Hydroxylated 2-(5′-Salicyl)naphthalenes as Protein-Tyrosine Kinase Inhibitors

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The salicyl group figures prominently in several potent protein-tyrosine kinase (PTK) inhibitors, including the fermentation product lavendustin A (**3**), the salicylsulfonyl nitrostyryl **30**, and our recently reported salicyl-containing stilbene **7**. Taking compound **7** and the isomeric **8** as lead structures, bicyclic nuclei **9–12** were prepared as conformationally constrained mimetics in which the hydroxyphenyl rings of **7** and **8** are held coplanar with the stilbene ethylene bridge. A similar approach with styryl-based PTK inhibitors of structure **1** previously yielded analogues **2** with enhanced potency. In the present case, however, the resulting salicyl-containing bicyclics exhibited extremely poor inhibitory potency when examined against autophosphorylation of immunoprecipitated p56^{lck} PTK preparations. The implications of these results are discussed as they relate to the potential ways in which salicyl-containing stilbenes may be oriented relative to styryl-based inhibitors of type **1** and to an emerging class of potent aryl-substituted bicyclic inhibitors exemplified by compound **31**.

Protein-tyrosine kinases (PTKs) play critical roles in both normal and neoplastic cellular signal transduction.[1] The development of specific PTK inhibitors as pharmocological tools and potential antiproliferative agents has therefore become an active area of research.[2] We have previously approached the design of new inhibitors directed against the PTK catalytic site in two different ways. In the first instance; we assumed by analogy to the X-ray structure of the catalytic subunit of the cyclic AMP-dependent protein kinase[3] (which has high-sequence homology to a typical PTK catalytic domain[4]) that the overall geometry of a PTK catalytic domain is that of a deep planar cleft in which ATP binds to the rear and the phosphotyrosyl-bearing substrate binds toward the cleft's opening. Based on this assumption we hypothesized that extended planarity could be a key feature for improved interaction of some classes of PTK inhibitors at such a putative cleft-like catalytic center.[2a] This view is supported by the ability of several known PTK inhibitors to assume low-energy conformations which are highly planar. Exemplary is the "styryl-based" class of PTK inhibitors, which constitute a broad family of compounds of general structure **1** that include the natural product erbstatin **5**. We initially designed bicyclic aryl compounds as conformationally constrained mimetics of the styryl nucleus in which the phenyl ring is held at an angle coplanar with the vinyl side chain. These bicyclic arylamides **2** exhibited both high potency and interkinase specificity when examined in the nonreceptor PTK, p56^{lck}, and the epidermal growth factor receptor (EGFR), which is an example of a receptor PTK.[5]

While this first study[6] was predicated on a hypothetical preferential planar mode of binding, our second approach was different, in that we made no assumptions as to the mode of interaction of the prototypical parent compound [in this case the active pharmacophore **4** of the potent natural product PTK inhibitor, lavendustin A (**3**)] with the PTK catalytic site. Instead, note was taken of structural motifs of **4** shared with two other natural product

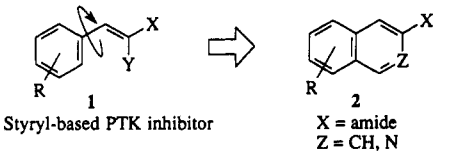
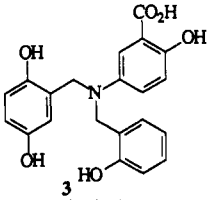
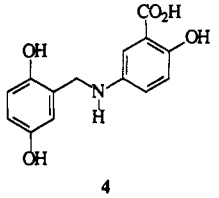


Figure 1. Design of bicyclic compounds **2** as conformationally constrained mimetics of open-chain styryl-based PTK inhibitors **1**.

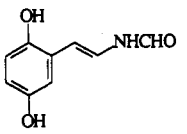
PTK inhibitors, erbstatin (**5**) and piceatannol (**6**). New analogues of **4** were prepared which combined different features of these other two inhibitors. The resulting analogues **7** and **8** contained, in addition to the salicyl ring of lavendustin A, the styryl or stilbene moieties of erbstatin and piceatannol and either the 2,5-dihydroxy pattern of erbstatin (compound **7**) or the 3,4-dihydroxy pattern of piceatannol (compound **8**). The 2,5-dihydroxy analogue **7**, which represents a desaminostilbene variation of the parent lavendustin A pharmacophore **4**, is one of the most potent inhibitors yet reported against p56^{lck} (IC_{50} = 0.06 μM)[6] and is 160-fold more potent than the parent **4** (IC_{50} = 10 μM).



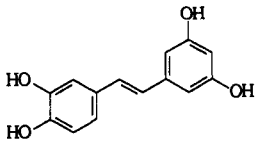
3
lavendustin A



4
lavendustin A
active pharmacophore



5
erbstatin



6
piceatannol

The present work seeks to build upon both of these two previous studies by employing a bicyclic naphthalene ring

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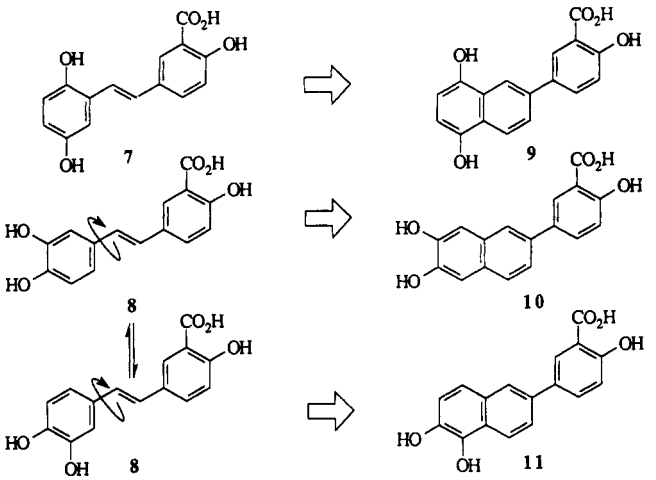


Figure 2. Design of naphthyl-based compounds 9–11 as conformationally constrained mimetics of open-chain styryls 7 and 8.

system, in a manner similar to the first approach, to conformationally restrain the rotation of the vinylic phenyl rings of analogues 7 and 8, which were themselves the product of the second study. The resulting compounds 9–11 are therefore mimetics of the parent salicyl-containing stilbenes 7 and 8 in which the phenyl ring is held coplanar with the vinyl bridge (Figure 2). The design of these naphthyl compounds is based on the assumption that similar to the styryl PTK inhibitors examined in the first studies, the phenyl rings of the open chain analogues 7 and 8 are close to being coplanar with the ethylene bridge when binding inside the putative flat PTK catalytic cleft. The synthesis and inhibitory potency of analogues 9–11 as well as that of the unsubstituted compound 12 against immunoprecipitated p56^{lck} are reported herein.

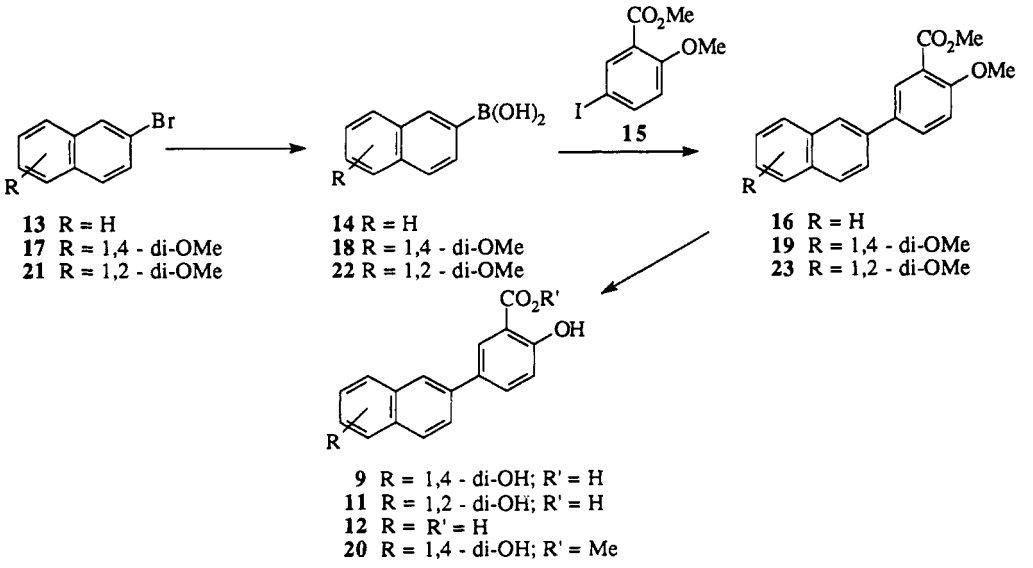
Synthesis

Compounds 15,[7] 17,[8] 21, and 24[9] were prepared according to literature procedures. The synthesis of analogues 9, 11, and 12 (Scheme I) was accomplished via Suzuki-coupling of the appropriate aryl boronic acid with iodosalicylate 15, followed by demethylation utilizing either BBr_3 (e.g., 16 to 12) or pyridine·HCl. Attempted demethylation of 19 using BBr_3 resulted in removal of only three methyl groups leaving the methyl ester intact (compound 20). Subsequent treatment of 20 with pyridine·HCl cleanly provided 9. It should be noted that basic conditions are not compatible with the free aromatic hydroxyls due to rapid oxidation/decomposition. The preparation of analogue 10 (Scheme II) required a slightly different approach due to the unavailability of bromide 29. The synthesis began with the Baeyer–Villiger oxidation of 24 followed by hydrolysis of the intermediate acetate with NH_4OH to provide 25. Conversion of naphthol 25 to triflate 26 followed by Stille-coupling with aryl stannane 27 (obtained from 15) afforded intermediate 28, which was then demethylated with pyridine·HCl to yield the final analogue 10.

Results and Discussion

In the absence of any direct three-dimensional information regarding the interaction of PTK inhibitors with a PTK catalytic site, we have attempted to design new PTK inhibitors by rational modification of preexisting inhibitors. One approach which has proven useful assumes that a typical PTK catalytic cleft has a high degree of planarity, similar to that observed with the serine/threonine protein kinase A.[3b,4b] Applying this premise to the styryl-based PTK inhibitors 1, bicyclic nuclei were previously developed as planar, conformationally restricted analogues, which showed both enhanced potency and interkinase selectivity relative to the open-chain, parent styryl compound.[5] In separate work,[6] we also showed that the hydroxylated stilbene 7, bearing a 5-salicyl ring, exhibited very good potency against the p56^{lck} PTK. Since the stilbene analogues 7 and 8 contain within their structures the "styryl nucleus" 1 common to many PTK inhibitors, a logical extension of our structure–activity studies was to apply to the stilbenes 7 and 8 the concept of conformational restriction which had previously proved successful in the styryl series. As shown in Figure 2, the resulting hydroxylated 2-(5′-salicyl)naphthalene 9 represents an analogue of the 2,5-dihydroxystilbene 7 in which the phenyl ring is held coplanar with the vinyl side chain. The isomeric 2,3-dihydroxynaphthalene 10 and 1,2-dihydroxynaphthalene 11 are designed to approximate the two possible rotamers of the open-chain parent 8. Isomeric constrained analogues mimicking the two phenyl rotational

Scheme I



Scheme II

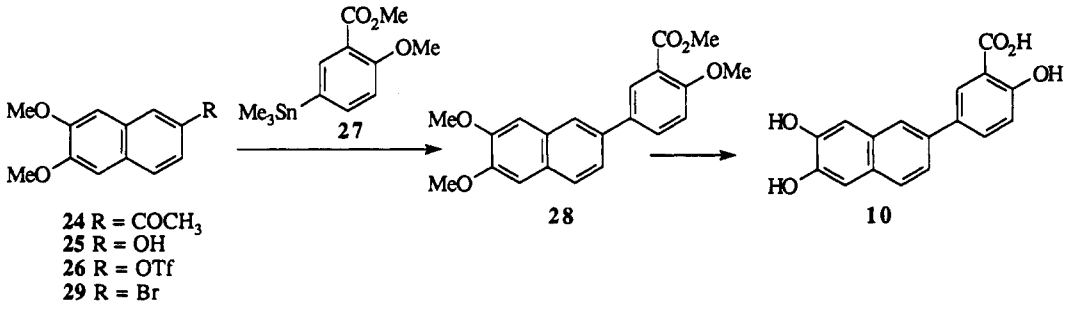
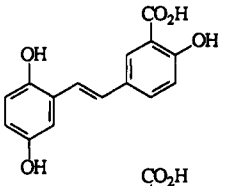
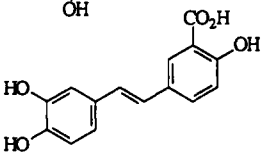
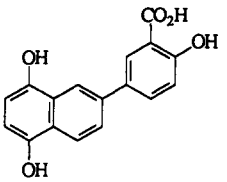
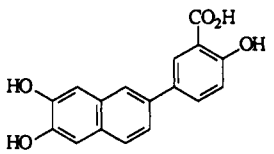
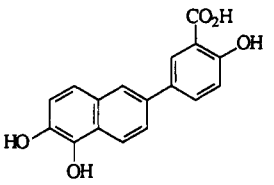
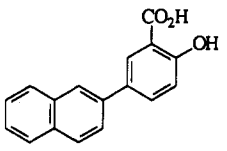


Table I. Inhibition of Immunoprecipitated PTK Autophosphorylation (IC_{50} μM)

no.		p56lck
7		0.06[6]
8		** [6]
9		65
10		150
11		42
12		>200

**Could not be determined: See reference 6.

isomers of styryl-based inhibitors have been previously shown to exhibit both differences in potency[5,10] and interkinase specificity.[5a]

When analogues **9–12** were examined for their ability to inhibit autophosphorylation of immunoprecipitated p56lck it was seen that all compounds exhibited extremely poor potency (Table I). Ring-constrained compound **9** (IC_{50} = 65 μM) was 1000-fold less active than the parent open-chain **7** (IC_{50} = 0.06 μM).[6] Isomeric *o*-hydroxy analogues **10** (IC_{50} = 150 μM) and **11** (IC_{50} = 42 μM), while

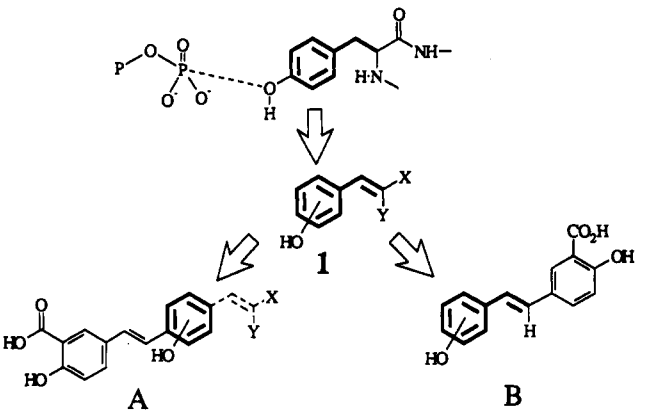


Figure 3. Potential models of salicyl-containing stilbenes relative to a putative enzyme bound ATP-tyrosyl bisubstrate complex.

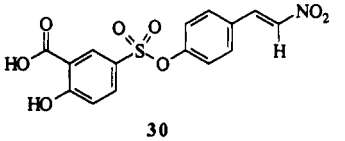
having poor potency, did show relative potencies consistent with that previously seen for p56lck using hydroxylated isoquinoline-3-carboxamides, where the 7,8-dihydroxy isomer (corresponding to the substitution pattern of naphthalene **11**) was more potent than the 5,6-dihydroxy isomer (which corresponds to the substitution pattern of naphthalene **10**). Compound **12**, which is devoid of hydroxyl substituents on the naphthyl ring, was totally inactive, indicating the importance of hydroxyl groups for even marginal potency.

These data may indicate that the salicyl-containing stilbenes cannot be directly compared to styryl-based PTK inhibitors in the manner attempted by this study. As shown in Figure 3, styryl-based PTK inhibitors **1** can be viewed as peptidomimetics competing with the tyrosyl portion of the ATP·peptide bisubstrate complex which would normally be bound within the catalytic cavity. Bicyclic ring-constrained mimetics of styryl-based inhibitors[5] were conceptually designed to lock the vinyl side chain of these molecules into a coplanar orientation with the phenyl ring (Figure 1). Viewed in this manner, the bicyclic analogues would also function as tyrosyl peptidomimetics. This concept is supported by the finding that a bicyclic PTK inhibitor was not competitive with respect to ATP.[5b] A direct application of these principles to the salicyl-containing stilbenes **7** and **8** would assume that the salicyl ring occupies vinylic position "X" of structure **1** (Figures 1 and 3), resulting in model "B" of Figure 3.

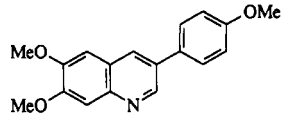
Using the hydroxylated phenyl ring as an anchor which occupies the same binding site as the tyrosyl phenyl ring, an alternative comparison is possible in which the salicyl ring extends toward the ATP binding domain (model A, Figure 3). Models A and B differ from each other with respect to the orientation of the "salicyl-bearing side chain" relative to the "tyrosyl phenyl ring." Model A is more

consistent with previously reported salicyl-containing styryl-based inhibitors such as **30** which were designed as potential bisubstrate analogues.[11] In these 4-substituted nitrostyryls, the salicyl ring was envisioned to interact at the catalytic cleft by mimicing portions of the ATP phosphate chain, while the nitrostyryl-portion was thought to bind as a tyrosyl mimetic. If compounds **7** and **8** bind similarly (model A, Figure 3), then the loss of potency incurred by construction of constrained bicyclic mimetics **9–11** may indicate that conformational constraints cannot be applied equally to both "right" and "left" sides of the tyrosyl phenyl ring.

While it is disappointing that none of the target compounds exhibited potent PTK inhibition, the study has yielded valuable insights into the design of PTK inhibitors, since it has explored a logical extension of previously successful SAR techniques. The fact that the salicyl ring figures prominently in a number of potent PTK inhibitors[6,11,12] makes this study useful in that it helps to delineate limits of salicyl-containing PTK inhibitory motifs. This has particular relevance to the recent report[13] of a series of extremely potent aryl-substituted bicyclic PTK inhibitors including compound **31** which are structurally similar to the inactive target compounds **9–12**. This latter report shows that when bearing the proper substituents, the aryl-substituted bicyclic nucleus can serve as the basis for very potent inhibitors. Our present work may also indicate that a salicyl ring is not compatible as the aryl unit for such compounds; however, this would need to be more fully explored.



30



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Experimental Section

Biochemical Assay. In vitro p56[lck] PTK kinase assays were conducted as previously described[5b] with phosphoprotein products being resolved by 7.5% reducing SDS-PAGE gel. The resulting gels were scanned by a Hoefer Scientific Instruments Scanning Densitometer and inhibition calculated from the relative band densities.

Synthesis. Petroleum ether was of the boiling range 35–60 °C, and removal of solvents was performed by rotary evaporation under reduced pressure. Silica gel filtration was carried out using TLC grade silica gel (5–25 μ; Aldrich). Melting points were determined on a Mel Temp II melting point apparatus and are uncorrected. Elemental analyses were obtained from Atlantic Microlab Inc., Norcross, GA, and are within 0.4% of theoretical values unless otherwise indicated. Fast atom bombardment mass spectra (FABMS) were acquired with a VG Analytical 7070E mass spectrometer under the control of a VG 2035 data system. ^{1}H NMR data were obtained on a Bruker AC250 (250 MHz) instrument.

2-Naphthylboronic Acid (14). Using an adaptation of a previously reported procedure,[14] to 2-bromonaphthalene **13** (1.00 g, 4.80 mmol) in THF (10 mL) at −78 °C was slowly added *n*-BuLi (1.6 M, 3.3 mL, 5.30 mmol). After stirring (15 min) $B(OMe)_3$ (1.2 mL, 10.6 mmol) in THF (2 mL) was added, and stirring was maintained as the temperature rose slowly to −50 °C (1.5 h). The reaction was quenched with 1 N HCl (5 mL) and warmed to room temperature. Extractive workup (Et_2O/1 N HCl), drying of the organic extracts with $MgSO_4$, and removal of solvent gave a white solid. Trituration with petroleum ether at room temperature, followed by cooling to −50 °C afforded **14** as a white powder (629 mg, 76%): mp 263–266 °C (lit.[15] mp 266 °C).

2-[3′-(Methylcarboxy)-4′-methoxyphenyl]naphthalene (16). A mixture of compounds **14** (100 mg, 0.58 mmol) and **15** (170 mg, 0.58 mmol), $Pd(PPh_3)_4$ (20 mg, 0.013 mmol), 2 M K_2CO_3 (0.6 mL, 1.2 mmol), and benzene (0.6 mL) was stirred at 75–80 °C (3 h), cooled to room temperature, and partitioned between $CHCl_3$ (2 mL) and saturated $NaHCO_3$ (2 mL). The $CHCl_3$ was washed with saturated $NaHCO_3$ (1 × 2 mL), dried ($MgSO_4$), and evaporated to give crude **16**. Silica gel chromatography (hexanes/EtOAc 6:1) afforded coupled product **16** (118 mg, 70%). An analytically pure sample was obtained by recrystallization from CH_2Cl_2/hexanes: mp 126–127 °C; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, 1H, J = 2.5 Hz, $H_{8'}$), 7.99 (d, 1H, J = 1.9 Hz, H_1), 7.89 (d, 1H, J = 8.7 Hz, H_4), 7.85 (m, 2H, H_5 and H_8), 7.82 (dd, 1H, J = 8.7, 2.5 Hz, $H_{4'}$), 7.70 (dd, 1H, J = 8.6, 1.9 Hz, H_3), 7.48 (m, 2H, H_6 and H_7), 7.09 (d, 1H, J = 8.7 Hz, $H_{3'}$), 3.96 (s, 3H, CO_2CH_3), 3.93 (s, 3H, OCH_3). Anal. ($C_{19}H_{16}O_3$) C, H.

2-(5′-Salicyl)naphthalene (12). To compound **16** (105 mg, 0.36 mmol) in dry CH_2Cl_2 (7 mL) at −78 °C was slowly added BBr_3 (1 M in CH_2Cl_2, 1.1 mL) followed by slow warming to room temperature over 5.5 h. After recooling to −78 °C, the reaction was quenched by addition of H_2O (5 mL), warmed to room temperature, partitioned between H_2O (25 mL) and EtOAc (2 × 25 mL), washed with brine (25 mL), dried ($MgSO_4$), and evaporated to give crude **12** as a yellow solid (99 mg). Trituration with petroleum ether/$CHCl_3$ (10:1, 30 mL) followed by cooling to −50 °C and filtration provided pure **12** as a light yellow crystalline powder (53 mg, 56%): mp 221–222 °C; ^{1}H NMR (DMSO-d_6) δ 11.3 (br s, 1H, CO_2H), 8.18 (br s, 2H, H_1 and $H_{6'}$), 7.99 (apparent d, 3H, J = 8.4 Hz, H_4 and H_5 and H_8), 7.92 (d, 1H, J = 8.7 Hz, $H_{4'}$), 7.81 (d, 1H, J = 8.6 Hz, H_3), 7.51 (m, 2H, H_6 and H_7), 7.11 (d, 1H, J = 8.6 Hz, $H_{3'}$); FABMS *m/z* 263 $(M-H)^-$. Anal. ($C_{17}H_{12}O_3 \cdot {}^1/_4H_2O$) C, H.

1,4-Dimethoxy-6-naphthylboronic acid (18). Following a procedure analogous to that utilized for the preparation of compound **14**, compound **18** was obtained from 6-bromo-1,4-dimethoxynaphthalene **17**,[8] as an off-white powder (65%); mp 277–279 °C; ^{1}H NMR (DMSO-d_6) δ 8.62 (s, 1H, H_5), 8.02 (d, 1H, J = 8.4 Hz, H_8), 7.87 (d, 1H, J = 8.4 Hz, H_7), 6.83 (q, 2H, J = 8.4 Hz, H_2 and H_3), 3.91 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3).

1,4-Dimethoxy-6-[3′-(methylcarboxy)-4′-methoxyphenyl]naphthalene (19). Reaction of boronic acid **18** and iodosalicylate **15** in a manner similar t that used for the synthesis of compound **16**, afforded crude **19** which was purified by silica gel chromatography (hexanes/EtOAc, 5:1) to give **19** (83%). Recrystallization from CH_2Cl_2/hexanes provided an analytically pure sample: mp 77–79 °C; ^{1}H NMR ($CDCl_3$) δ 8.37 (d, 1H, J = 1.8 Hz, H_5), 8.24 (d, 1H, J = 8.7 Hz, H_8), 8.18 (d, 1H, J = 2.5 Hz, $H_{6'}$), 7.83 (dd, 1H, J = 8.7, 2.5 Hz, $H_{4'}$), 7.72 (dd, 1H, J = 8.7, 1.9 Hz, H_7), 7.07 (d, 1H, J = 8.7 Hz, $H_{3'}$), 6.70 (q, 2H, J = 8.4 Hz, H_2 and H_3), 3.97 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3). Anal. ($C_{21}H_{20}O_5$) C, H.

1,4-Dihydroxy-6-[3′-(methylcarboxy)-4′-hydroxyphenyl]naphthalene (20). Following a procedure analogous to that utilized for the preparation of **12**, compound **20** was obtained as a dark purple solid (123 mg, 94%) which was contaminated with a small amount of **9**: ^{1}H NMR (DMSO-d_6) δ 10.53 (s, 1H, 2′-OH), 9.42 (s, 1H, OH), 9.38 (s, 1H, OH), 8.21 (d, 1H, J = 1.7 Hz, H_5), 8.13 (d, 1H, J = 2.3 Hz, $H_{6'}$), 8.10 (d, 1H, J = 8.8 Hz, H_8), 7.94 (dd, 1H, J = 8.6, 2.3 Hz, $H_{4'}$), 7.70 (dd, 1H, J = 8.8, 1.7 Hz, H_7), 7.12 (d, 1H, J = 8.6 Hz, $H_{3'}$), 6.66 (q, 2H, J = 8.1 Hz, H_2 and H_3), 3.92 (s, 3H, OCH_3).

1,4-Dihydroxy-6-(5′-salicyl)naphthalene (9). A mixture of **20** (108 mg, 0.34 mmol) and a large excess of pyridine·HCl was warmed to 180 °C and stirred for 15 min. The clear yellow solution was cooled to room temperature and mixed with H_2O (3 mL), and the resulting suspension was poured into 5 mL of H_2O and filtered to afford **9** as an off-white solid (83 mg, 82%): mp > 200 °C dec, ^{1}H MNR (DMSO-d_6) δ 11.4 (br s, 1H, CO_2H), 9.42 (s, 1H, OH), 9.38 (s, 1H, OH), 8.21 (d, 1H, J = 1.7 Hz, H_5), 8.14 (d, 1H, J = 2.3 Hz, $H_{6'}$), 8.10 (d, 1H, J = 8.7 Hz, H_8), 7.94 (dd, 1H, J = 8.7, 2.3 Hz, $H_{4'}$), 7.70 (dd, 1H, J = 8.8, 1.7 Hz, H_7), 7.09 (d, 1H, J = 8.7 Hz, $H_{3'}$), 6.66 (q, 2H, J = 8.1 Hz, H_2 and H_3); FABMS *m/z* 295 $(M-H)^-$; high-resolution FABMS calcd for $C_{17}H_{11}O_5$ 295.0606, found 295.0572. Anal. Calcd for $C_{17}H_{12}O_5 \cdot {}^1/_4H_2O$: C, 67.89; H, 4.19. Found: C, 68.35; H, 4.29.

1,2-Dimethoxy-6-naphthylboronic Acid (22). Following a procedure analogous to that utilized for the preparation of **14**, compound **22** was obtained from 6-bromo-1,2-dimethoxynaphthalene **21**,[16] as an off-white powder (64%): mp 220–222 °C; ^{1}H NMR (DMSO-d_6) δ 8.81 (s, 1H, H_5), 8.27 (q, 2H, J = 8.7 Hz, H_7 and H_8), 7.86 (d, 1H, J = 9.0 Hz, H_3), 7.37 (d, 1H, J = 9.0 Hz, H_4), 4.05 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3).

1,2-Dimethoxy-6-[3'-(methylcarboxy)-4'-methoxyphenyl]naphthalene (23). Following a procedure analogous to that utilized for the synthesis of compound **19**, crude **23** was obtained (177 mg). Silica gel chromatography (Hexanes/EtOAc, 6:1) afforded **23** as a yellow solid (106 mg, 70%). Recrystallization from hexanes/CH_2Cl_2 using an isothermal distillation technique provided an analytical sample of **23** as colorless plates: mp 141–142 °C; ^{1}H NMR (benzene-d_6) δ 8.39 (d, 1H, J = 2.5 Hz, $H_{6'}$), 8.35 (d, 1H, J = 8.8 Hz, H_8), 7.90 (d, 1H, J = 1.5 Hz, H_5), 7.64 (dd, 1H, J = 8.8, 1.8 Hz, H_7), 7.54 (dd, 1H, J = 8.6, 2.5 Hz, $H_{4'}$), 7.38 (d, 1H, J = 9.0 Hz, H_3), 6.98 (d, 1H, J = 9.0 Hz, H_4), 6.58 (d, 1H, J = 8.6 Hz, $H_{3'}$), 3.89 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3). Anal. ($C_{21}H_{20}O_5$) C, H.

1,2-Dihydroxy-6-(5'-salicyl)naphthalene (11). Treatment of **23** with pyridine·HCl for 1 h as described for compound **9** afforded **11** as a dark green solid (83%): mp > 200 °C dec; ^{1}H NMR (DMSO-d_6) δ 11.3 (br s, 1H, CO_2H), 9.33 (s, 1H, OH), 8.88 (s, 1H, OH), 8.12 (d, 1H, J = 2.0 Hz, $H_{6'}$), 8.05 (d, 1H, J = 8.8 Hz, H_8), 7.95 (br s, 1H, H_5), 7.93 (dd, 1H, J = 8.7, 2.0 Hz, $H_{4'}$), 7.63 (d, 1H, J = 8.8 Hz, H_7), 7.35 (d, 1H, J = 8.7 Hz, H_3), 7.14 (d, 1H, J = 8.7 Hz, H_4), 7.07 (d, 1H, J = 8.7 Hz, $H_{3'}$); FABMS *m/z* 295 (M − H)$^-$. Anal. ($C_{17}H_{12}O_5 \cdot {}^3/_4H_2O$) C, H.

2,3-Dimethoxy-6-hydroxynaphthalene (25). To a mixture of **24** [2.0 g, 8.7 mmol; prepared in 80% yield using a slight modification (substituting CH_2Cl_2 for nitrobenzene as solvent) of a literature procedure[9]] and pTsOH·H_2O (1.2 g, 6.1 mmol) in CH_2Cl_2 (35 mL) was added 80% *m*-CPBA (3.8 g, 17.4 mmol). After stirring at room temperature overnight, the solution was partitioned between $NaHCO_3$ (100 mL) and CH_2Cl_2 (2 × 50 mL), washed with brine (50 mL), dried ($MgSO_4$), and evaporated. The residue was dissolved in THF (15 mL) and treated with NH_4OH (10 mL). After stirring 2 h, the reaction was partitioned between H_2O (20 mL) and Et_2O (3 × 20 mL), washed with brine (20 mL), and dried ($MgSO_4$), and solvent was removed to give **25** as an off-white solid (640 mg, 36%). Recrystallization from CH_2Cl_2/hexanes provided an analytical sample of **25** as a colorless solid: mp 166–167 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 1H, J = 8.7 Hz, H_8), 7.05 (s, 1H), 7.03 (d, 1H, J = 2.5 Hz, H_5), 6.96 (s, 1H), 6.93 (dd, 1H, J = 8.7, 2.5 Hz, H_7), 4.73 (s, 1H, OH), 3.98 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3). Anal. ($C_{12}H_{12}O_3$) C, H.

2,3-Dimethoxy-6-[(trifluoromethyl)sulfonyl)oxy]naphthalene (26). Using an adaptation of a previously reported procedure,[17] a mixture of **25** (475 mg, 2.33 mmol) and *N*-phenyltriflamide (873 mg, 2.4 mmol) in CH_2Cl_2 (8.0 mL) at 0 °C was treated with Et_3N (0.36 mL, 2.6 mmol) and brought to room temperature with stirring (2.5 h). The reaction was diluted with Et_2O (50 mL) and sequentially washed with H_2O (25 mL), 1 N NaOH (2 × 25 mL), H_2O (25 mL), and brine (25 mL). Drying ($MgSO_4$) and removal of solvent gave crude **26** (735 mg). Chromatographic purification (hexanes/EtOAc, 5:1) afforded pure **26** as an orange tinted oil (408 mg, 53%): ^{1}H NMR ($CDCl_3$) δ 7.72 (d, 1H, J = 8.9 Hz, H_8), 7.57 (d, 1H, J = 2.5 Hz, H_5), 7.20 (dd, 1H, J = 8.9, 2.5 Hz, H_7), 7.13 (s, 1H), 7.11 (s, 1H), 4.01 (s, 6H, 2-OCH_3). Anal. ($C_{13}H_{11}O_5F_3S$) C, H.

Methyl 2-Methoxy-5-(trimethylstannyl)benzoate (27). Using an adaptation of a previously reported procedure,[18] compound **15** (1.0 g, 3.4 mmol), anhydrous LiCl (440 mg, 10.2 mmol), $Pd(PPh_3)_4$ (40 mg, 0.034 mmol), hexamethylditin (2.23 g, 6.8 mmol), and anhydrous dioxane (14 mL) were combined under argon and stirred at 105 °C overnight. The solution was cooled to room temperature, diluted with EtOAc (50 mL), filtered, and washed with 1 M KF (30 mL), phosphate buffer (pH = 7; 30 mL), and brine (30 mL). After drying ($MgSO_4$) and removal of solvent, the crude material was chromatographed (hexanes/EtOAc, 6:1) to afford arylstannane **27** as a colorless oil (303 mg, 27%): ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1H, J = 1.5 Hz, H_6), 7.54 (dd, 1H, J = 8.15, 1.5 Hz, H_4), 6.95 (d, 1H, J = 8.15 Hz, H_3), 3.90 (s, 6H, 2-OCH_3), 0.29 (s, 9H, 3-CH_3Sn).

2,3-Dimethoxy-6-[3'-(methylcarboxy)-4'-methoxyphenyl]naphthalene (28). Similarly to previously reported,[18] triflate **26** (100 mg, 0.30 mmol), arylstannane **27** (103 mg, 0.31 mmol), anhydrous LiCl (38 mg, 0.90 mmol), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol), and anhydrous dioxane (1.7 mL) were combined under argon and stirred at 105 °C overnight. The reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL), filtered, and then washed sequentially with 1 M KF (10 mL), phosphate buffer (pH = 7; 10 mL), and brine (10 mL). After drying ($MgSO_4$) and removal of solvent, the crude material was chromatographed (hexanes/EtOAc, 6:1) to afford coupled product **28** (49 mg, 46%). Recrystallization from hexanes/CH_2Cl_2 using an isothermal distillation technique provided analytically pure **28** as colorless plates: mp 169–170 °C; ^{1}H NMR ($CDCl_3$) δ 8.13 (d, 1H, J = 2.5 Hz, $H_{6'}$), 7.85 (d, 1H, J = 1.9 Hz, H_5), 7.78 (dd, 1H, J = 8.7, 2.5 Hz, $H_{4'}$), 7.73 (d, 1H, J = 8.5 Hz, H_8), 7.55 (dd, 1H, J = 8.5, 1.9 Hz, H_7), 7.16 (s, 1H), 7.12 (s, 1H), 7.07 (d, 1H, J = 8.7 Hz, $H_{3'}$), 4.02 (s, 6H, 2-OCH_3), 3.94 (s, 3H, CO_2CH_3), 3.92 (s, 3H, OCH_3). Anal. ($C_{21}H_{20}O_5$) C, H.

2,3-Dihydroxy-6-(5'-salicyl)naphthalene (10). Treatment of **28** with pyridine·HCl (1 h) as described for compound **9** afforded **10** as a brown powder (63%): mp 231–233 °C; ^{1}H NMR (DMSO-d_6) δ 11.3 (br s, 1H, CO_2H), 9.59 (s, 1H, OH), 9.56 (s, 1H, OH), 8.09 (d, 1H, J = 2.3 Hz, $H_{6'}$), 7.88 (dd, 1H, J = 8.6, 2.3 Hz, $H_{4'}$), 7.80 (s, 1H, H_5), 7.63 (d, 1H, J = 8.5 Hz, H_8), 7.44 (dd, 1H, J = 8.5, 1.7 Hz, H_7), 7.18 (s, 1H), 7.10 (s, 1H), 7.05 (d, 1H, J = 8.6 Hz, $H_{3'}$); FABMS *m/z* 295 (M − H)$^-$. Anal. ($C_{17}H_{12}O_5 \cdot {}^1/_2H_2O$) C, H.

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