, J = 14.5, 5.1 Hz), 2.45 (br s, 1H), 1.87 (ddd, 1H, J = 14.5, 9.6, 2.4 Hz), 1.28 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.3, 136.1, 120.3 (q, J = 225 Hz), 118.3, 110.2, 74.0, 72.0, 68.3, 67.0 (sept, J = 28 Hz), 32.7, 27.3, 26.3; ^{19}F (ppm) −72.1, −72.9; IR (film) ν_{max} 2995, 1762, 1383, 1224, 1110, 1074; $[\alpha]_D^{23}$ = +134° (c = 0.1, $CHCl_3$).

Bromocyclohexene Acetonide Hexafluoro-carboxylate 27. A 0.5 M aqueous KOH solution (1.2 mL) was added to a stirring solution of methyl ester **24** (48 mg, 0.157 mmol) in THF (1.5 mL) at room temperature. The resulting solution was stirred for 20 h. The solution was then acidified to pH 2 using 0.5 M HCl and extracted into EtOAc (3 × 50 mL). The organics were then dried over Na_2SO_4, filtered, and concentrated to a light yellow oil. DMAP (2.9 mg, 0.024 mmol) and hexafluoroisopropanol (0.08 mL, 0.80 mmol) were added to a stirring solution of the crude oil in CH_2Cl_2 (3.6 mL). The resulting solution was cooled to 0 °C, and DCC (39 mg, 0.19 mmol) was added. The reaction mixture was slowly allowed to warm up to rt and continued to stir for 14 h. The reaction mixture was then filtered through Celite and finally concentrated under reduced pressure to yield a white solid. The solid was purified on a flash silica column using a 0−20% EtOAc in hexanes solvent system to yield **27** as a clear oil (41 mg, 60%): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 5.87 (hept, 1H, J = 6.0 Hz), 4.87 (dd, 1H, J = 5.0, 1.9 Hz), 4.53 (td, 1H, J = 4.6, 2.4 Hz), 4.49 (dq, 1H, J = 6.2, 3.9, 2.4 Hz), 2.82 (d, 1H, J = 4.1 Hz), 2.69 (ddd, 1H, J = 14.4, 5.6, 4.2 Hz), 1.93 (ddd, 1H, J = 14.4, 9.5, 2.5 Hz), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz) δ (ppm) 162.7, 136.0, 129.9, 120.3 (q, J = 223 Hz), 110.2, 76.7, 74.2, 71.7, 66.5, 66.9 (quint, J = 28 Hz), 32.8, 27.3, 26.2; ^{19}F (ppm) −72.4, −73.0; IR (film) ν_{max} 2993, 2937, 2856, 1763, 1238, 1196, 111, 1076; $[\alpha]_D^{23}$ = +95° (c = 0.1, $CHCl_3$).

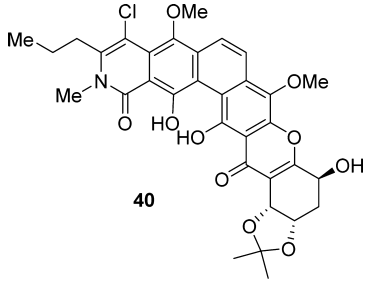
(3a*S*,5*S*,11b*R*)-5,8-Dihydroxy-10-methoxy-2,2-dimethyl-3a,4,5,11b-tetrahydro-11*H*-[1,3]dioxolo[4,5-a]xanthen-11-one (30). DMA (1.0 mL, previously freeze pumped thawed) was added to a purged flask with argon containing monomethoxy phloroglucinol **28**[18] (5.6 mg, 0.040 mmol), HFIP ester **26** (9.7 mg, 0.020 mmol), and K_3PO_4 (12.6 mg, 0.059 mmol). The solution was stirred at room temperature for 18 h. The reaction mixture was then heated at 60 °C for 18 h. The solution was dissolved in EtOAc (10 mL), and an aqueous saturated solution of NH_4Cl was added. The resulting mixture was concentrated under reduced pressure (genevac) and redissolved in EtOAc, filtered through cotton and concentrated under reduced pressure to a light brown oil. The oil was purified by column chromatography (30% EtOAc in CH_2Cl_2 to 100% EtOAc then 5−15% MeOH in EtOAc) to yield **30** as a white foam (2.7 mg, 41%): ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 6.47 (d, 1H, J = 2.1 Hz), 6.40 (d, 1H, J = 2.2 Hz), 5.32 (dd,1H, J = 6.0, 0.8 Hz), 4.73 (dd, 1H, J = 9.0, 5.0 Hz), 4.64 (td, 1H, J = 5.5, 3.1 Hz), 3.89 (s, 3H), 2.45 (dt, 1H, J = 13.8, 5.1 Hz), 1.95 (ddd, 1H, J = 13.8, 9.0, 3.3 Hz), 1.42 (s, 3H), 1.31 (s, 3H).^{13}C NMR (100 MHz, CD_3OD) δ (ppm)179.8, 163.6, 163.4, 161.2, 159.5, 115.8, 108.3, 107.0, 96.1, 94.9, 70.9, 69.4, 62.2, 55.0, 34.3, 26.4, 24.4; IR (film) ν_{max} 2925, 1625, 1580, 1500, 1467, 1331, 1203, 1078; HRMS m/z calcd. for $C_{17}H_{19}O_7$ $(MH)^+$ 335.1131, found 335.1121 $[\alpha]_D^{23}$ = +4° (c = 0.05, MeOH).

(1*R*,2*S*,4*S*)-1,2,4,6-Tetrahydroxy-8-methoxy-1,2,3,4-tetrahydro-9*H*-xanthen-9-one (31). 0.37 mL of an aqueous 3 N HCl solution was added to a stirring solution of tetrahydroxanthone **30** (3.4 mg, 0.010 mmol) in THF (1.9 mL). The resulting mixture was degassed for 15 min and heated at 50 °C for 30 min. The reaction mixture was allowed to cool to room temperature and diluted with EtOAc (5 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated to a brownish white solid. The solid was purified by preparative HPLC using a 2−90% CH_3CN/water gradient to afford **31** as a clear/whitish oil (1.0 mg, 33%): ^{1}H NMR (500 MHz, CD_3OD) δ (ppm) 6.36 (d, 1H, J = 2.1 Hz), 6.34 (d, 1H, J = 2.1 Hz), 4.90 (d, 1H, J = 3.6 Hz), 4.66 (dd, 1H, J = 4.9, 2.7 Hz), 4.07 (dt, 1H, J = 11.7, 3.5 Hz), 3.88 (s, 3H), 2.34 (td, 1H, J = 12.7, 4.9 Hz), 1.93 (d, 1H, J = 13.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 177.0, 161.4, 161.2, 161.2, 159.9, 118.0, 102.0, 96.7, 95.3, 65.3, 64.9, 62.9, 54.9, 33.3; IR (film) ν_{max} 3600−3100 (br), 1653, 1614, 1434, 1204, 1092, 1040; $[\alpha]_D^{23}$ = +42° (c = 0.1, MeOH).

Vinylogous Carbonate 33. Phenanthrene **5**[4a] (7.1 mg, 0.046 mmol) was dissolved in DMF (1.0 mL) and added to an argon purged flask containing trifluoroethylester **25** (6.8 mg, 0.016 mmol) and K_3PO_4 (9.3 mg, 0.044 mmol), and the solution was stirred at rt for 30 h. The reaction mixture was then dissolved in EtOAc (5 mL), cooled to 0 °C, acidified with 0.5 N $KHSO_4$, and extracted with EtOAc (3 × 5 mL). The organics were combined, dried over Na_2SO_4, filtered, and concentrated to a brown oil. The oil was purified on a flash silica column (0−20% EtOAc in CH_2Cl_2) to yield **33** as a yellow foam (6.6 mg, 56%): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 17.95 (s, 1H), 10.11 (s, 1H), 8.20 (d, 1H, J = 9.5 Hz), 8.13 (d, 1H, J = 9.5 Hz), 7.10 (s, 1H), 5.18 (dd, 1H, J = 5.5, 0.9 Hz), 4.72−4.61 (m, 2H), 4.61−4.51 (m, 1H), 4.47−4.44 (m, 1H), 4.00 (s, 3H), 3.91 (s, 3H), 3.75 (s, 3H), 3.18 (d, 1H, J = 3.1 Hz), 3.08−3.01 (m, 2H), 2.28 (ddd, 1H, J = 13.9, 7.4, 4.9 Hz), 2.05−1.98 (m, 1H), 1.76 (dq, 2H, J = 15.2, 7.4 Hz), 1.53 (s, 3H), 1.43 (s, 3H), 1.16 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.8, 164.1, 162.7, 154.2, 152.9, 146.2, 142.7, 140.4, 138.8, 133.1, 128.4, 125.1, 124.5 (d, J = 79 Hz), 123.2, 121.2, 117.7, 117.2, 111.1, 110.4, 110.2, 109.5, 107.0, 72.7, 70.7, 63.9, 62.9, 62.8, 60.2 (q, J = 29 Hz), 33.9, 32.5, 32.1, 28.1, 26.1, 21.0, 14.1; ^{19}F (ppm) −73.6; IR (film) ν_{max} 2970, 2936, 2874, 2856, 1739, 1588, 1411, 12283, 1163, 1003; HRMS m/z calcd. for $C_{35}H_{36}ClF_3NO_{11}$ $(MH)^+$ 738.19299, found 738.1898; $[\alpha]_D^{23}$ = −34° (c = 0.1, $CHCl_3$).

Vinylogous Carbonate 34. HFIP ester **26** (44 mg, 0.090 mmol) was dissolved in DMA (4 mL) and added to a stirring solution of phenanthrene **5** (44 mg, 0.100 mmol) and K_3PO_4 (57 mg, 0.27 mmol) in DMA (3 mL) at rt and stirred for 39 h. The solution was then dissolved in EtOAc (15 mL), and a saturated solution of ammonium chloride (5 mL) was added. The resulting solution was extracted with EtOAc (3 × 15 mL). The organics were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a yellow oil foam. The foam was purified on a flash silica column (0−25% EtOAc in CH_2Cl_2) to yield **34** as a bright yellow oil (44 mg, 61%): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 17.98 (s, 1H), 10.14 (s, 1H), 8.18 (d, 1H, J = 9.5 Hz), 8.14 (d, 1H, J = 9.5 Hz), 7.08 (s, 1H), 5.94 (p, 1H, J = 6.1 Hz), 5.16 (d, 1H, J = 5.5 Hz), 4.59 (dt, 1H, J = 8.5, 4.5 Hz), 4.52−4.43 (m, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 3.75 (s, 3H), 3.20 (s, 1H), 3.09−3.02 (m, 2H), 2.25 (ddd, 1H, J = 15.5, 7.5, 4.9 Hz), 2.03 (ddd, 1H, J = 14.0, 6.5, 3.9 Hz), 1.76 (h, 2H, J = 7.3 Hz), 1.52 (s, 3H), 1.42 (s, 3H), 1.16 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.7, 165.0, 162.4, 154.2, 153.0, 148.3, 145.8, 142.7, 140.4, 138.6, 133.1, 128.4, 125.0, 123.2, 121.3, 117.6, 117.4, 110.2, 109.7, 108.0 (d, J = 216 Hz), 72.4, 70.6, 66.5 (quint, J = 27 Hz), 63.8, 63.0, 62.8, 33.3, 32.5, 32.1, 28.0, 26.0, 21.0, 14.1; ^{19}F (ppm) −73.0; IR (film) ν_{max} 3018, 2964, 1744, 1588, 1263, 1210, 1169, 1001; HRMS m/z calcd. for $C_{36}H_{35}ClF_6NO_{11}(MH)^+$ 806.1803, found 806.1808; $[\alpha]_D^{23}$ = −74° (c = 0.1, $CHCl_3$).

Tetrahydroxanthone (40).



40

A solution of 0.5 M KOH (0.70 mL) was added to a stirring solution of vinyloguous carbonate **34** (35 mg, 0.043 mmol) in THF (2.6 mL) at 0 °C. The reaction mixture was allowed to stir for 2.5 h. The solution was then dissolved with EtOAc (20 mL), acidified to pH = 2 using a 0.5 M $KHSO_4$ solution, and the phases separated. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the organics were combined, dried over Na_2SO_4, filtered and concentrated to a yellow/

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brown oil. The oil (28 mg, 0.043 mmol) was resuspended in 1,2-dichloroethane (3.4 mL). Pyridine (17 μL, 0.21 mmol) and cyanuric chloride (8.3 mg, 0.045 mmol) were added to the reaction mixture. The solution was allowed to stir at rt for 30 min, and then the reaction mixture was stirred at 75 °C for 15 h. The reaction mixture was allowed to cool to rt, quenched with ice and diluted with 5 mL of cold 1.0 N HCl and 10 mL of CH_2Cl_2. The combined organics were filtered through Celite, dried over sodium sulfate, filtered, and concentrated to an orange oil/solid. Purification on preparative HPLC using a 5−90% CH_3CN in H_2O gradient afforded **40** as an orange solid (14.3 mg, 52%, 2 steps): mp 90−94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 14.96 (s, 1H), 13.88 (s, 1H), 8.15 (d, 1H, J = 9.4 Hz), 8.06 (d, 1H, J = 9.4 Hz), 5.44 (d, 1H, J = 6.0 Hz), 5.05 (dd, 1H, J = 9.9, 5.2 Hz), 4.77−4.68 (m, 1H), 4.06 (s, 3H), 3.90 (s, 3H), 3.69 (s, 3H), 3.06−2.98 (m, 2H), 2.73 (dt, 1H, J = 14.0, 4.8 Hz), 2.10−1.98 (m, 2H), 1.72 (h, 2H, J = 7.4 Hz), 1.47 (s, 3H), 1.37 (s, 3H), 1.13 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 182.9, 166.3, 165.1, 157.4, 156.0, 145.3, 141.2, 140.5, 133.4, 132.0, 132.0, 124.8, 124.1, 123.1, 116.0, 114.5, 113.9, 109.2, 109.0, 107.9, 70.7, 69.2, 63.9, 63.0, 62.7, 34.3, 32.5, 31.6, 29.7, 27.5, 25.4, 21.0, 14.0; IR (film) ν_{max} 3009, 2960, 2932, 2872, 1624, 1581, 1474, 1444, 1263, 1218, 1014; HRMS m/z calcd. for $C_{33}H_{33}ClNO_{10}$ $(MH)^+$ 638.1783, found 638.1791; $[\alpha]_D^{23}$ = +210° (c = 0.1, $CHCl_3$).

Tetrahydroxanthone (35). 0.83 mL of an aqueous 3 N HCl solution was added to a stirring solution of tetrahydroxanthone **40** (14.3 mg, 0.0224 mmol) in tetrahydrofuran (4.2 mL). The resulting mixture was degassed for 15 min and was heated at 50 °C for 1.5 h. The reaction mixture was allowed to cool to rt, diluted with EtOAc (10 mL), washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated to an orange solid. The solid was purified by preparative HPLC (5 to 90% CH_3CN in water) to yield **35** as a bright orange oil/solid (9.6 mg, 72%): mp 165−175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 15.04 (s, 1H), 14.07 (s, 1H), 8.12 (d, 1H, J = 9.4 Hz), 8.09 (d, 1H, J = 9.4 Hz), 6.04 (d, 1H, J = 6.3 Hz), 4.99 (d, 1H, J = 5.0 Hz), 4.75 (d, 1H, J = 6.2 Hz), 4.73−4.69 (m, 1H), 4.03 (s, 3H), 3.96 (ddd, 1H, J = 12.2, 6.4, 3.3 Hz), 3.84 (s, 3H), 3.67 (s, 3H), 3.07−2.99 (m, 2H), 2.34−2.24 (m, 1H), 1.81 (d, 1H, J = 12.7 Hz), 1.70 (q, 3H, J = 7.7 Hz), 1.09 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 183.7, 166.1, 165.9, 157.0, 155.4, 145.8, 142.1, 141.0, 133.6, 131.7, 131.5, 125.0, 124.2, 123.9, 118.0, 115.4, 112.8, 108.4, 107.9, 107.5, 65.7, 64.6, 64.1, 62.7, 62.0, 34.3, 32.3, 32.3, 20.8, 14.3; IR (film) ν_{max} 3022, 2984, 2929, 2850, 1643, 1583, 1474, 1443, 1260, 1050, 1023; HRMS m/z calcd. for $C_{30}H_{29}ClNO_{10}$ $(MH)^+$ 598.1480, found 598.1481; $[\alpha]_D^{23}$ = +74° (c = 0.1, $CHCl_3$).

Kibdelone A (1). A solution of ceric ammonium nitrate (9.2 mg, 0.017 mmol) in 1:1 H_2O/MeCN (1.8 mL) was added dropwise to a solution of tetrahydroxanthone **35** (4.8 mg, 0.0080 mmol) in acetonitrile (2.5 mL) at 0 °C. The solution was stirred for 6.5 h while slowly warming to room temperature. (Note: Reaction must be monitored by UPLC analysis.) The reaction mixture was then diluted with EtOAc (5 mL) and filtered through Celite. The Celite pad was washed with EtOAc (5 mL), and the resulting filtrate was washed with H_2O. The layers were separated, and the aqueous layer was extracted twice with EtOAc (2 × 5 mL). The organics were combined, dried over Na_2SO_4, filtered, and concentrated to afford an orange brown solid. The solid was purified by preparative HPLC (5−90% CH_3CN in H_2O) to yield kibdelone A as a bright orange solid (2.5 mg, 54% yield, 66% yield brsm): ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 14.29 (s, 1H), 8.41 (d, 1H, J = 9.0 Hz), 8.14 (d, 1H, J = 9.0 Hz), 6.10 (d, 1H, J = 6.4 Hz), 5.08 (d, 1H, J = 5.1 Hz), 4.79 (d, 1H, J = 6.2 Hz), 4.76−4.68 (m, 2H), 4.03 (s, 3H), 3.95 (ddd, 1H, J = 12.8, 6.6, 3.4 Hz), 3.68 (s, 3H), 3.07−2.96 (m, 2H), 2.27 (ddd, 1H, J = 12.9, 4.7, 4.7 Hz), 1.79 (br d, 1H, J = 13.3 Hz), 1.65 (h, 2H, J = 7.3 Hz), 1.06 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 183.5, 181.2, 180.7, 166.2, 156.5, 156.3, 156.2, 145.3, 138.6, 137.5, 133.5, 133.1, 131.3, 125.7, 124.2, 120.8, 116.9, 113.1, 106.8, 105.5, 65.0, 63.9, 62.0, 61.2, 33.6, 33.1, 32.9, 19.5, 13.7; IR (film) ν_{max} 3688 (br), 2959, 2919, 2850, 1695, 1613, 1514, 1436, 1272, 1059, 756; HRMS m/z calcd. for $C_{29}H_{25}ClNO_{10}$ $(MH)^+$ 582.1167, found 582.1174; $[\alpha]_D^{23}$ = +192° (c = 0.1, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds and NCI 60 data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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