

Published in final edited form as:

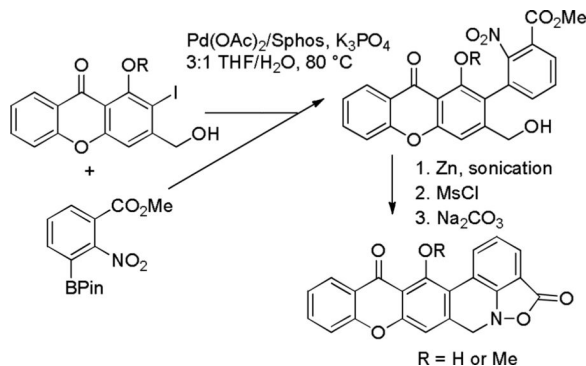
J Org Chem. 2010 December 3; 75(23): 8224–8233. doi:10.1021/jo101826p.

Synthesis of Hexacyclic Parnafungin A and C Models

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Abstract



A convergent, practical route to unstable hexacyclic parnafungin A and C models has been developed. Two iodoxanthones were prepared in four or five steps (33–50% overall yield). Suzuki-Miyaura coupling of the iodoxanthones with excess readily available 3-carbomethoxy-2-nitrophenyl pinacol boronate afforded the hindered highly functionalized 2-arylxanthones (53–58%) in the first key step. In the second key step, zinc reduction gave benzisoxazolinones that were treated with MsCl and then base to generate the unstable hexacyclic parnafungin A (13% overall yield for 8 steps) and C (8% overall yield for 9 steps) models. Analogously to the parnafungins, hexacyclic parnafungin C model decomposes to a phenanthridine with a half-life of 2 d in CDCl_3 .

Introduction

Parnafungins A1 (**1a**), A2 (**1b**), B1 (**2a**), and B2 (**2b**) are antifungal agents recently isolated from the *Fusarium larvarum* complex and other Hypocrealean fungi by a Merck group (see Scheme 1).¹ They inhibit fungal polyadenosine polymerase (PAP) and show broad spectrum antifungal activity with in vivo efficacy against *Candida albicans* in a mouse model.^{1b} Affinity selection/mass spectrometry studies indicated that the linear parnafungins A (**1**) bind preferentially to PAP.^{1c} More recently, the same group isolated two stereoisomers of parnafungin C (**5**), the *O*-methylated analogues of parnafungins A1 and A2, and parnafungin D (**6**) which has an additional epoxide.

Parnafungins A1, A2, B1 and B2 equilibrate readily (1–2 h) by a retro conjugate addition that opens the pyranone ring giving a bisphenol enedione. Conjugate addition then occurs from either face of the enone and either phenol to give a mixture of the four isomers. The two stereoisomers of parnafungin C undergo a similar equilibration, but the *O*-methyl group

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Supporting Information Available: A figure showing the crystal structure of **30a**, X-ray crystallographic data for **30a** (CIF), and copies of ^1H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

prevents the formation of structures analogous to parnafungins B1 and B2. The fused benzisoxazolinone ring of the parnafungins (**1**, **2**, **5**, and **6**) is unstable. At neutral or basic pH, parnafungins A (**1**) and B (**2**) decompose to phenanthridines **3** and **4**, respectively in less than 1 h.¹ Decomposition at pH 3 is slower, but the same compounds are generated in 10-20 h. Phenanthridines **3** and **4** are unfortunately not biologically active. The synthesis of parnafungins A1, A2, B1, and B 2 that exist as a mixture of four equilibrating isomers with a half-life in solution of less than a day at optimal pH poses a very challenging problem.

The biosynthesis of the parnafungins might involve the oxidative coupling of **7** with anthranilic acid to give **8** (see Scheme 2). Oxidation of both the benzylic methyl group and the aniline might give rise to parnafungins A1 (**1a**) and A2 (**2**). Blenolide C (**7b**) was recently isolated² and numerous natural products are known that result from either oxidative dimerization of **7** or oxidative coupling with other components at the asterisk-marked carbon. Bräse³ and Nicolaou⁴ recently synthesized blenolide C (**7b**) and related compounds have also been synthesized.⁵

The novel structural feature of the parnafungins is the fused benzisoxazolinone ring, which is necessary for biological activity. We therefore decided to initiate our studies by developing a route to 4*H*,7*H*-isoxazolo[4,3,2-*de*]phenanthridin-4-one (**12**), which could then be extended to the synthesis of the parnafungins. We were guided by Wierenga's report,⁶ which was based on earlier work of Bamberger⁷ and Cohen,⁸ that reduction of methyl *o*-nitrobenzoate (**9**) with zinc, NH₄Cl, and Na₂CO₃ in MeOH containing formaldehyde afforded hydroxymethylbenzisoxazolinone (**11**) in 44% yield (see Scheme 3). Alcohol **11** was also prepared by the reaction of basic formaldehyde with **10**, which was formed in low yield by the zinc reduction of **9**.

4*H*,7*H*-Isioxazolo[4,3,2-*de*]phenanthridin-4-one (**12**) might be accessible by an intramolecular Friedel–Crafts alkylation of **13** (see Scheme 4).

Hydroxymethylbenzisoxazolinone **13** will be formed by Wierenga's procedure from biphenylcarboxylate **14**, which has been prepared by Liu⁹ from methyl 3-chloro-2-nitrobenzoate (**18**) by Suzuki-Miyaura coupling with phenylboronic acid (**17**, R = H). An alternate approach involves the synthesis of **12** from **15** by an intramolecular S_N2 reaction with C–N bond formation. Suzuki-Miyaura coupling of **18** with the appropriate boronic acid **17**, R = CH₂OH, should form **16**, which will be converted to **15** by zinc reduction in the absence of formaldehyde. The Friedel–Crafts route via **13** is appealing because it is highly convergent and uses phenylboronic acid (**17**, R = H). However, the Friedel–Crafts reaction may not work well with an unactivated aromatic ring. The S_N2 route via **15** requires the more complex arylboronic acid **17**, R = CH₂OH, but may be more versatile.

Results and Discussion

Suzuki-Miyaura coupling of **18** and phenylboronic acid (**19a**) by Liu's procedure⁹ afforded **14** in 65% yield (see Scheme 5).¹⁰ The yield was improved to 99% using SPhos, Pd(OAc)₂, and K₃PO₄ in wet THF by Buchwald's procedure.¹¹ Reduction of **14** with Zn and NH₄Cl with sonication for 30 minutes in THF/MeOH/H₂O afforded a 3:1 mixture of the desired benzisoxazolinone **21a** and the over reduction product amino ester **22a**. Benzisoxazolinone **21a**, which decomposed on chromatography, was isolated in 60% yield by washing the mixture of **21a** and **22a** with 9:1 hexanes/Et₂O to remove **22a**. The desired hydroxymethylbenzisoxazolinone **13** was obtained in 61% yield by reaction of **21a** with formaldehyde and Na₂CO₃ in aqueous THF. Unfortunately, all attempts to form **12** by intramolecular Friedel–Crafts alkylation on the phenyl ring of **13** were unsuccessful.

We repeated this sequence with 3,5-dimethoxyphenylboronic acid (**19b**) to see if the Friedel–Crafts alkylation could be accomplished with an electron rich aromatic ring. Suzuki-

Miyaura coupling of **18** with **19b** with SPhos proceeded analogously to give **20b** in 99% yield. Zinc reduction provided **21b** in 66% yield, which was treated with formaldehyde to afford **23b** in 76% yield. We were pleased to find that treatment of **23b** with 10% TFA in CH₂Cl₂ afforded **24b** in 27% yield, presumably by formation of an iminium cation that added to the aromatic ring. Although this route to **24b** provided the first synthesis of a 4*H*, 7*H*-isoxazolo[4,3,2-*de*]phenanthridin-4-one, it can't be used for the synthesis of the parnafungins because the Friedel-Crafts reaction would have to occur at a deactivated carbon meta to the oxygen substituents and para to the carbonyl group. We therefore turned to the second route using an S_N2 reaction to form the C-N bond.

Suzuki-Miyaura coupling of **18** with 1.5 equiv of 2-hydroxymethylphenylboronic acid (**25a**) using SPhos afforded biphenyl **26a** in 95% yield (see Scheme 6). Zinc reduction provided a mixture of benzisoxazolinone **27a** and the over reduced amino ester analogous to **22**. This mixture was treated with MsCl and Et₃N in CH₂Cl₂ for 15 min at 0 °C to provide the mesylate of **27a**. Reaction of the mesylate with Na₂CO₃ in 1:1 THF/H₂O for 40 minutes gave the desired tetracyclic isoxazolo[4,3,2-*de*]phenanthridinone **12** in 37% overall yield for the three steps from **26a**.

Suzuki-Miyaura coupling of **18** with 3 equiv of boronic acid **25b**¹² provided biphenyl **26b** (83%) with the oxygen substituents on the same carbons as in the parnafungins. Reduction of **26b** with zinc afforded benzisoxazolinone **27b**, which was reacted with MsCl and Et₃N to give the mesylate. Reaction of the mesylate with Na₂CO₃ in 1:1 THF/H₂O provided **28b** in 47% overall yield for the three steps from **26b**. This sequence provides a short and efficient route to the unstable tetracyclic isoxazolo[4,3,2-*de*]phenanthridinone moiety of the parnafungins.

We now turned our attention to the preparation of hexacyclic models **29a** and **29b** of parnafungins A and C that differ from the natural product only in the substituents on and the oxidation state of the ring furthest from the benzisoxazolinone (see Scheme 7). This could be carried out by Suzuki-Miyaura coupling of chloride **18** or bromide **33** with boronate **32**. However, this approach is not appealing because excess boronic acid **32**, which requires many steps to prepare, will be needed. A more appealing approach is to use an excess of the simpler boronate **31** with iodides **30a** or **30b**. The preparation of iodides **30a** and **30b** will be more straightforward than that of boronic acid **32**. Pinacol boronate **31** should also be suitable for coupling with the fully functionalized tricyclic iodide needed for parnafungin synthesis.

Oxidation of **34** with potassium dichromate and sulfuric acid gave 3-bromo-2-nitrobenzoic acid,¹³ which was treated with K₂CO₃ and MeI in DMF to give **33** in 69% overall yield (see Scheme 8). The preparation of pinacol boronate **31** was challenging because of the nitro and ester groups. Reaction of **33** with PinBBPin or HBPin and Pd(OAc)₂/SPhos in dioxane at 80 °C resulted in debromination. A similar reaction with neopBBneop gave mainly the biphenyl dimer. Eventually we prepared **31** efficiently by a Barbier-type procedure developed by a Merck group for the synthesis of 3-pyridyl boronic acid.¹⁴ A mixture of bromide **33** and 2 equiv of isopropyl pinacol boronate in 4:1 toluene/THF was cooled to -98 °C and treated very slowly with 2 equiv *n*-BuLi. Transmetalation occurred readily and the resulting aryllithium was then trapped immediately by the isopropyl pinacol boronate. Quenching with acetic acid gave a precipitate that was removed by filtration. The filtrate was concentrated to give crude **31** that was crystallized from hexanes at -20 °C to give **31** in 52% yield. The yield was lower and some **33** was recovered if less than 2 equiv of both isopropyl pinacol boronate and *n*-BuLi were used.

Xanthone **37a** was prepared in 91% yield by condensation of salicylic acid (**35**) with orcinol (**36a**) using methanesulfonic acid on alumina at 150 °C for 60 min (see Scheme 9).¹⁵ The hydroxymethylxanthone **37b**,¹⁶ rather than **37a**, is needed for the construction of iodoxanthone **30**, but the analogous condensation with 5-hydroxymethylresorcinol (**36b**) did not provide **37b**. We therefore investigated procedures to oxidize the methyl group of **37a**. Attempted benzylic bromination of **37a** with NBS and AIBN in CCl₄ afforded a 2:1 mixture of ortho and para ring bromination products **38**.^{17,18} We therefore postponed the oxidation of the methyl group of **37a** until after the Suzuki-Miyaura coupling. Iodination¹⁹ of **37a** with iodine and periodic acid in ethanol/THF/H₂O afforded the desired *ortho*-iodophenol **39** in 95% yield that was converted to acetate **40** containing a little inseparable deiodination product **44** in 90% yield on treatment with Ac₂O, pyridine, and DMAP in CH₂Cl₂ for 2 h. Extensive deiodination of **40** occurred at longer reaction times.²⁰

Suzuki-Miyaura coupling of **40** with 3 equiv of **31** afforded the desired 2-arylxanthone **41** in 60% yield. Benzylic bromination of the hindered methyl group with NBS and AIBN required heating in CCl₄ in a sealed tube at 100 °C and gave benzylic bromide **42** in 50-60% yield. Hydrolysis of the acetate and benzylic bromide with CaCO₃ in aqueous dioxane at 120 °C proceeded in low yield giving **43** in only 20% yield. We therefore investigated other approaches to functionalize the methyl group of **37a**.

Reaction of **37a** with Ac₂O, DMAP, and pyridine in CH₂Cl₂ afforded aryl acetate **44** (see Scheme 10). The acetate makes the aromatic ring of **44** less nucleophilic than that of phenol **37a** so that benzylic bromination of **44** with NBS and AIBN in CCl₄ for 16 h at 77 °C proceeded smoothly to give benzylic bromide **45**. Hydrolysis of both the acetate and benzylic bromide of **45** with CaCO₃ in aqueous dioxane at 120 °C for 16 h provided hydroxymethylxanthone **37b** in 50% overall yield for the three steps from **37a**.

Iodination¹⁹ of **37b** with iodine and periodic acid in ethanol/THF/H₂O afforded the desired *ortho*-iodophenol **30a** in 99% yield that was converted to methyl ether **30b** in 69% yield (see Scheme 11). The single regioisomeric iodide was expected to be the desired *ortho*-iodophenol **30a** based on literature precedent.¹⁹ However, the position of the iodide could not be confirmed by analysis of the spectral data. We therefore established the structure of **30a** by X-ray crystal structure determination (see Supporting Information).

Suzuki-Miyaura coupling of **30a** with 2.6 equiv of pinacol boronate **31** using SPhos afforded phenol **43** in 58% yield. A similar coupling of **30b** with 2.8 equiv of **31** provided methyl ether **46** in 53% yield. These reactions proceed well with 30-50 mol% of both Pd(OAc)₂ and SPhos. Use of Pd₂(dba)₃ instead of Pd(OAc)₂ afforded only the deiodination product, methyl 2-nitrobenzoate, and the biphenyl from homo coupling of boronate **31**. Use of water as a co-solvent is essential and use of degassed solvents was also important. Under these optimal conditions, hindered, highly functionalized 2-arylxanthone **43** was obtained in reasonable yield without protection of the primary alcohol or phenol.

The three-step sequence developed for the conversion of **26a** (**26b**) to **12** (**28b**) proceeded uneventfully to complete the synthesis of hexacyclic models **29a** and **29b**. Reduction of **43** and **46** with Zn and NH₄Cl in MeOH/THF/H₂O with sonication afforded **47** and **48**, respectively. Mesylation with MsCl and Et₃N in CH₂Cl₂ afforded the mesylates, which were treated with Na₂CO₃ in 1:1 THF/H₂O to give hexacyclic parnafungin A model **29a** (46% for three steps) and parnafungin C model **29b** (43% for three steps), respectively. The ¹H NMR spectral data of the three right-hand rings of **29a** and **29c** correspond closely to those reported for parnafungins A (**1**) and C (**5**). The proton para to the phenol of the central ring of **29a** absorbs at δ 6.97, whereas the analogous proton absorbs at δ 6.72 and 6.74 in parnafungins A1 and A2. The proton para to the methoxy group of the central ring of **29b**

absorbs at δ 7.30, which is downfield by 0.33 ppm from that of **29a**. The proton para to the methoxy group of parnafungin C absorbs at δ 7.06, which is also downfield by 0.32-0.34 ppm from those of parnafungins A1 and A2.

The Merck group proposed that parnafungins A (**1**) and B (**2**) decomposed to **3** and **4**, respectively, by either an E2 reaction or by hydrolysis of the benzisoxazolinone followed by loss of water. We explored the stability of tetracyclic models **12**, **24b**, **28b**, and hexacyclic parnafungin C model **29b** in CDCl₃. Hexacyclic parnafungin A model **29a** was not sufficiently soluble in CDCl₃ or other solvents suitable for NMR spectroscopic analysis. All four benzisoxazolinones decomposed cleanly to the respective phenanthridines **49a**, **49b**, **49c**, and **50** without any evidence for the formation of an intermediate (see Scheme 12). This suggests that the reaction proceeds by an E2 elimination unless loss of water is much faster than hydrolysis of the benzisoxazolinone.

If the reaction occurs by an E2 elimination, the rate of the reaction should be proportional to the kinetic acidity of the methylene protons because deprotonation occurs in the rate determining step, even if protonation of the carbonyl group by adventitious HCl is the initial step. The C-methyl group of *m*-methoxytoluene is deprotonated twice as fast as that of toluene by lithium amide bases, whereas the C-methyl group of *o*-methoxytoluene is deprotonated ten times slower than that of toluene.²³ The observed rates of decomposition of the four parnafungin models correlate well with expected effect of the methoxy groups on the acidity of the methylene group providing further support for an E2 mechanism. Hexacyclic parnafungins C model **29b** with two meta methoxy groups that each double the rate of deprotonation of toluene and a para ketone that should also increase the acidity of the methylene group decomposed most rapidly with a half-life of 2 days at a rate similar to that of parnafungins A-C. Tetracycle **28b** with two meta methoxy groups, but lacking the para ketone decomposed next most rapidly with a half-life of 6 days. Tetracycle **12** with no methoxy groups decomposed with a half-life of 10 days and tetracycle **22b** with ortho and para methoxy groups that decrease the rate of deprotonation decomposed slowest with a half-life of 27 days.

In conclusion, a convergent, practical route to the unstable hexacyclic parnafungin A and C models **29a** and **29b** has been developed. Iodoxanthone **30a** was prepared in four steps (50% overall yield from the readily available xanthone **37a**). Suzuki-Miyaura coupling of **30a** and **30b** with excess readily available pinacol boronate **31** afforded the hindered highly functionalized 2-arylxanthenes **43** (58%) and **46** (53%) in the first key step. In the second key step, zinc reduction of **43** and **46** gave benzisoxazolinones **47** and **48** that were treated with MsCl and then base to generate the unstable hexacyclic parnafungin A and C models **29a** (46% from **43**, 13% overall yield for 8 steps from **37a**) and **29b** (42% from **46**, 8% overall yield for 9 steps from **37a**). Analogously to the parnafungins, hexacyclic parnafungin C model **29b** decomposed to **50** with a half-life of 2 d in CDCl₃. We are now exploring routes to the iodo hydroxymethyl phenol from blenolide C (**7**) that will be coupled with **31** to give parnafungins A (**1**) and B (**2**).

Experimental Section

General Experimental Methods

Reactions were conducted in flame- or oven-dried glassware under a nitrogen atmosphere and were stirred magnetically. The phrase “concentrated” refers to removal of solvents by means of a rotary evaporator attached to a diaphragm pump (15-60 Torr) followed by removal of residual solvents at < 1 Torr with a vacuum pump. Flash chromatography was performed on silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed using silica gel 60 F-254 pre-coated glass plates (0.25 mm). TLC Plates were

analyzed by short wave UV illumination, or by dipping in vanillin stain (27 g of vanillin in 380 mL of EtOH, 50 mL of water and 20 mL of concentrated sulfuric acid) and heating on a hot plate or by spray with permanganate spray (5 g of KMnO_4 in 495 mL of water). THF and ether were dried and purified by distillation from sodium/benzophenone. DIPEA, Et_3N , MeOH, and benzene were distilled from CaH_2 . ^1H and ^{13}C NMR spectra were obtained on a 400 MHz spectrometer in CDCl_3 with tetramethylsilane as internal standard unless otherwise indicated. Chemical shifts are reported in δ (ppm downfield from tetramethylsilane). Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and br (broad). COSY spectra were recorded for all compounds and used to assign ^1H NMR spectra. IR spectra were acquired on an FT-IR spectrometer and are reported in wave numbers (cm^{-1}). High resolution mass spectra were obtained using the following ionization techniques: chemical ionization (CI), electron impact (EI), electrospray ionization analyzed by quadrupole time of flight (QTOF). Activated Zn was prepared by the procedure of Kishi.²⁵

Methyl 2-Nitro-[1,1'-biphenyl]-3-carboxylate (**14**)

A mixture of methyl 3-chloro-2-nitrobenzoate (**18**) (101 mg, 0.47 mmol), 2-phenylboronic acid (**19a**) (86 mg, 0.70 mmol, 1.5 equiv), $\text{Pd}(\text{OAc})_2$ (2.1 mg, 0.02 equiv), SPhos (12 mg, 0.06 equiv), and K_3PO_4 (300 mg, 1.41 mmol, 3 equiv) in THF (1 mL) and H_2O (10 μL) was heated at 40 °C under N_2 for 4 h. The mixture was cooled, diluted with Et_2O , and filtered. The filtrate was concentrated to give 179 mg of crude **14**. Flash chromatography on silica gel (6:1 hexanes/ EtOAc) gave 116 mg (99%) of pure **14**, with spectral data identical to those of a sample prepared by the literature procedure: mp 110-111 °C; ^1H NMR (CDCl_3) 8.02 (d, 1, $J = 4.8$); 7.60 (d, 2, $J = 4.8$), 7.45-7.39 (m, 3), 7.37-7.31 (m, 2), 3.91 (s, 3); ^{13}C NMR (CDCl_3) 163.8, 149.4, 135.4, 135.3, 135.1, 130.0, 129.9, 128.8, 128.7 (2 C), 128.1 (2 C), 123.1, 53.1; IR 1732, 1543, 1310.

Methyl 3',5'-Dimethoxy-2-nitro-[1,1'-biphenyl]-3-carboxylate (**20b**)

A mixture of methyl 3-chloro-2-nitrobenzoate (**18**) (104 mg, 0.48 mmol), 3,5-dimethoxyphenylboronic acid (**19b**) (132 mg, 0.72 mmol, 1.5 equiv), $\text{Pd}(\text{OAc})_2$ (2.1 mg, 0.02 equiv), SPhos (12 mg, 0.06 equiv), and K_3PO_4 (305 mg, 1.44 mmol, 3 equiv) in THF (1 mL) and H_2O (10 μL) was heated at 40 °C under N_2 for 4 h. The mixture was cooled, diluted with Et_2O , and filtered. The filtrate was concentrated to give 252 mg of crude **20b**. Flash chromatography on silica gel (5:1 hexanes/ EtOAc) gave 144 mg (99%) of pure **20b**: mp 156-157 °C; ^1H NMR (CDCl_3) 8.02 (dd, 1, $J = 7.3, 2.2$), 7.65-7.57 (m, 2), 6.50 (t, 1, $J = 2.2$), 6.47 (d, 2, $J = 2.2$), 3.92 (s, 3), 3.79 (s, 6); ^{13}C NMR (CDCl_3) 163.8, 160.8 (2 C), 149.4 (weak), 137.1, 135.2, 135.1, 130.2, 129.9, 123.1, 106.5 (2 C), 100.9, 55.4 (2 C), 53.1; IR (neat) 1729, 1541, 1344; HRMS (EI) calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_6$ (M^+) 317.0899, found 317.0904.

7-Phenyl-2,1-benzisoxazolin-3-one (**21a**)

A solution of **14** (110 mg, 0.43 mmol) in 5 mL of 2:2:1 THF/MeOH/ H_2O was treated with activated Zn (160 mg) and NH_4Cl (120 mg). The resulting mixture was sonicated at 25 °C for 30 minutes. The mixture was then diluted with Et_2O and filtered. The filtrate was washed with brine, dried (Na_2SO_4), and concentrated to give 90 mg of a 3:1 mixture of benzisoxazolinone **21a** and methyl 2-amino-[1,1'-biphenyl]-3-carboxylate (**22a**)⁹ as a white solid. The crude product was washed with 10 mL of 9:1 hexanes/ Et_2O twice, which removed amino ester **22a** giving 55 mg (60%) of pure **21a**: mp 98 °C (decomposition); ^1H NMR (CDCl_3) 8.53 (br s, 1, NH), 7.85 (d, 1, $J = 8.0$), 7.75 (d, 1, $J = 8.0$), 7.64 (br d, 2, $J = 8.0$), 7.51 (dd, 2, $J = 8.0, 8.0$), 7.43 (t, 1, $J = 8.0$), 7.41 (dd, 1, $J = 8.0, 8.0$); ^{13}C NMR (CDCl_3) 169.0, 153.1, 135.1, 134.2, 129.4 (2 C), 128.8, 127.6 (2 C), 126.4, 125.5, 124.6, 113.2; IR 1734; HRMS (ESI+) calcd for $\text{C}_{13}\text{H}_{10}\text{NO}_2$ (MH^+) 212.0712, found 212.0702.

7-(3,5-Dimethoxyphenyl)-2,1-benzisoxazolin-3-one (21b)

A solution of **20b** (100 mg, 0.32 mmol) in 5 mL of 2:2:1 THF/MeOH/H₂O was treated with activated Zn (56 mg) and NH₄Cl (30 mg). The resulting mixture was sonicated at 25 °C for 30 minutes. Additional activated Zn (30 mg) and NH₄Cl (34 mg) were added and the reaction was sonicated at 25 °C for another 30 minutes. The mixture was then diluted with EtOAc and filtered. The filtrate was washed with brine, dried (Na₂SO₄), and concentrated to give 94 mg of a 3:1 mixture of benzisoxazolinone **21b** and methyl 2-amino-3',5'-dimethoxy-[1,1'-biphenyl]-3-carboxylate (**22b**) as a semisolid. The crude product was washed with 10 mL of 3:1 hexanes/EtOAc, which removed the amino ester giving 56 mg (66%) of pure **21b**: mp 124 °C (decomposition); ¹H NMR (CDCl₃) 8.53 (br s, 1, NH), 7.85 (d, 1, *J* = 7.3), 7.75 (d, 1, *J* = 7.3), 7.40 (dd, 1, *J* = 7.3, 7.3), 6.77 (d, 2, *J* = 2.0), 6.52 (t, 1, *J* = 2.0), 3.85 (s, 6); ¹³C NMR (CDCl₃) 169.0, 161.5 (2 C), 153.0, 137.0, 134.0, 126.3, 125.4, 124.8, 113.1, 105.7 (2 C), 100.5, 55.5 (2 C); IR (neat) 1742, 1736, 1605, 1156; HRMS (ESI+) calcd for C₁₅H₁₄NO₄ (MH⁺) 272.0923, found 272.0919.

Flash chromatography of the 3:1 mixture of **21b** and **22b** on silica gel (5:1 hexanes/EtOAc) resulted in the decomposition of **21b**. Only **22b** was isolated in 15-25% yield: ¹H NMR (CDCl₃) 7.89 (dd, 1, *J* = 8.0, 1.8), 7.23 (dd, 1, *J* = 8.0, 1.2), 6.68 (dd, 1, *J* = 8.0, 8.0), 6.55 (d, 2, *J* = 2.0), 6.48 (t, 1, *J* = 2.0), 6.04 (br, 2, *w*_{1/2} = 19, NH₂), 3.88 (s, 3), 3.81 (s, 6); ¹³C NMR (CDCl₃) 168.8, 161.2 (2 C), 147.8, 140.4, 134.6, 130.8, 128.6, 115.5, 110.5, 107.1 (2 C), 99.8, 55.4 (2 C), 51.6; HRMS (ESI+) calcd for C₁₆H₁₈NO₄ (MH⁺) 288.1236, found 288.1222.

1-Hydroxymethyl-7-phenyl-2,1-benzisoxazolin-3-one (13)

A solution of **21a** (50 mg, 0.23 mmol) in 8 mL of 1:1 THF/H₂O was treated with Na₂CO₃ (60 mg) and 37% aqueous CH₂O (0.7 mL). The reaction was stirred at 25 °C for 2.5 h. The solution was then diluted with EtOAc, washed with water and brine, and dried (Na₂SO₄). Concentration gave 44 mg of crude **13** as a white solid, which was washed with 10:1 hexanes/EtOAc to give 34 mg (61%) of pure **13**: mp 119 °C (decomposition); ¹H NMR (CDCl₃) 7.82 (d, 1, *J* = 8.0), 7.64 (d, 1, *J* = 8.0), 7.59 (d, 2, *J* = 7.2), 7.50 (dd, 2, *J* = 7.2, 7.2), 7.44 (t, 1, *J* = 7.2), 7.42 (dd, 1, *J* = 8.0, 8.0), 4.81 (s, 2), 3.14 (br s, 1, *w*_{1/2} = 21.6, OH); ¹³C NMR (CDCl₃) 168.6, 152.1, 136.1, 136.0, 129.2 (2 C), 128.8, 128.2 (2 C), 128.1, 126.0, 124.7, 116.3, 74.1; IR 1764 1739; HRMS (ESI+) calcd for C₁₄H₁₁NO₃Na (MNa⁺) 264.0637, found 264.0636.

7-(3,5-Dimethoxyphenyl)-1-hydroxymethyl-2,1-benzisoxazolin-3-one (23b)

A solution of **21b** (51 mg, 0.21 mmol) in 8 mL of 1:1 THF/H₂O was treated with Na₂CO₃ (60 mg) and 37% aqueous CH₂O (0.7 mL). The reaction was stirred at 25 °C for 12 h. The solution was then diluted with EtOAc, washed with water and brine, and dried (Na₂SO₄). Concentration gave 48 mg of white solid crude **23b**, which was washed with 5:1 hexanes/EtOAc to give 43 mg (76%) of pure **23b**: mp 136 °C (decomposition); ¹H NMR (CDCl₃) 7.80 (d, 1, *J* = 8.0), 7.64 (d, 1, *J* = 8.0), 7.39 (dd, 1, *J* = 8.0, 8.0), 6.71-6.76 (m, 2), 6.51-6.55 (m, 1), 4.89 (d, 2, *J* = 8.0), 3.83 (s, 6), 3.50 (t, 1, *J* = 8.0, OH); ¹³C NMR (CDCl₃) 168.7, 161.2 (2 C), 152.0, 137.9, 135.7, 128.0, 125.8, 124.8, 116.2, 106.2 (2 C), 100.6, 74.3, 55.5 (2 C); IR (neat) 3413, 1767, 1746, 1602, 1157; HRMS (ESI+) calcd for C₁₆H₁₅NO₅Na (MNa⁺) 324.0848, found 324.0842.

8,10-Dimethoxy-4*H*,7*H*-isoxazolo[4,3,2-*de*]phenanthridin-4-one (24b)

A solution of **23b** (24 mg, 0.08 mmol) in CH₂Cl₂ (3 mL) was treated with TFA (0.3 mL) in one portion at 0 °C. The reaction was slowly warmed to 25 °C and stirred for 30 minutes. Concentration and flash chromatography of the residue on silica gel (6:2:1 hexanes/EtOAc/

CH₂Cl₂) gave 6 mg (27%) of pure **24b**: mp 222 °C (decomposition); ¹H NMR (CDCl₃) 7.76 (d, 1, *J* = 7.3), 7.70 (d, 1, *J* = 8.0), 7.26 (dd, 1, *J* = 8.0, 7.3), 6.90 (d, 1, *J* = 1.8), 6.49 (d, 1, *J* = 1.8), 4.63 (s, 2), 3.90 (s, 3), 3.87 (s, 3); ¹³C NMR (CDCl₃) 168.0, 161.1, 157.8, 156.5, 130.7, 127.1, 124.9, 124.5, 121.6, 112.2, 110.7, 99.3, 99.0, 55.7, 55.6, 48.7; IR (neat) 1762; HRMS (ESI+) calcd for C₁₆H₁₄NO₄ (MH⁺) 284.0923, found 284.0920.

Methyl 2'-Hydroxymethyl-2-nitro-[1,1'-biphenyl]-3-carboxylate (**26a**)

A mixture of methyl 3-chloro-2-nitrobenzoate (**18**) (220 mg, 1.0 mmol), 2-(hydroxymethyl)phenylboronic acid (**25a**) (228 mg, 1.5 mmol, 1.5 equiv), Pd(OAc)₂ (7 mg, 0.03 equiv), SPhos (13 mg, 0.03 equiv), and K₃PO₄ (636 mg, 3.0 mmol, 3 equiv) in THF (1 mL) and H₂O (10 μL) was heated at 40 °C under N₂ for 4 h. The mixture was cooled, diluted with Et₂O, and filtered. The filtrate was concentrated to give 400 mg of crude **26a**. Flash chromatography on silica gel (6:1 hexanes/EtOAc) gave 273 mg (95%) of pure **26a**: mp 109.5-111 °C; ¹H NMR (CDCl₃) 8.08 (d, 1, *J* = 8.0), 7.62 (dd, 1, *J* = 8.0, 8.0), 7.56 (d, 1, *J* = 8.0), 7.56 (d, 1, *J* = 8.0), 7.46 (dd, 1, *J* = 8.0, 8.0), 7.33 (dd, 1, *J* = 8.0, 8.0), 7.14 (d, 1, *J* = 8.0), 4.50 (dd, 1, *J* = 12.8, 4.4), 4.41 (dd, 1, *J* = 12.8, 7.6), 3.92 (s, 3), 1.79 (dd, 1, *J* = 7.6, 4.4, OH); ¹³C NMR (CDCl₃) 163.6, 149.8, 139.0, 135.5, 133.8, 133.4, 130.5, 129.7, 129.6, 129.4, 128.7, 127.7, 123.0, 63.0, 53.1; IR 1730, 1540, 1372, 1440; HRMS (ESI+) calcd for C₁₅H₁₃NO₅Na (MNa⁺) 310.0691, found 310.0703.

4*H*,7*H*-Isoxazolo[4,3,2-*de*]phenanthridin-4-one (**12**)

A solution of **26a** (73 mg, 0.26 mmol) in 5 mL of 2:2:1 MeOH/THF/H₂O was treated with activated Zn (80 mg) and NH₄Cl (60 mg). The resulting mixture was sonicated at 25 °C for 30 minutes. The reaction was diluted with EtOAc, filtered. The filtrate was washed with H₂O and brine, and dried (Na₂SO₄). Concentration gave 64 mg of a 3:1 mixture of 7-(2-hydroxymethylphenyl)-2,1-benzisoxazolin-3-one (**27a**) and methyl 2-amino-2'-hydroxymethyl-[1,1'-biphenyl]-3-carboxylate as a solid.

The crude mixture of **27a** and the amino ester was dissolved in anhydrous CH₂Cl₂ (5 mL) and cooled to 0 °C. NEt₃ (0.1 mL, 0.75 mmol) and MsCl (40 μL, 0.5 mmol) were added and the resulting reaction was stirred at 0 °C for 15 minutes. The reaction was diluted with Et₂O and washed with water and brine. The organic layer was dried (Na₂SO₄) and concentrated to give 102 mg of crude 7-(2-methanesulfonyloxymethylphenyl)-2,1-benzisoxazolin-3-one.

The crude mesylate was dissolved in 4 mL of 1:1 THF/H₂O and Na₂CO₃ (80 mg) was added at 25 °C. The resulting mixture was stirred at 25 °C for 40 minutes. The reaction was diluted with Et₂O and washed with brine. The organic layer was dried (Na₂SO₄) and concentrated to give 62 mg of crude **12**. Flash chromatography (7:1 hexanes/EtOAc) gave 21 mg (37% from **26a**) of pure **12**: mp 137-138 °C; ¹H NMR (CDCl₃) 7.83 (d, 1, *J* = 8.0), 7.81 (d, 1, *J* = 8.0), 7.71 (d, 1, *J* = 8.0), 7.46 (dd, 1, *J* = 8.0, 8.0), 7.37 (dd, 1, *J* = 8.0, 8.0), 7.32 (d, 1, *J* = 8.0), 7.31 (dd, 1, *J* = 8.0, 8.0), 4.65 (s, 2); ¹³C NMR (CDCl₃) 167.9, 156.4, 131.1, 129.35, 129.29, 129.2, 128.4, 127.0, 125.4, 124.4, 123.2, 121.7, 111.1, 55.3; IR 1766; HRMS (EI) calcd for C₁₄H₉NO₂ (M⁺) 223.0633, found 223.0636.

Methyl 2'-Hydroxymethyl-4',6'-dimethoxy-2-nitro-[1,1'-biphenyl]-3-carboxylate (**26b**)

Boronic acid **25b** was prepared from 886 mg (2.68 mmol) of the THP ether of 2-bromo-3,5-dimethoxybenzyl alcohol by the literature procedure,¹² except that the recrystallization step was not carried out. The entire batch of crude **25b** was used directly in the Suzuki coupling.

Freshly distilled THF (1 mL) was added to a mixture of Pd(OAc)₂ (11.5 mg, 0.07 equiv) and SPhos (64 mg, 0.21 equiv). The resulting solution was stirred at 25 °C under N₂ for 30 minutes to form a Pd stock solution. A mixture of methyl 3-chloro-2-nitrobenzoate (**18**) (160

mg, 0.74 mmol), crude boronic acid **25b** (900 mg, 3 equiv), and K_3PO_4 (530 mg, 2.5 mmol, 3.4 equiv) were mixed in a flask. The flask was purged with N_2 three times. Freshly distilled toluene (3 mL) and the Pd stock solution were then added. The resulting mixture was refluxed for 90 minutes. The mixture was cooled, diluted with Et_2O , and filtered through a pad of Celite. The filtrate was concentrated to give 946 mg of crude **26b**. Flash chromatography (hexanes/ $EtOAc$ 3:1 to 2:1) gave 213 mg (83%) of pure **26b**: mp 129-131 °C; 1H NMR ($CDCl_3$) 8.03 (d, 1, $J = 8.0$), 7.60 (dd, 1, $J = 8.0, 7.3$), 7.47 (d, 1, $J = 7.3$), 6.72 (d, 1, $J = 1.8$), 6.42 (d, 1, $J = 1.8$), 4.38 (dd, 1, $J = 12.8, 3.6$), 4.29 (dd, 1, $J = 12.8, 7.3$), 3.90 (s, 3), 3.85 (s, 3), 3.66 (s, 3), 1.90 (dd, 1, $J = 7.3, 3.6$, OH); ^{13}C NMR ($CDCl_3$) 164.0, 161.5, 158.0, 150.6, 141.7, 136.7, 130.6, 130.2, 130.0, 123.3, 114.7, 104.2, 98.0, 62.9, 55.8, 55.4, 53.0; IR 1730, 1540, 1370, 1155; HRMS (EI) calcd for $C_{17}H_{17}NO_7$ (M^+) 347.1005, found 347.1006.

9,11- Dimethoxy-4*H*,7*H*-isoxazolo[4,3,2-*de*]phenanthridin-4-one (**28b**)

A solution of **26b** (55 mg, 0.16 mmol) in 5 mL $MeOH/THF/H_2O$ 2:2:1 was treated with activated Zn (80 mg) and NH_4Cl (60 mg). The resulting mixture was sonicated at 25 °C for 25 minutes. The reaction was diluted with $EtOAc$, and filtered. The filtrate was washed with H_2O and brine, and dried (Na_2SO_4). Concentration gave 44 mg of a 6:1 mixture of 7-(2-hydroxymethyl-4,6-dimethoxyphenyl)-2,1-benzisoxazolin-3-one (**27b**) and methyl 2-amino-2'-hydroxymethyl-4',6'-dimethoxy-[1,1'-biphenyl]-3-carboxylate.

The crude mixture of **27b** and the amino ester was then dissolved in anhydrous CH_2Cl_2 (5 mL) and cooled to 0 °C. NEt_3 (0.12 mL, 0.86 mmol) and $MsCl$ (32 μ L, 0.44 mmol) were added and the resulting reaction was stirred at 0 °C for 15 minutes. The reaction was diluted with Et_2O and washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated to give 88 mg 7-(2-methanesulfonyloxymethyl-4,6-dimethoxyphenyl)-2,1-benzisoxazolin-3-one.

The crude mesylate was dissolved in 4 mL of 1:1 THF/H_2O and Na_2CO_3 (80 mg) was added at 25 °C. The resulting mixture was stirred at 25 °C for 40 minutes. The reaction was diluted with Et_2O and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated to give 65 mg of crude **28b**. Flash chromatography (hexanes/ $EtOAc$ 3:1) gave 21 mg (47% from **26b**) of pure **28b**: mp 234 °C (decomposition); 1H NMR ($CDCl_3$) 8.31 (d, 1, $J = 7.4$), 7.61 (d, 1, $J = 8.0$), 7.26 (dd, 1, $J = 8.0, 7.4$), 6.55 (d, 1, $J = 1.8$), 6.47 (d, 1, $J = 1.8$), 4.52 (s, 2), 4.00 (s, 3), 3.87 (s, 3); ^{13}C NMR ($CDCl_3$) 168.4, 160.9, 158.9, 156.3, 134.1, 131.0, 125.5, 122.4, 120.4, 111.3, 110.5, 105.2, 99.0, 56.1, 55.64, 55.56; IR 1761; HRMS (EI) calcd for $C_{16}H_{13}NO_4$ (M^+) 283.0845, found 283.0844.

Methyl 3-Bromo-2-nitrobenzoate (**33**)

A suspension of 3-bromo-2-nitrotoluene (**34**, 3.55 g, 16.4 mmol) and potassium dichromate (9.0 g, 30.5 mmol) in 15 mL of water was prepared in a 100 mL two-neck flask. The mixture was treated with 26.5 mL of conc H_2SO_4 through an addition funnel and a thermometer was used to monitor the internal temperature. The temperature was kept between 50 and 56 °C during the addition using an ice bath during for cooling if needed. After the addition was complete (15 min), the reaction was stirred for 15 min and then heated at 65 °C for 3 h. The reaction was cooled and poured into 100 mL of ice-water. The resulting mixture was stirred for 5 min and filtered. The solid obtained was added to 30 mL of 2 M Na_2CO_3 solution and the resulting suspension was filtered. The filtrate was cooled to 0 °C and 21 mL of 25% aqueous HCl was added dropwise. The resulting slurry was extracted twice with $EtOAc$. The water layer was saturated with $NaCl$ and extracted with $EtOAc$. The combined $EtOAc$ layers were concentrated to give 3.42 g of crude 3-bromo-2-nitrobenzoic acid.¹³

The crude acid was dissolved in 10 mL of anhydrous DMF and the resulting solution was treated with 10 g (72 mmol) of K_2CO_3 and 4 mL (64 mmol) of methyl iodide. The reaction was stirred at 25 °C for 12 h. The mixture was then diluted with 100 mL of water and extracted with EtOAc (3 ×). The combined EtOAc layers were concentrated to give 4.13 g of crude **33**. Flash chromatography (6:1 hexanes/EtOAc) gave 2.96 g (69%) of pure **33**: $R_f = 0.41$ (3:1 hexanes/EtOAc); mp 116–117 °C; 1H NMR ($CDCl_3$) 8.04 (d, 1, $J = 8.0$), 7.88 (d, 1, $J = 8.0$), 7.46 (dd, 1, $J = 8.0, 8.0$), 3.92 (s, 3); ^{13}C NMR ($CDCl_3$) 162.4, 150.6, 137.9, 130.9, 130.3, 124.4, 114.4, 53.3; IR 1732, 1542, 1439, 1368, 1284.

Methyl 2-Nitro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**31**)

A solution of **33** (262 mg, 1.0 mmol) and isopropyl pinacol borate (400 μ L, 2.0 mmol) in 5 mL of 4:1 PhMe/THF was cooled in a MeOH/Liq N_2 bath (−97 °C). The solution turned milky and the resulting mixture was treated with 1.45 M *n*-BuLi (1.38 mL, 2.0 mmol) dropwise over 1 h. After the addition was complete, the reaction became yellow brown. This reaction was warmed to −78 °C and stirred at that temperature for 1 h. The reaction was then warmed to −20 °C over 10 min and AcOH (0.12 mL, 2.1 mmol) was added. The reaction was further warmed to 25 °C, diluted with EtOAc, and filtered. The filtrate was washed with 1:1 saturated NH_4Cl solution/ H_2O (twice), saturated $NaHCO_3$ solution, and brine and dried (Na_2SO_4). Concentration gave 401 mg of crude **31** that contained toluene. The product was taken up in hexanes (0.5 mL) and the resulting solution was cooled at −20 °C for 30 min resulting in the crystallization of **31**. The crystals were washed with 10:1 hexanes/EtOAc twice and air-dried to give 166 mg (52%) of pure **31**. This compound has an extremely weak UV absorption at 254 nm because of the twisted conformation and visualizes poorly with TLC stains: 1H NMR ($CDCl_3$) 7.94 (d, 1, $J = 7.2$), 7.89 (d, 1, $J = 7.2$), 7.59 (dd, 1, $J = 7.2, 7.2$), 3.90 (s, 3), 1.35 (s, 12); ^{13}C NMR ($CDCl_3$) 164.7, 153.4, 138.4, 135.0, 132.5, 130.5, 124.3, 85.0 (2 C), 53.1, 24.5 (4 C); IR 1735, 1546, 1358, 1270, 1139; HRMS (ESI+) calcd for $C_{14}H_{18}NO_6BNa$ (MNa^+) 330.1125, found 330.1118.

1-Hydroxy-3-hydroxymethyl-9H-xanthen-9-one (**37b**)

1-Hydroxy-3-methyl-9H-xanthen-9-one (**37a**) (511 mg, 2.26 mmol) in 10 mL of anhydrous CH_2Cl_2 was treated with acetic anhydride (0.64 mL, 6.78 mmol), pyridine (1.10 mL, 13.6 mmol) and DMAP (55 mg, 0.45 mmol) and the resulting solution was stirred at 25 °C for 4 h. 10 mL of H_2O was added to the reaction and the mixture was stirred for another 30 min to hydrolyze the excess Ac_2O . The reaction was then diluted with CH_2Cl_2 , washed with 5% aqueous HCl, saturated $NaHCO_3$ solution, and brine, and dried (Na_2SO_4). Concentration gave 610 mg of crude 1-acetoxy-3-methyl-9H-xanthen-9-one (**44**) that was used for the next step without purification. An analytical sample was prepared by recrystallization from hexanes/EtOAc: $R_f = 0.37$ (3:1 hexanes/EtOAc); 1H NMR ($CDCl_3$) 8.24 (d, 1, $J = 8.0$), 7.69 (dd, 1, $J = 8.0, 8.0$), 7.43 (d, 1, $J = 8.0$), 7.34 (dd, 1, $J = 8.0, 8.0$), 7.21 (s, 1), 6.83 (s, 1), 2.49 (s, 3), 2.49 (s, 3); ^{13}C NMR ($CDCl_3$) 175.6, 170.0, 157.2, 155.3, 149.7, 146.3, 134.6, 126.5, 124.0, 122.2, 119.4, 117.6, 116.1, 112.7, 21.9, 21.2; IR 1770, 1655, 1630, 1609, 1192. The spectral data are identical to those previously reported.²⁴

The crude acetate was transferred to a resealable tube and 5 mL of CCl_4 was added. The mixture was heated to 77 °C, and AIBN (74 mg, 0.45 mmol) and NBS (480 mg, 2.70 mmol) were then added. The tube was sealed and heated at that temperature for 16 h. The reaction was cooled, diluted with CH_2Cl_2 , washed with water, 10% aqueous hydrochloric acid, and brine, and dried (Na_2SO_4). Concentration gave 913 mg of crude product, which was a 7:4:2 mixture of 1-acetoxy-3-bromomethyl-9H-xanthen-9-one (**45**), 1-acetoxy-3-dibromomethyl-9H-xanthen-9-one and recovered 1-acetoxy-3-methyl-9H-xanthen-9-one (**44**) that was used for the next step. An analytical sample of **45** was prepared by flash chromatography (6:1 to 3:1 hexanes/EtOAc) to remove 1-acetoxy-3-methyl-9H-xanthen-9-

one (**44**) and recrystallization from hexanes/EtOAc: $R_f = 0.35$ (3:1 hexanes/EtOAc); $^1\text{H NMR}$ (CDCl_3) 8.24 (d, 1, $J = 8.0$), 7.72 (dd, 1, $J = 8.0, 8.0$), 7.46 (d, 1, $J = 8.0$), 7.45 (s, 1), 7.37 (dd, 1, $J = 8.0, 8.0$), 7.04 (s, 1), 4.51 (s, 2), 2.50 (s, 3); $^{13}\text{C NMR}$ (CDCl_3) 175.4, 169.7, 157.2, 155.3, 150.3, 144.7, 135.3, 126.6, 124.3, 122.2, 118.8, 117.6, 116.4, 114.6, 30.9, 21.2; IR 1772, 1657, 1632, 1610, 1194.

Crude benzyl bromide **45** and CaCO_3 (500 mg, 5 mmol) in 6 mL of 1:1 1,4-dioxane/ H_2O in a sealed tube were heated at 120 °C for 16 h. The reaction was cooled and K_2CO_3 (500 mg, 3.62 mmol) was added. The reaction was stirred at 25 °C for 2 h. The reaction was diluted with EtOAc, washed with water and brine, and dried (Na_2SO_4). Concentration gave 743 mg of crude **37b**. Flash chromatography (3:1 to 2:1 hexanes/EtOAc) gave 275 mg (50%) of pure **37b**: $R_f = 0.38$ (1:1 hexanes/EtOAc); mp 149-150 °C; $^1\text{H NMR}$ (CDCl_3) 12.63 (s, 1, ArOH), 8.27 (d, 1, $J = 8.0$), 7.76 (dd, 1, $J = 8.0, 8.0$), 7.47 (d, 1, $J = 8.0$), 7.40 (dd, 1, $J = 8.0, 8.0$), 6.98 (s, 1), 6.77 (s, 1), 4.79 (d, 2, $J = 5.6$), 1.93 (t, 1, $J = 5.6$, OH); $^{13}\text{C NMR}$ (CDCl_3) 182.0, 161.9, 156.5, 156.2, 151.3, 135.5, 125.9, 124.1, 120.6, 117.9, 108.0, 107.8, 104.4, 64.5; IR 3501 (br), 1655, 1609; HRMS (EI+) calcd for $\text{C}_{14}\text{H}_{10}\text{O}_4$ (M^+) 242.0579, found 242.0582.

1-Hydroxy-3-hydroxymethyl-2-iodo-9H-xanthen-9-one (**30a**)

A solution of benzyl alcohol **37b** (106 mg 0.44 mmol), I_2 (89 mg, 0.35 mmol, 0.8 equiv), and H_5IO_6 (40 mg, 0.18 mmol, 0.4 equiv) in 7.5 mL of 2:2:1 THF/EtOH/ H_2O was stirred at 25 °C for 40 h. The reaction was quenched with 5 mL of 10% $\text{Na}_2\text{S}_2\text{O}_3$ solution, and diluted with EtOAc. The mixture was washed with water and brine, and dried (Na_2SO_4). Concentration gave 159 mg (99%) of crude **30a**, which can be used directly without further purification: $R_f = 0.56$ (1:1 hexanes/EtOAc); mp 220-221 °C (darkens at 199 °C); $^1\text{H NMR}$ ($\text{DMSO}-d_6$) 13.51 (s, 1, ArOH), 8.18 (d, 1, $J = 8.0$), 7.93 (dd, 1, $J = 8.0, 8.0$), 7.69 (d, 1, $J = 8.0$), 7.52 (dd, 1, $J = 8.0, 8.0$), 7.23 (s, 1), 5.83 (t, 1, $J = 5.6$, OH), 4.50 (d, 2, $J = 5.6$); $^{13}\text{C NMR}$ ($\text{DMSO}-d_6$) 180.8, 159.3, 155.9, 155.6, 154.1, 136.6, 125.6, 124.8, 119.5, 118.2, 107.0, 105.9, 77.5, 67.9; IR 3445 (br), 1638, 1602, 1571, 1267; HRMS (EI+) calcd for $\text{C}_{14}\text{H}_9\text{IO}_4$ (M^+) 367.9546, found 367.9545. A sample for X-ray crystallography was prepared by recrystallization from THF.

3-Hydroxymethyl-2-iodo-1-methoxy-9H-xanthen-9-one (**30b**)

Iodo-9H-xanthen-9-one **30a** (100 mg, 0.27 mmol) in anhydrous DMF (4 mL) was treated with MeI (0.05 mL, 2.7 mmol, 10 equiv) and K_2CO_3 (373 mg, 2.7 mmol, 10 equiv). The reaction was stirred at 25 °C for 12 h. The reaction was filtered and the filtrate was concentrated. The solid was re-dissolved in a minimum amount of THF and silica gel (6 g) was added to the solution. The solvent was removed and **30b** adsorbed on silica gel was purified by flash chromatography (2:1 hexanes/EtOAc) to give 72 mg (69%) of pure **30b**: $R_f = 0.54$ (1:1 hexanes/EtOAc); mp 216-217 °C (darkens at 214 °C); $^1\text{H NMR}$ ($\text{DMSO}-d_6$) 8.18 (d, 1, $J = 8.0, 1$), 7.85 (dd, 1, $J = 8.0, 8.0$); 7.64 (d, 1, $J = 8.0$), 7.51 (s, 1), 7.47 (dd, 1, $J = 8.0, 8.0$), 5.86 (t, 1, $J = 5.6$, OH), 4.51 (d, 2, $J = 5.6$), 3.84 (s, 3); $^{13}\text{C NMR}$ ($\text{DMSO}-d_6$) 173.9, 158.3, 157.4, 154.6, 152.2, 135.2, 126.2, 124.4, 121.8, 117.8, 114.6, 112.2, 89.7, 67.8, 61.3; IR 3467 (br) 1656, 1600; HRMS (EI+) calcd for $\text{C}_{15}\text{H}_{11}\text{IO}_4$ (M^+) 381.9702, found 381.9695.

1-Hydroxy-3-hydroxymethyl-2-(2-nitro-3-methoxycarbonylphenyl)-9H-xanthen-9-one (**43**)

Iodo-9H-xanthen-9-one **30a** (30 mg, 81 μM), boronate **31** (65 mg, 211 μM , 2.6 equiv), $\text{Pd}(\text{OAc})_2$ (5.5 mg, 24 μM , 0.30 equiv) and SPhos (9.6 mg, 24 μM , 0.30 equiv) were added to a sealed tube. The tube was evacuated and backfilled with N_2 three times. Freshly distilled THF (1.5 mL) and degassed water (freeze-thaw cycle three times) (0.5 mL) were then added to the mixture. The reaction was heated at 80 °C for 2 h. The reaction was cooled, diluted with EtOAc, washed with H_2O and brine, and dried (Na_2SO_4). Concentration

gave 90 mg of crude **43**. Flash chromatography (2:1 hexanes/EtOAc) gave 20 mg (58%) of pure **43**: $R_f = 0.28$ (1:1 hexanes/EtOAc); $^1\text{H NMR}$ (DMSO- d_6) 12.77 (s, 1, ArOH), 8.20 (d, 1, $J = 8.0$), 8.10 (d, 1, $J = 8.0$), 7.96 (dd, 1, $J = 8.0, 8.0$), 7.88 (dd, 1, $J = 8.0, 8.0$), 7.77 (d, 1, $J = 8.0$), 7.74 (d, 1, $J = 8.0$), 7.54 (dd, 1, $J = 8.0, 8.0$), 7.29 (s, 1), 5.64 (t, 1, $J = 5.6$, OH), 4.33 (dd, 1, $J = 15.6, 5.6$), 4.26 (dd, 1, $J = 15.6, 5.6$), 3.87 (s, 3); $^{13}\text{C NMR}$ (DMSO- d_6) 181.5, 163.8, 157.9, 156.1, 155.8, 152.2, 149.5, 136.8, 136.7, 131.8, 130.8, 127.9, 125.4, 124.9, 123.8, 119.9, 118.2, 113.8, 106.6, 104.4, 60.7, 53.3; IR 3543 (br), 3416 (br), 1727, 1649, 1612, 1543, 1472, 1434, 1283; HRMS (ESI+) calcd for $\text{C}_{22}\text{H}_{16}\text{NO}_8$ (MH^+) 422.0876, found 422.0867.

3-Hydroxymethyl-1-methoxy-2-(2-nitro-3-methoxycarbonylphenyl)-9H-xanthen-9-one (**46**)

Iodide **30b** (20 mg, 52 μM), boronate **31** (45 mg, 147 μM , 2.8 equiv), $\text{Pd}(\text{OAc})_2$ (5.6 mg, 25 μM , 0.50 equiv) and SPhos (11 mg, 27 μM , 0.55 equiv) were added to a sealed tube. The tube was evacuated and backfilled with N_2 for three times. Freshly distilled THF (0.6 mL) and degassed water (freeze-thaw cycle three times) (0.2 mL) were then added to the mixture. The reaction was heated at 80 $^\circ\text{C}$ for 2 h. The reaction was cooled, diluted with EtOAc, washed with H_2O and brine, and dried (Na_2SO_4). Concentration gave 51 mg of crude **46**. Flash chromatography (1:1 hexanes/EtOAc) gave 12 mg (53%) of pure **46**: $R_f = 0.18$ (1:1 hexanes/EtOAc); $^1\text{H NMR}$ (DMSO- d_6) 8.16 (d, 1, $J = 8.0$), 8.10 (d, 1, $J = 8.0$), 7.88 (dd, 1, $J = 8.0, 8.0$), 7.87 (d, 1, $J = 8.0, 8.0$), 7.81 (d, 1, $J = 8.0$), 7.67 (d, 1, $J = 8.0$), 7.56 (s, 1), 7.48 (dd, 1, $J = 8.0, 8.0$), 5.64 (t, 1, $J = 5.6$, OH), 4.26 (d, 2, $J = 5.6$), 3.87 (s, 3), 3.57 (s, 3); $^{13}\text{C NMR}$ (DMSO- d_6) 174.5, 163.8, 157.6, 157.0, 154.6, 150.2, 149.0, 136.3, 135.3, 131.5, 130.8, 128.5, 126.0, 124.5, 123.9, 122.4, 122.1, 117.8, 113.7, 110.7, 62.1, 60.5, 53.3; IR 3440 (br), 1733, 1657, 1605, 1541, 1468, 1416, 1290, HRMS (ESI+) calcd for $\text{C}_{23}\text{H}_{17}\text{NO}_8\text{Na}$ (MNa^+) 458.0852, found 458.0850.

4,7-Dihydro-15-hydroxy-[1]benzopyrano[2,3-*f*]isoxazolo[4,3,2-*de*]phenanthridine-4,14-dione (**29a**)

A solution of Suzuki-Miyaura coupling product **43** (18 mg, 49 μmol), Zn (40 mg, 0.61 mmol), and NH_4Cl (60 mg, 1.12 mmol) in 5 mL of 2:2:1 MeOH/THF/ H_2O was sonicated at 25 $^\circ\text{C}$ for 15 min. The reaction was diluted with 5 mL of THF and filtered. The filtrate was further diluted with 10 mL of EtOAc, and the resulting solution was washed with brine and dried (MgSO_4). Concentration gave 20 mg of crude hydroxymethyl benzisoxazolinone **47**.

A suspension of the crude hydroxymethyl benzisoxazolinone **47** in 5 mL of anhydrous CH_2Cl_2 was cooled to 0 $^\circ\text{C}$. NEt_3 (24 μL , 4 equiv) and MsCl (10 μL , 3 equiv) were added. The reaction was stirred at 0 $^\circ\text{C}$ for 15 min and warmed to 25 $^\circ\text{C}$ and stirred for another 45 min. The solid dissolved as the reaction proceeded. The solution was diluted with CH_2Cl_2 , washed with water and brine, and dried (Na_2SO_4). Concentration gave 24 mg of the benzisoxazolinone mesylate.

A solution of the crude mesylate in 6 mL of 1:1 THF/ H_2O was cooled to 0 $^\circ\text{C}$. Na_2CO_3 (106 mg, 1 mmol) was added to this solution. The reaction was stirred at 0 $^\circ\text{C}$ for 5 min and 25 $^\circ\text{C}$ for another 55 min. A precipitate formed as the reaction proceeded. The reaction was diluted with 20 mL of THF to dissolve the precipitate and the resulting aqueous THF solution was washed with brine and dried (MgSO_4). Concentration gave 7.5 mg of crude orange **29a**. Crude **29a** was washed twice with chloroform and air dried to give 7 mg (46%) of pure **29a** as a poorly soluble yellow-orange solid that was too insoluble in all common NMR solvents for a $^{13}\text{C NMR}$ spectrum to be obtained: $^1\text{H NMR}$ (CDCl_3) 13.84 (s, 1, ArOH), 8.62 (d, 1, $J = 8.0$), 8.34 (d, 1, $J = 8.0$), 7.83 (dd, 1, $J = 8.0, 8.0$), 7.72 (d, 1, $J = 8.0$), 7.54 (d, 1, $J = 8.0$), 7.48 (dd, 1, $J = 8.0, 8.0$), 7.38 (dd, 1, $J = 8.0, 8.0$), 6.99 (s, 1), 4.69 (s, 2); HRMS (ESI+) calcd for $\text{C}_{21}\text{H}_{12}\text{NO}_5$ (MH^+) 358.0715, found 358.0707.

4,7-Dihydro-15-methoxy-[1]benzopyrano[2,3-*j*]isoxazolo[4,3,2-*de*]phenanthridine-4,14-dione (29b)

A solution of Suzuki-Miyaura coupling product **46** (14 mg, 32 μmol), Zn (34 mg, 0.55 mmol) and NH_4Cl (54 mg, 1 mmol) in 5 mL of 2:2:1 MeOH/THF/ H_2O was sonicated at 25 $^\circ\text{C}$ for 15 min. The reaction was diluted with EtOAc, and filtered. The filtrate was washed with brine, and dried (Na_2SO_4). Concentration gave 18 mg of crude hydroxymethyl benzisoxazolinone **48**.

A solution of hydroxymethyl benzisoxazolinone **48** in 3 mL of anhydrous CH_2Cl_2 was cooled to 0 $^\circ\text{C}$ and treated with NEt_3 (18 μL , 4 equiv) and MsCl (8 μL , 3 equiv). The reaction was stirred at 0 $^\circ\text{C}$ for 15 min and warmed to 25 $^\circ\text{C}$ and stirred for another 45 min. The solution was diluted with CH_2Cl_2 , washed with water and brine, and dried (Na_2SO_4). Concentration gave 18 mg of the benzisoxazolinone mesylate.

A solution of the crude mesylate in 6 mL of 1:1 THF/ H_2O solution was cooled to 0 $^\circ\text{C}$. Na_2CO_3 (106 mg, 1 mmol) was added to this solution. The reaction was stirred at 0 $^\circ\text{C}$ for 5 min and 25 $^\circ\text{C}$ for another 55 min. The resulting mixture was diluted with EtOAc, washed with water and brine, and dried (Na_2SO_4). Concentration gave 12 mg of crude **29b**. Flash chromatography (2:1 hexanes/EtOAc) gave 5 mg (42%) of pure **29b**: $R_f = 0.59$ (1:1 hexanes/EtOAc); $^1\text{H NMR}$ (CDCl_3) 8.62 (d, 1, $J = 8.0$), 8.34 (d, 1, $J = 8.0$), 7.77 (d, 1, $J = 8.0$), 7.76 (dd, 1, $J = 8.0, 8.0$), 7.48 (d, 1, $J = 8.0$), 7.45 (dd, 1, $J = 8.0, 8.0$), 7.40 (dd, 1, $J = 8.0, 8.0$), 7.30 (s, 1), 4.66 (s, 2), 4.02 (s, 3); $^{13}\text{C NMR}$ (CDCl_3) 175.5, 167.9, 158.9, 157.4, 156.8, 155.0, 139.1, 135.0, 132.2, 126.8, 126.4, 124.57, 124.55, 122.7, 119.09, 119.07, 117.5, 116.8, 114.1, 111.3, 61.8, 56.0; IR 1765, 1652, 1609, 1470, 1415; HRMS (ESI+) calcd for $\text{C}_{22}\text{H}_{14}\text{NO}_5$ (MH^+) 372.0872, found 372.0868.

Decomposition of 4*H*,7*H*-Isoxazolo[4,3,2-*de*]phenanthridinones 12, 24b and 28b in CDCl_3

A sample (3 mg) of each compound was dissolved in 0.5 mL of CDCl_3 in an NMR tube at 25 $^\circ\text{C}$. The decomposition was monitored by $^1\text{H NMR}$ spectroscopy. The reaction formed only the phenanthridine-4-carboxylic acids **49a**, **49b**, and **49c**, respectively. No intermediates were observed.

Data for phenanthridine-4-carboxylic acid (**49a**): $^1\text{H NMR}$ (CDCl_3) 9.33 (s, 1), 8.86 (d, 1, $J = 8.0$), 8.82 (d, 1, $J = 8.0$), 8.72 (d, 1, $J = 8.0$), 8.21 (d, 1, $J = 8.0$), 8.05 (dd, 1, $J = 8.0, 8.0$), 7.90 (dd, 1, $J = 8.0, 8.0$), 7.87 (dd, 1, $J = 8.0, 8.0$). An authentic sample of **49a** was prepared by the literature procedure.^{21b} The $^1\text{H NMR}$ spectrum of the authentic sample of **49a** is identical to that of the product of decomposition of **12** in CDCl_3 .

The data for the mixture of **24b** and **49b** matched those of authentic samples. An authentic sample of **49b** was prepared from **22b** as previously described.¹⁰

Data for 8,10-dimethoxyphenanthridine-4-carboxylic acid (**49c**): $^1\text{H NMR}$ (CDCl_3) 9.60 (dd, 1, $J = 8.0, 1.3$), 9.12 (s, 1), 8.70 (dd, 1, $J = 8.0, 1.3$), 7.78 (dd, 1, $J = 8.0, 8.0$), 7.08 (d, 1, $J = 2.2$), 7.05 (d, 1, $J = 2.2$), 4.16 (s, 3), 4.03 (s, 3); HRMS (ESI+) calcd for $\text{C}_{16}\text{H}_{14}\text{NO}_4$ (MH^+) 284.0923, found 284.0910. The 10-methoxy group deshields H-1 which absorbs far downfield at δ 9.60.26

Decomposition of 4,7-Dihydro-15-methoxy-[1]benzopyrano[2,3-*j*]isoxazolo[4,3,2-*de*]phenanthridine-4,14-dione (29b) in CDCl_3

A solution of benzisoxazolinone **29b** in CDCl_3 was monitored at 25 $^\circ\text{C}$. The compound slowly rearranged with a half life of 2 days to give acid 14-hydroxy-13-oxo-13*H*-[1]benzopyrano[2,3-*j*]phenanthridine-4-carboxylic acid (**50**) as the major product: $^1\text{H NMR}$

(CDCl₃) 9.83 (d, 1, *J* = 8.0), 9.34 (s, 1), 8.82 (d, 1, *J* = 8.0), 8.39 (d, 1, *J* = 8.0), 8.06 (s, 1), 7.95 (dd, 1, *J* = 8.0, 8.0), 7.81 (dd, 1, *J* = 8.0, 8.0), 7.54 (d, 1, *J* = 8.0, 1), 7.46 (dd, 1, *J* = 8.0, 8.0), 4.15 (s, 3).

X-Ray Data Collection, Solution, and Refinement for 1-Hydroxy-2-iodo-3-hydroxymethyl-9*H*-xanthen-9-one (30a)

All operations were performed on a Bruker-Nonius Kappa Apex2 diffractometer, using graphite-monochromated MoK α radiation. All diffractometer manipulations, including data collection, integration, scaling, and absorption corrections were carried out using the Bruker Apex2 software.²⁷ Preliminary cell constants were obtained from three sets of 12 frames. Data collection was carried out at 120K, using a frame time of 10 sec and a detector distance of 60 mm. The optimized strategy used for data collection consisted of 4 phi and 4 omega scan sets, with 0.5° steps in phi or omega; completeness was 100.0%. A total of 2870 frames were collected. Final cell constants were obtained from the xyz centroids of 5788 reflections after integration.

From the systematic absences, the observed metric constants and intensity statistics, space group *P*2₁/*c* was chosen initially; subsequent solution and refinement confirmed the correctness of this choice. The structure was solved using Superflip,²⁸ and refined (full-matrix-least squares) using the Oxford University *Crystals for Windows* program.²⁹ All ordered non-hydrogen atoms were refined using anisotropic displacement parameters; ordered hydrogen atoms were first regularized with the use of restraints and subsequently allowed to ride on the corresponding carbon atoms. Compound **30a** exhibited disorder of the H atom attached to atom O(4) (–CH₂OH group). After location of the two disordered atoms by a combination of Fourier and geometric considerations, each H atom (H41 and H42) was assigned an occupancy of 0.5, and allowed to ride on atom O(4). The final least-squares refinement converged to *R*₁ = 0.0593 (*I* > 2σ(*I*), 3102 data) and w*R*₂ = 0.1234 (*F*², 3488 data, 172 parameters). The final CIF is available as supporting material.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

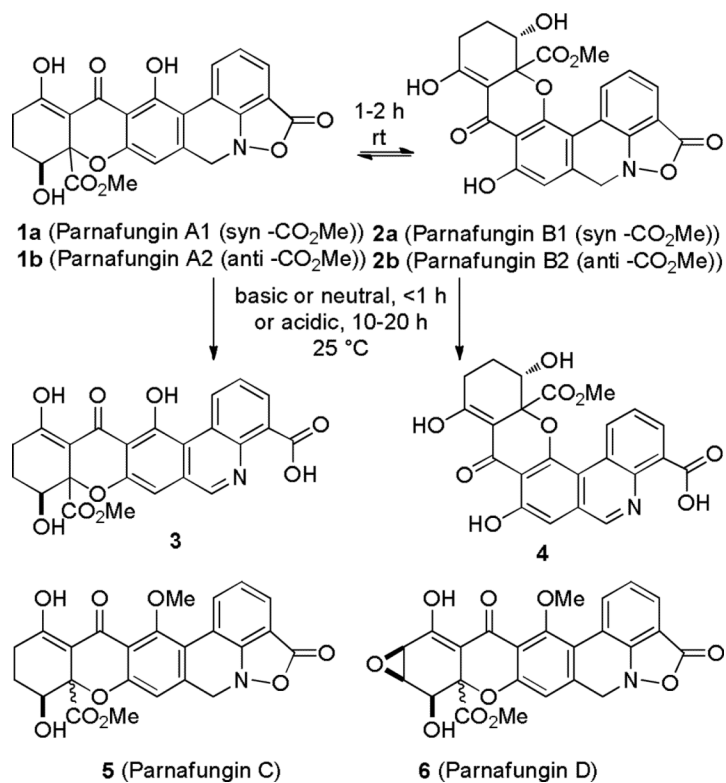
We are grateful to the National Institutes of Health (GM-50151) for support of this work. We thank the National Science Foundation for partial support of this work through grant CHE-0521047 for the purchase of a new X-ray diffractometer. We thank Professor Stephen Buchwald, Massachusetts Institute of Technology, for advice on Suzuki-Miyaura couplings.

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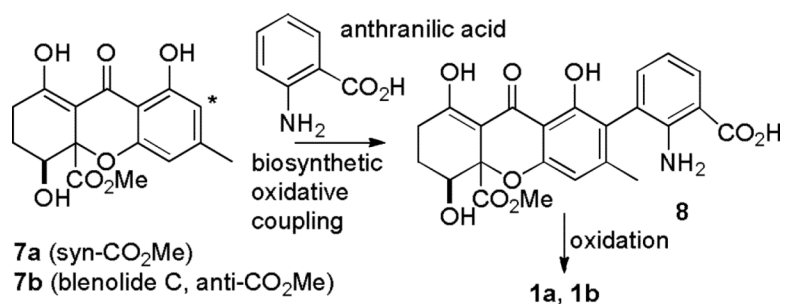
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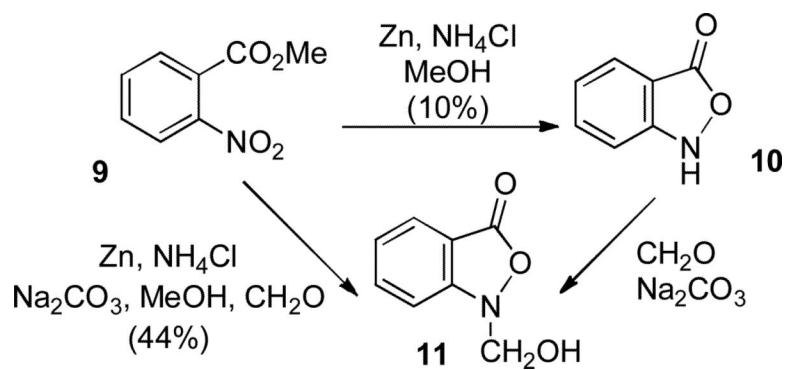
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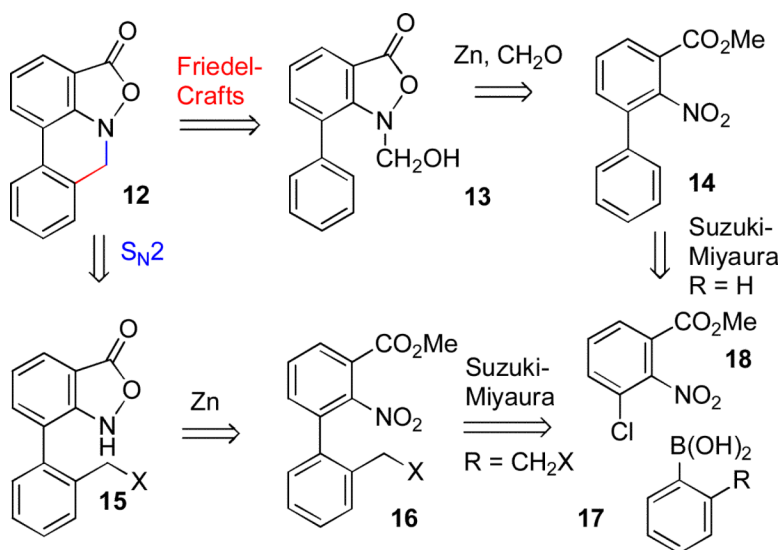
SCHEME 1.
Parnafungin Structures and Decomposition Products



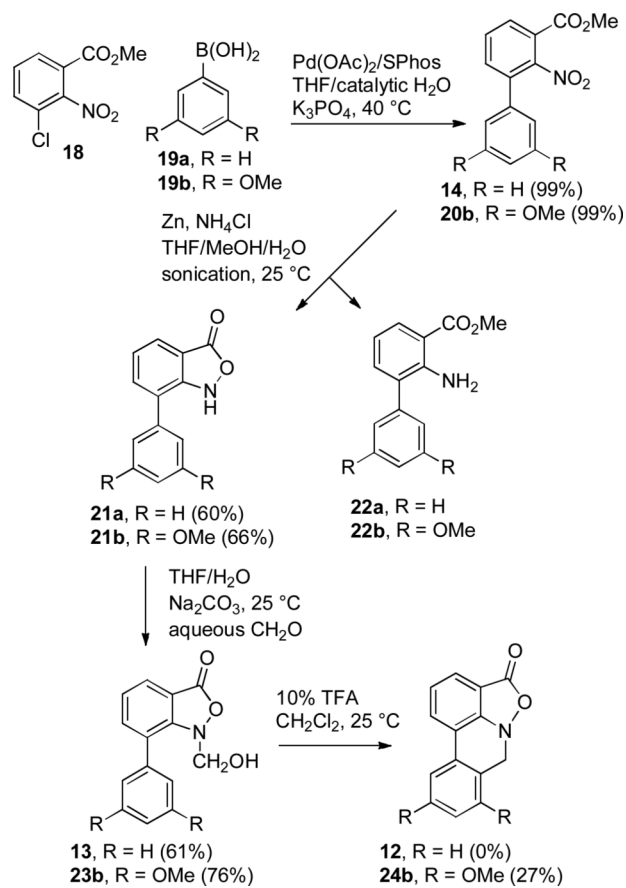
SCHEME 2.
Possible Biosynthesis of the Parnafungins



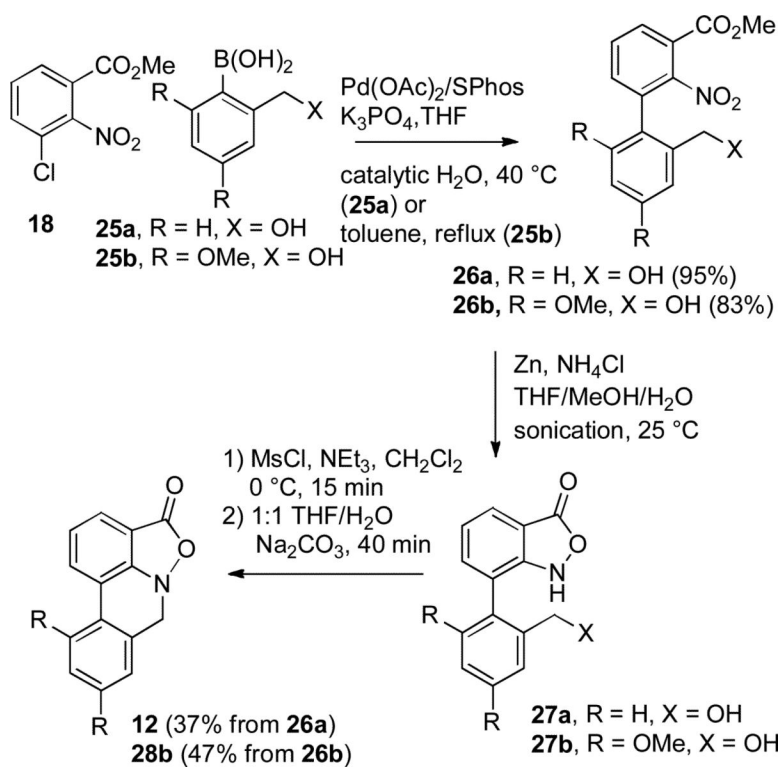
SCHEME 3.
Wierenga Benzisoxazolinone Synthesis



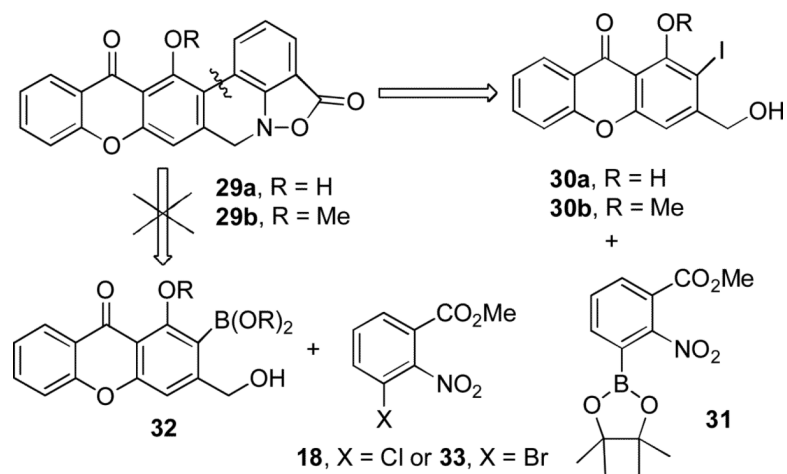
SCHEME 4.
Retrosynthesis of Tetracycle **12**



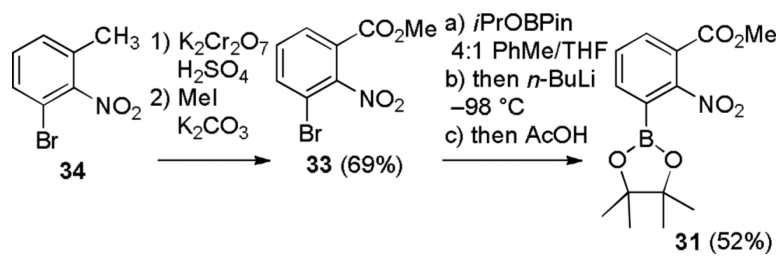
SCHEME 5.
 Synthesis of Tetracycle **24b**



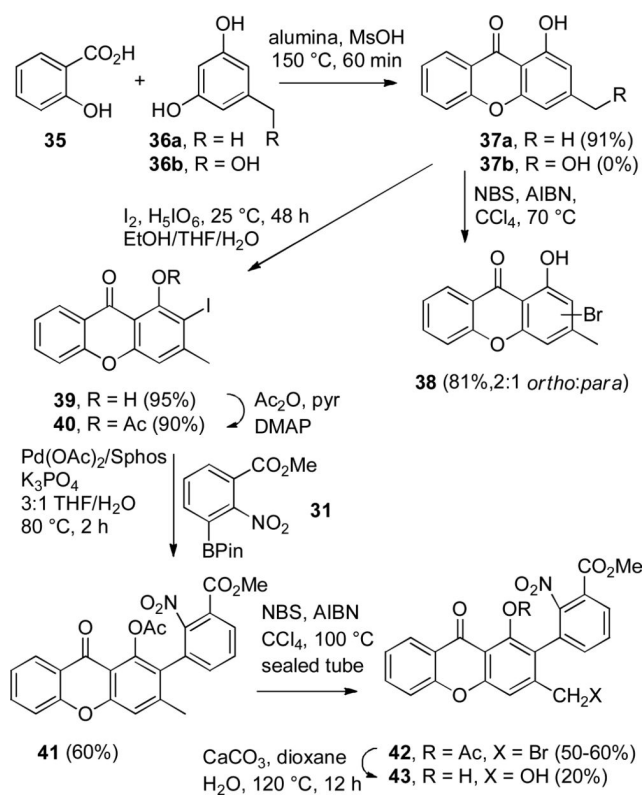
SCHEME 6.
Synthesis of Tetracycles **12** and **28c**



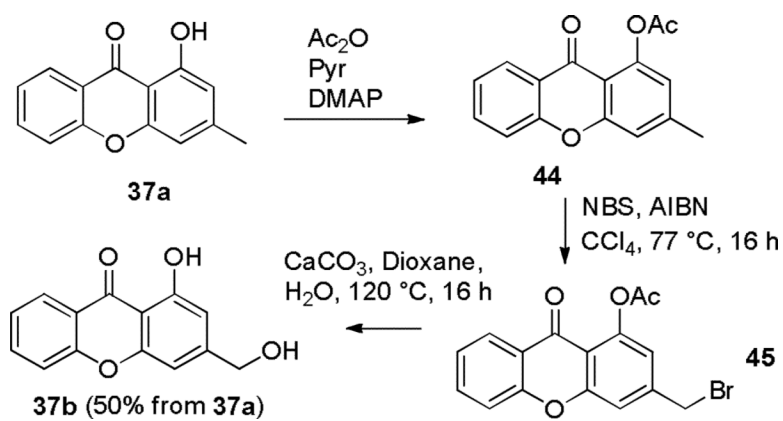
SCHEME 7.
Retrosynthesis of Hexacyclic Models **29a** and **29b**



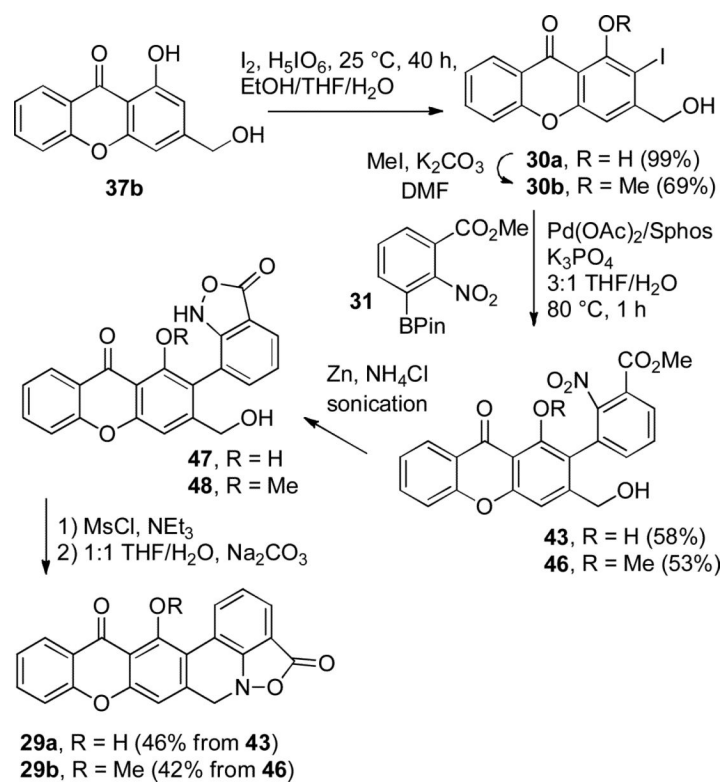
SCHEME 8.
Synthesis of Pinacol Boronate **31**



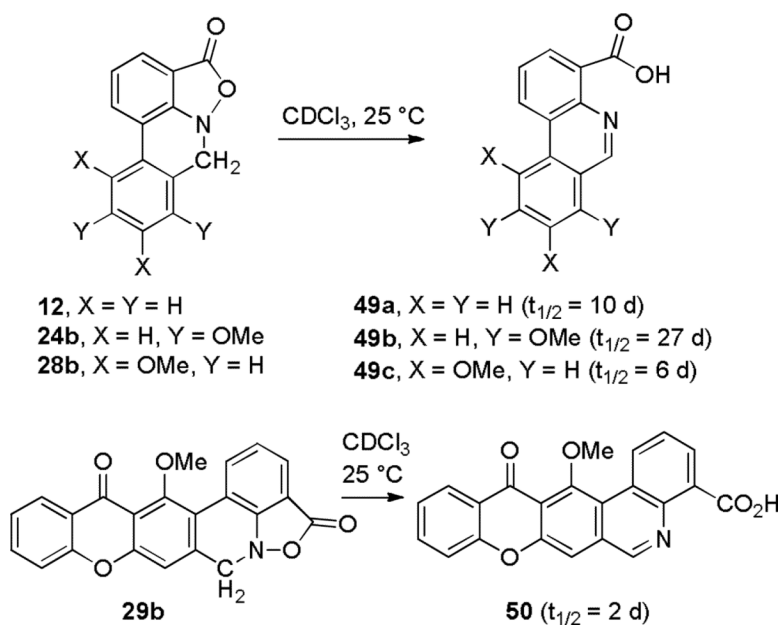
SCHEME 9.
Unsuccessful Route to **43**



SCHEME 10.
Oxidation of **37a** to give **37b**



SCHEME 11.
 Synthesis of Hexacyclic Parnafungin Models **29a** and **29b**



SCHEME 12.
Decomposition of Benzisoxazolinones **12**, **24b**, **28b** and **29b**