Heterotricyclic Himbacine Analogs as Potent, Orally Active Thrombin Receptor (Protease Activated Receptor-1) Antagonists

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Received June 18, 2007

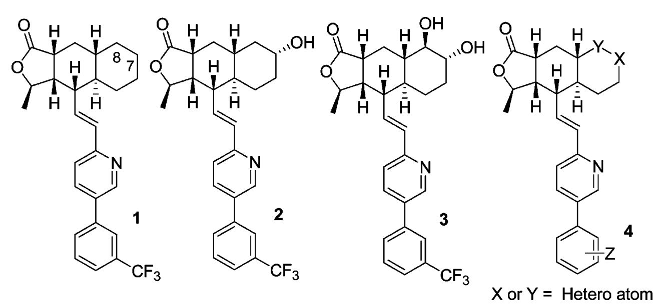
Pursuing our earlier efforts in the himbacine-based thrombin receptor antagonist area, we have synthesized a series of compounds that incorporate heteroatoms in the C-ring of the tricyclic motif. This effort has resulted in the identification of several potent heterocyclic analogs with excellent affinity for the thrombin receptor. Several of these compounds demonstrated robust inhibition of platelet aggregation in an ex vivo model in cynomolgus monkeys following oral administration. A detailed profile of **28b**, a benchmark compound in this series, with a K_i of 4.3 nM, is presented.

Introduction

Platelet activation plays an important role in arterial thrombosis.[1−3] When the rupture of a vulnerable atherosclerotic plaque occurs, platelets are recruited to the site of injury where they form an initial haemostatic plug by binding to von Willebrand factor and collagen. Further activation of platelets by collagen and thrombin in the local milieu causes platelet shape changes and the release of platelet activating granular contents, which in turn amplify the platelet activation process. Activated platelets express GpIIb/IIIa receptors on their surfaces which bind to fibrinogen causing platelets to aggregate. Aggregated platelets are trapped by fibrin meshwork, produced by thrombin-mediated cleavage of fibrinogen, to form a rapidly growing thrombus that further traps red blood cells and other plasma particles, leading to an occlusive clot that can result in unstable angina and myocardial infarction.

Antiplatelet drugs constitute an integral part of antithrombotic therapy.[4,5] Platelets are activated by a variety of agonists such as thrombin, ADP,[a] thromboxane A2, epinephrine, collagen, and so on. Among these, thrombin is the most potent activator of platelets. The most widely used antiplatelet agents are ADP antagonists such as clopidogrel, thromboxane A2 biosynthetic inhibitors, such as aspirin, and GpIIb/IIIa antagonists, which inhibit platelet aggregation irrespective of the mode of activation of the platelets. Among these three classes of antiplatelet agents, ADP antagonists and aspirin have a relatively modest level of potency. However, several of them have the advantage of being orally active. The GpIIb/IIIa antagonists are potent antiplatelet agents; however, the currently used GpIIb/IIIa antagonists are all IV formulations. Efforts to achieve orally active GpIIb/IIIa antagonists have uniformly failed in clinical trials.[6] Therefore, there exists an unmet clinical need for novel, orally active antiplatelet agents.

Besides its central role in hemostasis and wound healing, thrombin activates platelets and other cell types via proteolytic activation of specific cell-surface receptors known as protease activated receptors (PARs).[7−12] PARs are activated by a unique “tethered ligand mechanism” in which a proteolytic enzyme such as thrombin cleaves the extracellular domain of the receptor and the newly unmasked amino terminus binds to the proximally located transmembrane loop of the GPCR, eliciting intracellular signaling.[13−16] Four PARs are known, PAR-1, PAR-2, PAR-3, and PAR-4. PAR-1, PAR-3, and PAR-4 are activated by thrombin, and PAR-2 is activated by trypsin. PAR-1, also known as the thrombin receptor, is the major thrombin-activated receptor on human and monkey platelets. PAR-4 is a second thrombin receptor on human and monkey platelets, but it is activated only at high thrombin concentration, as in the case of a severe injury. PAR-3 and PAR-4 are the major protease activated receptors on rodent platelets. Because thrombin is the most potent activator of human platelets, a thrombin receptor antagonist (TRA) is expected to show potent antiplatelet effects.



We have reported potent, orally active thrombin receptor (PAR-1) antagonists **1** and **2** based on the structure of the natural product himbacine.[17,18] Compared with previously known peptide-mimetic[19−21] and nonpeptide[22−24] antagonists, these compounds are high affinity thrombin receptor antagonists (**1**, K_i = 2.7 nM; **2**, K_i = 8.7 nM) with excellent oral efficacy in an ex vivo platelet aggregation model in cynomolgus monkeys. Although the enzyme induction issues surrounding the earlier

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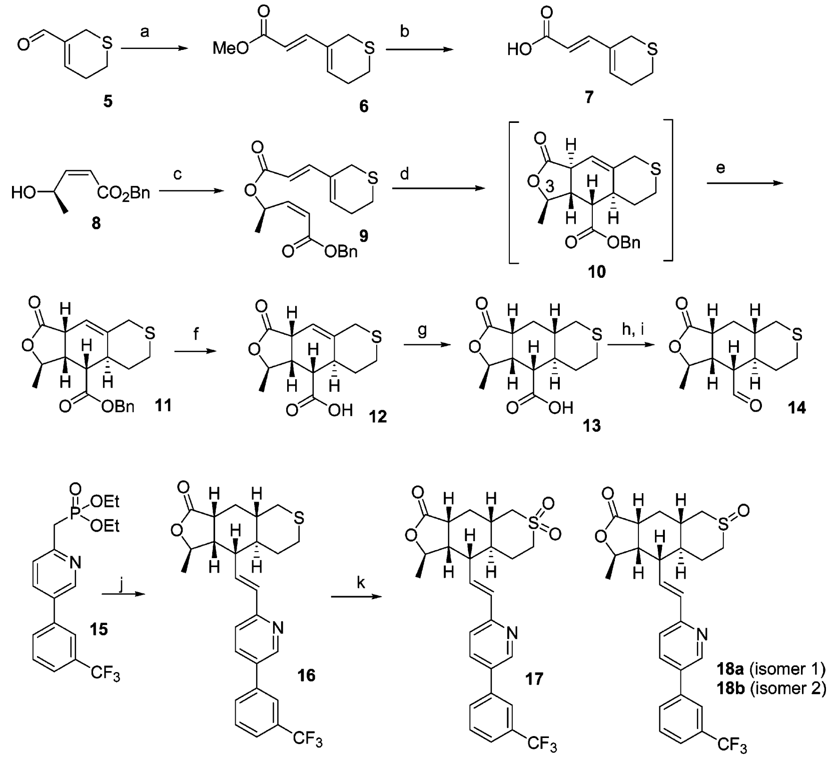
[a] Abbreviations: ADP, adenosine diphosphate; GPCR, G-protein-coupled receptor; PAR, protease activated receptor; TRAP, thrombin receptor activating peptide.

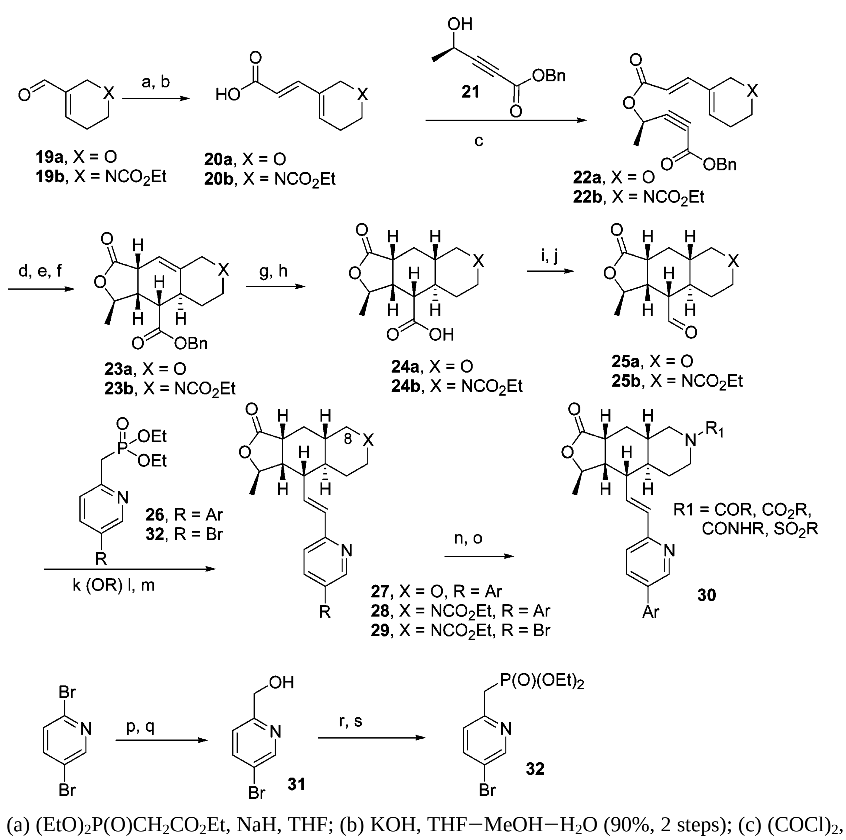
10.1021/jm070704k CCC: $37.00
Published on Web 09/14/2007

Scheme 1[a]



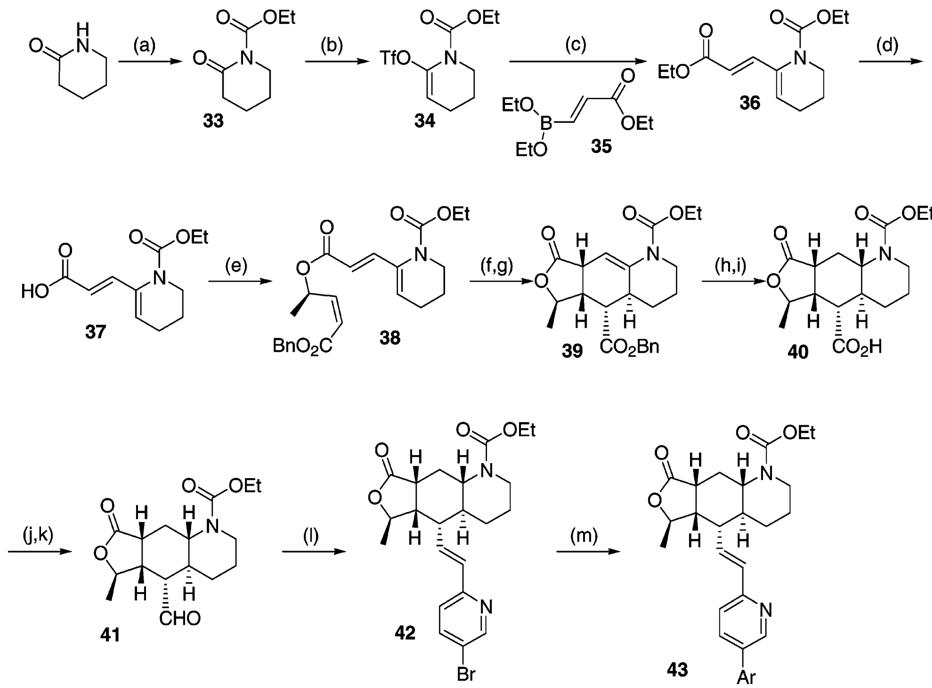
[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Me$, NaHMDS, THF, 58%; (b) KOH, THF−MeOH−H_2O, 97%; (c) **7**, DCC, DMAP, 41%; (d) toluene, 200 °C, 6 h; (e) DBU, rt, 69% from **9**; (f) BBr_3, CH_2Cl_2, 89%; (g) 40psi H_2, PtO_2, MeOH−AcOH, 79%; (h) $(COCl)_2$, cat. DMF, CH_2Cl_2; (i) Bu_3SnH, $Pd(PPh_3)_4$, toluene, 80% from **13**; (j) BuLi, THF, then **14**, 91%; (k) $NaBO_3{\cdot}4H_2O$, $MeSO_3H$, AcOH.

Scheme 2[a]



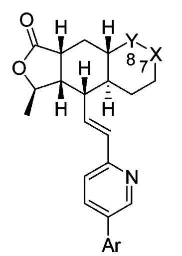
[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (b) KOH, THF−MeOH−H_2O (90%, 2 steps); (c) $(COCl)_2$, cat. DMF, then **21**, DMAP, Et_3N (78%); (d) H_2, Lindlar catalyst, quinoline; (e) *m*-xylene, 185 °C, 6 h; (f) DBU, rt (56%, 3 steps); (g) 1 atm H_2, Pd−C, EtOAc; (h) 50 psi H_2, PtO_2, MeOH (96%, 2 steps); (i) $(COCl)_2$, cat. DMF, CH_2Cl_2; (j) Bu_3SnH, $Pd(PPh_3)_4$, toluene (83%-91%, 2 steps); (k) **26**, BuLi, THF, then **25a**,**b**; (l) **32**, LHMDS, $Ti(O\textit{i}\text{-}Pr)_4$ then **25b**; (m) $ArB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3; (n) **28**, TMSI, CH_2Cl_2; (o) acid chlorides, chloroformates, isocyanates, and sulfonyl chlorides, Et_3N; (p) BuLi, toluene then DMF; (q) $NaBH_4$ (51%, 2 steps); (r) MsCl, Et_3N, CH_2Cl_2; (s) NaH, $HP(O)(OEt)_2$, THF (97%, 2 steps).

Scheme 3[a]



[a] Reagents and conditions: (a) *n*-BuLi, EtOCOCl, THF, −78 °C-rt (99%); (b) LHMDS, 2-[*N*,*N*-bis(trifluoromethylsulfonyl)-amino]-5-chloropyridine, THF, −78 °C−rt (61%); (c) **35**, $Pd(OAc)_2$, 2-(di-*t*-butylphosphino)biphenyl, KF, THF, 55 °C (89%); (d) NaOH, H_2O, MeOH, THF (93.5%); (e) DCC, ppy, **8**, CH_2Cl_2 (66%); (f) *m*-xylene 150 °C; (g) DBU, THF (46%, 2 steps); (h) Pd(C), H_2, EtOAc; (i) PtO_2, H_2 (50 psi), MeOH (98%, 2 steps); (j) $(COCl)_2$, DMF (1 drop), CH_2Cl_2; (k) $Pd(Ph_3P)_4$, Bu_3SnH, PhMe, 0 °C−rt (60%, 2 steps); (l) **32**, LHMDS, Ti(O*i*-Pr)$_4$, THF, 0 °C−rt (75%); (m) $Pd(Ph_3P)_4$, K_2CO_3, $ArB(OH)_2$, PhMe/EtOH/H_2O (65%).

Table 1. Binding Data for **16**, **17**, **18a**,**b**, **27a−g**, **28a**, **43a−e**



cmpd	X	Y	Ar	IC_{50} (nM) ± SEM[a]	rat AUC[b]
16	S	CH_2	(*m*-CF_3)-phenyl	22 ± 6.5	
17	SO_2	CH_2	(*m*-CF_3)-phenyl	200 ± 0	
18a	SO	CH_2	(*m*-CF_3)-phenyl	80 ± 20	
18b	SO	CH_2	(*m*-CF_3)-phenyl	375 ± 125	
27a	O	CH_2	(*m*-CF_3)-phenyl	17 ± 1.5	545
27b	O	CH_2	(*m*-F)-phenyl	26 ± 2.1	850
27c	O	CH_2	(*o*-F)-phenyl	25 ± 6.6	1050
27d	O	CH_2	(*o*,*m*-difluoro)-phenyl	26 ± 6.5	1190
27e	O	CH_2	(*m*-Cl)-phneyl	19 ± 1.0	
27f	O	CH_2	(*o*-Cl)-phneyl	13 ± 3.0	
27g	O	CH_2	(*o*,*m*-dichloro)-phenyl	21 ± 0.5	
28a	NCO_2Et	CH_2	(*m*-CF_3)-phenyl	11 ± 0	
43a	CH_2	NCO_2Et	(*m*-F)-phenyl	224 ± 73.5	
43b	CH_2	NCO_2Et	(*o*-F)-phenyl	153 ± 16.5	
43c	CH_2	NCO_2Et	(*o*-Me)-phenyl	600 ± 101	
43d	CH_2	NCO_2Et	(*m*-CN)-phenyl	295 ± 81.5	
43e	CH_2	NCO_2Et	*m*-pyridyl	inactive	

[a] $n = 2$ or more. [b] AUC from 0 to 6 h in ng·hr/mL, following a 10 mg/kg oral dose (0.4% methylcellulose).

compound **1** were effectively addressed by the discovery of the second generation compound **2**, the latter compound showed a less than optimal clearance profile.[25] Compound **2** also generated a considerable amount of 7,8-dihydroxy metabolites such as **3**. This prompted us to identify a replacement candidate for **2** with an improved metabolic profile. In this pursuit, we decided to incorporate heteroatoms into the C-ring of the tricyclic motif to prepare analogs represented by structure **4**. In addition to potentially altering the metabolic pattern of the C-ring, this approach would increase the overall polarity of these compounds.

Synthesis

The synthesis of tetrahydrothiopyranyl derivatives represented by structures **16−18b** is shown in Scheme 1. The synthesis started with the known[26] enal **5**, which was subjected to the

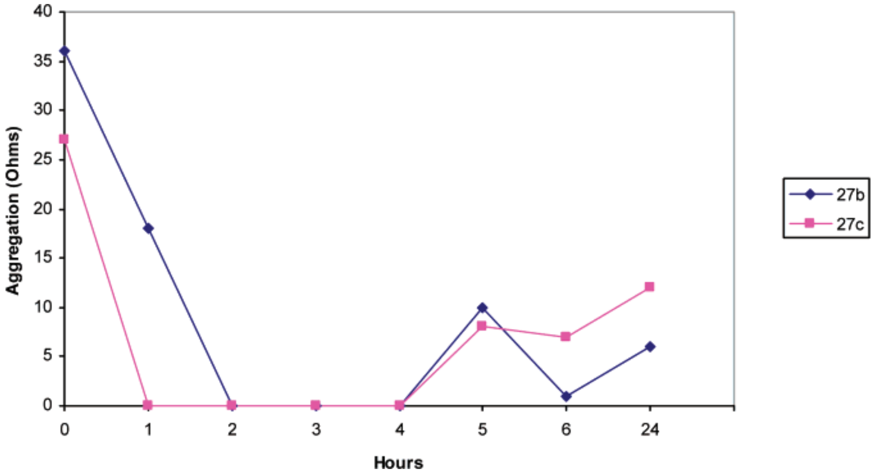
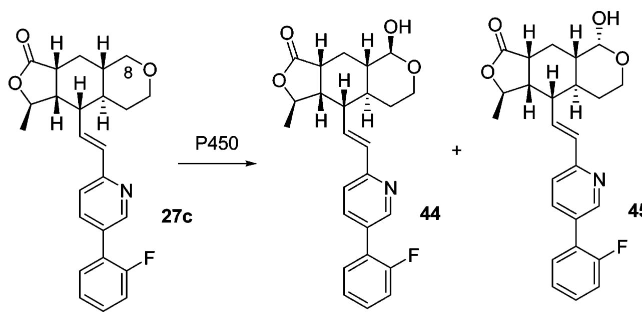


Figure 1. Ex vivo platelet aggregation inhibition in cynomolgus monkey, following a single oral dose (1 mg/kg in 20% PEG-HPBCD) of **27b** and **27c**.

Horner–Wadsworth–Emmons reaction using methyl diethylphosphonoacetate to give the ester **6**, which was hydrolyzed to the dienoic acid **7**. The Diels–Alder precursor **9** was obtained by coupling the dienoic acid **7** and alcohol **8**, which was prepared from optically active (*R*)-3-butyn-2-ol,[27] as described before.[18] Intramolecular Diels–Alder reaction of **9** at 200 °C yielded the *exo*-adduct **10** as the major product. Based on our previous work, the facial selectivity of this reaction is attributed to the 1,3-allylic strain induced by the C_3-methyl group of the dienophile.[28] The *trans*-lactone **10** was epimerized in situ with DBU to provide the *cis*-lactone **11**. Debenzylation under Lewis acid conditions followed by hydrogenation over platinum oxide gave the tricyclic acid **13**. Conversion of acid **13** to aldehyde **14** was achieved by the reduction of the corresponding acid chloride with Bu_3SnH under palladium catalysis.[29] Finally, coupling of the aldehyde with the known[18] phosphonate **15** gave the desired target **16**. When **16** was oxidized with sodium perborate, it gave a mixture consisting of sulfone **17** and the sulfoxides **18a** and **18b**, which were separated by silica gel chromatography.

The synthesis of tetrahydropyranyl and the decahydroisoquinoline derivatives is outlined in Scheme 2. Enals **19a** and **19b** were converted to the corresponding dienoic acids **20a** and **20b** and esterified with the alcohol **21**[18] to give alkynes **22a** and **22b**, respectively. Lindlar reduction followed by thermal cyclization and base-catalyzed epimerization gave **23a** and **23b**, which were subsequently subjected to debenzylation and double bond reduction to give the corresponding acids **24a** and **24b**. Conversion of the acids to the corresponding acid chlorides, followed by reduction with tributyltin hydride, gave aldehydes **25a** and **25b**. The aldehydes were subjected to the Horner–Wadsworth–Emmons reaction using the phosphonate **26** to give tetrahydropyranyl derivative **27** and the decahydroisoquinoline derivative **28**, respectively. Alternatively, the aldehyde **25b** can be coupled with the bromo-substituted phosphonate **32** to give **29**, which can be subsequently coupled with aryl boronic acids under Suzuki coupling conditions to give **28**. Phosphonates, represented by **26**, with appropriately substituted aryl groups, were prepared using procedures similar to the preparation of **15** described previously.[18] Phosphonate **32** was prepared from 2,5-dibromopyridine, which was subjected to selective lithiation at the 2-position followed by quenching with dimethyl formamide.[30] The resultant aldehyde was reduced with sodium borohydride to give the alcohol **31**. The alcohol **31** was converted to the phosphonate **32** via its mesylate. To study the effect of substitution on the nitrogen of the decahydroisoquinoline analogs (**30**), the ethyl carbamate group of **28** was cleaved using iodotrimethylsilane, and the resultant amine was subsequently derivatized with acid chlorides, chloroformates, isocyanates, and sulfonyl chlorides to prepare the corresponding amides, carbamates, ureas, and sulfonamides, respectively.

Scheme 4

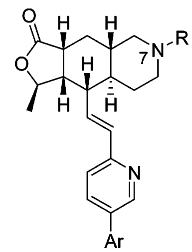


The synthesis of isomeric decahydroquinoline derivatives represented by **43** (Scheme 3) started with δ-valerolactam, which was protected as ethylcarbamate **33** and then converted to the vinyl triflate **34**. Initially we attempted to form dienoic ester **36** via a Heck reaction of **34**; this was met with limited success, generally resulting in low chemical yields. However, we found that coupling of the vinyl boronic ester **35** with **34** using potassium fluoride[31] as base led to good yields of the desired product in a reproducible manner. Coupling of an analogous vinyl tin reagent was moderately successful, but required more time-consuming purifications and was consequently less reproducible. Hydrolysis of **36** led to the dienoic acid **37**, which was subsequently converted to the target compounds represented by **43** using the route described in Scheme 3.

Results and Discussion

The in vitro binding assays were carried out on human platelet membrane-derived PAR-1 receptors using a tritiated high affinity thrombin receptor activating peptide ([^{3}H]haTRAP]) as described previously.[32] The tetrahydrothiopyran analog **16** (Table 1) showed good binding affinity (IC_{50} = 21.5 nM), which is comparable to the corresponding carbocyclic analog **1** (IC_{50} = 11 nM). Because **16** is likely to undergo in vivo oxidation by liver P450 enzymes to sulfoxides and sulfone, we also evaluated these potential metabolites in the binding assay. Although the incorporation of the sulfur atom in the ring is well-tolerated, as indicated by the binding affinity of **16**, the corresponding sulfone **17** and the sulfoxides **18a** and **18b** showed reduced binding

Table 2. Binding Data for **28b–d** and **30a–m**



cmpd	Ar	R	IC_{50} (nM) ± SEM ($n = 2$)	ex vivo[a]	rat AUC[b]
28b	(*m*-F)-phenyl	CO_2Et	10.5 ± 1.5	100% (6 h), 70% (24 h)	2220
28c	(*o*-F)-phenyl	CO_2Et	8.0 ± 1.0	55% (6 h), 55% (24 h)	3780
28d	*o*-pyridyl	CO_2Et	33.5 ± 14.0	67% (6 h), 29% (24 h)	
30a	(*m*-CF_3)-phenyl	H	600 ± 300		
30b	(*m*-CF_3)-phenyl	Me	762 ± 336		
30c	(*m*-CF_3)-phenyl	COMe	550 ± 50		
30d	(*m*-CF_3)-phenyl	CO*i*-Pr	113 ± 8.0		
30e	(*m*-CF_3)-phenyl	COCypr	37.5 ± 7.5		
30f	(*m*-F)-phenyl	COCypr	15.5 ± 4.5	100% (6 h), 72% (24 h)	4370
30g	(*o*-F)-phenyl	COCypr	8.0 ± 2.0	45% (6 h), 39% (24 h)	6010
30h	(*m*-F)-phenyl	$CONH_2$	1101 ± 351		
30i	(*m*-F)-phenyl	CONHEt	18.5 ± 6.5	47% (6 h), 34% (24 h)	2050
30j	(*m*-F)-phenyl	SO_2Me	15.0 ± 5.0	54% (6 h), 50% (24 h)	5350
30k	(*m*-F)-phenyl	SO_2Pr	101 ± 52.0		
30l	(*m*-CF_3)-phenyl	CO_2Bn	25 ± 4.0		
30m	(*m*-F)-phenyl	$CO_2C_2H_4OMe$	16.5 ± 2.5		88

[a] Reduction in haTRAP induced platelet aggregation in *c*. monkey following a 3 mg/kg oral dose (20% PEG-HPBCD). [b] AUC from 0 to 6 h in ng•hr/mL and at 10 mg/kg oral dose (0.4% methylcellulose).

affinity. As a result, this series was not pursued further. The incorporation of oxygen also was well-tolerated, as indicated by the in vitro binding potencies for compound **27a–g** (Table 1). Both *ortho*- and *meta*-substituted biaryl analogs showed good potency. The chloro and fluoro substitutions at the *ortho*- and the *meta*-positions (**27a–c**; **27e**,**f**) as well as the 2,3-dichloro and 2,3-difluoro substitutions (**27d**, **27g**) were well-tolerated. The in vitro affinity of this series is comparable to that of the carbocyclic analog **1**.[17] The incorporation of a nonbasic nitrogen at the 7-position is well-tolerated, as indicated by the excellent potency of the ethylcarbamate analog **28a**. Moving the ethylcarbamate-derived nitrogen from the 7-position to the 8-position resulted in analogs **43a–e** with marked reduction in in vitro binding affinity.

We also evaluated selected compounds in a rat pharmacokinetic model at 10 mg/kg oral dose and the plasma levels were assayed for a 6 h period (Table 1). The plasma levels (AUCs) were moderate and ranged from 545 to 1190 ng.hr/mL. The in vivo efficacy of the tetrahydropyranyl analogs **27b** and **27c** were evaluated in the ex vivo platelet aggregation inhibition assay in cynomolgus monkeys, as reported previously.[21] Cynomolgus monkeys were orally dosed with **27b** and **27c** and blood samples were drawn at 1 h intervals up to 6 h then at 24 h, while being chaired consciously. Subsequently, haTRAP was added to the samples as an agonist for the thrombin receptor activation to induce the platelet aggregation. The inhibition of the agonist induced platelet aggregation by the dosed analogs was assayed in a whole blood aggregometer. Both **27b** and **27c** showed complete inhibition of haTRAP-induced platelet aggregation at 1 mg/kg oral dose up to 6 h (Figure 1). At 24 h, **27c** produced about 55% inhibition, while **27b** showed about 80% inhibition

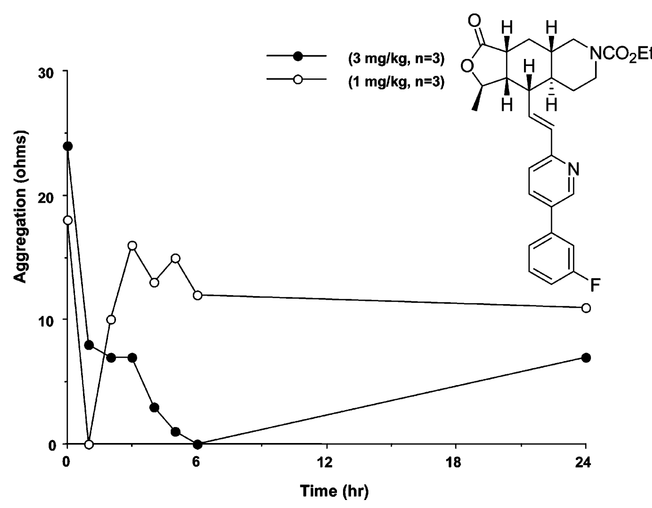


Figure 2. Ex vivo platelet aggregation inhibition in cynomolgus monkey following a single oral dose (1 and 3 mg/kg in 20% PEG-HPBCD) of **28b**.

in the platelet aggregation. The detailed pharmacokinetic profile of compound **27c** was also evaluated in the c. monkey at 1 mg/kg i.v. dose and 1.5 mg/kg oral dose, which showed very good oral bioavailability ($AUC_{0-24\,h} = 3700$ ng•hr/mL; $C_{max} = 610$ ng/mL; $T_{max} = 1.7$ h; half-life = 8.6 h; and $F = 71\%$).

Although both **27b** and **27c** showed excellent efficacy in the ex vivo platelet aggregation inhibition assay, analysis of the plasma samples for both compounds indicated a considerable amount of (M + 16) metabolites.[33] To identify the structure of the metabolites of **27c**, this compound was incubated with liver microsomes, and the metabolites were assayed using LC/NMR and MS/MS techniques. The metabolites were found to be a mixture of C_8-α and -β lactols **44** and **45** (Scheme 4).[34] Due to the reactive nature of the lactol metabolites and their considerable presence in the monkey plasma, this series was not further pursued.

Because the decahydroisoquinoline analog **28a** showed good in vitro potency, a variety of substitutions at the nitrogen as well as the biaryl portion of **28a** were carried out. The in vitro binding values for these analogs are given in Table 2. Similar to **28a**, the ethylcarbamate analogs **28b**−**d** showed very good potency. Compared to **1**, the unsubstituted amine **30a** and its *N*-methyl derivative **30b** showed substantial reduction in binding affinity. The isopropyl amide **30d** showed slightly better affinity than the acetamide **30c**, but the corresponding cyclopropyl amides **30e**−**g** showed potency comparable to **1**. The *N*-ethyl-substituted urea derivative **30i** showed good affinity, although the unsubstituted urea **30h** showed reduced affinity. Methanesulfonamide analog **30j** showed better affinity than the propanesulfonamide analog **30k**. Both the methoxyethylcarbamate **30m** and the bulkier benzylcarbamate derivative **30l** were well-tolerated.

Several analogs with promising in vitro binding affinities were evaluated in the c. monkey ex vivo platelet aggregation inhibition and the rat pharmacokinetic assay. Both of the cyclopropyl amide derivatives, **30f** and **30h**, showed good rat plasma levels following oral dose. Although analog **30g** exhibited platelet aggregation inhibition only up to ∼6 h, **30f** showed efficacy up to 24 h at a 3 mg/kg oral dose. The urea analog **30i** and the sulfonamide **30j** exhibited only moderate levels of efficacy despite excellent rat plasma levels, as indicated in Table 2. Carbamate **28b** showed excellent efficacy at a 3 mg/kg dose, showing ∼70% inhibition of platelet aggregation at the 24 h time point, whereas **28c** showed ∼55% inhibition of the platelet aggregation at the 24 h time point. Both of these analogs also showed good plasma levels in the rat pharmacokinetic model. In further dose-down experiments, carbamate **28b** showed efficacy even at a lower dose of 1 mg/kg oral dose, as indicated in Figure 2.

Due to the excellent efficacy profile exhibited by **28b**, this compound was subjected to a more detailed study. In the radioligand binding assay, **28b** showed a K_i of 4.5 nM against PAR-1. In cynomolgus monkeys, **28b** showed an oral bioavailability of 62% at a dose of 3 mg/kg. The C_{max} following the oral dose was 0.990 μM, and the half-life was 6.2 h following intravenous administration. The compound is absorbed rapidly, as indicated by a short T_{max} (0.7 h) with 85% absorption. More importantly, unlike compounds **1** and **27c**, no major presence of (M + 16) metabolites was observed. The compound was clean in an 8-day P450 enzyme induction model in the mouse at the tested doses ranging up to 100 mg/kg and no increase in mouse liver weights, liver-to-body weight ratio, or spectral CYP450 were observed. In a mass balance study using tritiated **28b**,[35] complete recovery or radioactivity within the targeted 10 days after intravenous administration of the compound was achieved.

In summary, our current studies exploring heterotricyclic himbacine analogs have led to the identification of potent thrombin receptor antagonists, as exemplified by **28b**, which is a potent thrombin receptor antagonist with a K_i of 4.5 nM and robust inhibition of agonist-induced ex vivo platelet aggregation in a cynomolgus monkey model. Compound **28b** was selective over other GPCRs, showed excellent oral bioavailability in rat and monkey models, and showed a clean profile in a mouse enzyme induction model and a cynomolgus monkey clearance model.

Experimental Section

General Comments. Flash chromatographic purification was performed using Universal Scientific or Selecto Scientific flash silica gel (particle size 32−63 μm). ^{1}H NMR spectra were determined on a Gemini 400 MHz instrument using either tetramethylsilane or residual solvent peaks as internal standards. Optical rotations were either determined on a Perkin-Elmer 243B polarimeter or by Quantitative Technologies, Inc., 291 Route 22 East, Salem Ind. Park, Bldg. 5, Whitehouse, NJ 08888-0470. Elemental analyses were determined by the Physical-Analytical Department of Schering-Plough Research Institute using either CEC 240-HA, CEC CE-440, or Fisons EA 1108 CHNS elemental analyzers. Elementals analyses were also performed by Quantitative Technologies, Inc. Unless specified, NMR spectra were determined using the free form of the compounds, and optical rotation and elemental analyses were carried out on the hydrochloride salts. Mass spectra were obtained on VG-ZAB-SE, Extrel-401, HP-MS Engine, JEOL HX-110, Sciex API 100, or Sciex API 150 mass spectrometers.

3-(5,6-Dihydro-2*H*-thiopyran-3-yl)-2-propenoic Acid, Methyl Ester (6). To a suspension of 60% NaH (6.3 g, 158 mmol, 1.3 equiv) in THF (200 mL) at 0 °C was added methyl diethylphosphonoacetate (29 mL, 158 mmol, 1.3 equiv), and the mixture was stirred at 0 °C for 30 min. The solution was then transferred to a solution of **3**[25] (15.6 g, 122 mmol) in THF (100 mL) and stirred at 0 °C for 1 h. The reaction was quenched by the addition of aq NH_4Cl (500 mL), and the THF was evaporated. The aqueous phase was extracted with Et_2O (3 × 200 mL), and the combined organic layer was washed with H_2O and brine (200 mL each). The solution was dried over $MgSO_4$ and concentrated, and the resultant residue was chromatographed with 5% EtOAc−hexane to provide 13.0 g (58%) of oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.26 (d, J = 15.9 Hz, 1H), 6.26 (t, J = 4.4 Hz, 1H), 5.78 (dd, J = 15.9, 0.6 Hz, 1H), 3.75 (s, 3H), 3.25−3.23 (m, 2H), 2.71 (t, J = 5.8 Hz, 2H), 2.57−2.53 (m, 2H).

3-(5,6-Dihydro-2*H*-thiopyran-3-yl)-2-propenoic Acid (7). To a solution of **6** (13.0 g, 70.6 mmol) in THF and MeOH (50 mL each) was added a solution of KOH (11.9 g, 212 mmol, 3.0 equiv) in H_2O (50 mL). The mixture was stirred at rt for 1 h, diluted with H_2O (100 mL), and acidified with 1 N HCl. The aqueous phase was extracted with EtOAc (3 × 200 mL), and the combined organic layer was washed with H_2O and brine (300 mL each). The solution was dried over $MgSO_4$, filtered, and evaporated to give 11.66 g (97%) of a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) 7.34 (d, J = 15.6 Hz, 1H), 6.32 (t, J = 4.4 Hz, 1H), 5.78 (d, J = 15.6 Hz, 1H), 3.26 (d, J = 1.6 Hz, 2H), 2.72 (t, J = 5.8 Hz, 2H), 2.59−2.55 (m, 2H).

(2*Z*,4*R*)-4-[[(2*E*)-3-(5,6-Dihydro-2*H*-thiopyran-3-yl)-1-oxo-2-propenyl]oxy]-2-pentenoic Acid, Phenylmethyl Ester (9). To a solution of **7** (2.45 g, 14.39 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added DCC (3.27 g, 15.85 mmol, 1.1 equiv) followed by DMAP (352 mg, 2.88 mmol, 0.2 equiv), and the mixture was stirred at 0 °C for 30 min. To this was added a solution of 3.27 g (15.85 mmol, 1.1 equiv) of **8** in 10 mL of CH_2Cl_2, and the mixture was stirred at 0 °C for 5 h and at rt for 1 h. The solution was diluted with 350 mL of Et_2O and washed with 2 × 200 mL of aq citric acid, 200 mL of aq $NaHCO_3$, and 200 mL of brine. The solution was dried over $MgSO_4$, filtered, and concentrated, and the resultant residue was chromatographed with 6% EtOAc−hexane to provide 2.1 g (41%) of **7** as resin. ^{1}H NMR (400 MHz, $CDCl_3$) 7.38−7.32 (m, 5H), 7.45 (d, J = 16.0 Hz, 1H), 6.38−6.34 (m, 1H), 6.26 (t, J = 4.6 Hz, 1H), 6.21 (d, J = 11.6 Hz, 1H), 6.19 (d, J = 11.2 Hz, 1H), 5.85 (dd, J = 11.6, 1.2 Hz, 1H), 5.76 (d, J = 16.0 Hz, 1H), 5.18 (d, J = 1.2 Hz, 2H), 3.24 (d, J = 2.0 Hz, 2H), 2.71 (t, 2H, J = 5.6 Hz, 2H), 2.56−2.52 (m, 2H), 1.41 (d, J = 6.4 Hz, 3H).

(1*R*,3a*R*,8a*S*,9*S*,9a*R*)-1,3a,5,7,8,8a,9,9a-Octahydro-1-methyl-3-oxo-3*H*-thiopyrano[3,4-*f*]isobenzofuran-9-carboxylic Acid, Phenylmethyl Ester (11). A solution of **9** (2.1 g, 5.85 mmol) in *m*-xylene (50 mL) was heated at 200 °C for 6 h in a sealed tube. The solution was cooled to rt and stirred with DBU (178 μL, 1.19 mmol, 0.2 equiv) for 1 h, concentrated, and chromatographed with 15%

EtOAc−hexane to provide 1.44 g (69%) of the desired *exo*-product. ^{1}H NMR (400 MHz, $CDCl_3$) 7.39−7.35 (m, 5H), 5.46 (br s, 1H), 5.16 (ABq, *J* = 21.6, 12.0 Hz, 2H), 4.42 (dq, *J* = 9.2, 6.0 Hz, 1H), 3.36−3.33 (m 2H), 3.08 (dd, *J* = 14.4, 2.4 Hz, 1H), 2.85 (ddd, *J* = 13.9, 12.4, 2.5 Hz, 1H), 2.72−2.57 (m, 4H), 2.27−2.21 (m, 1H), 1.47−1.25 (m, 1H), 1.12 (d, *J* = 6.4 Hz, 3H).

(1*R*,3a*R*,8a*S*,9*S*,9a*S*)-1,3a,5,7,8,8a,9,9a-Octahydro-1-methyl-3-oxo-3*H*-thiopyrano[3,4-*f*]isobenzofuran-9-carboxylic Acid (12). To a solution of **11** (750 mg, 2.09 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added BBr_3 in CH_2Cl_2 (4.2 mL of 1 M solution). The solution was stirred at −78 °C for 30 min and at 0 °C for 30 min and then poured into aq K_2CO_3 (100 mL). The aqueous phase was washed with Et_2O (2 × 50 mL), and the organic layer was back-extracted with aq K_2CO_3 (50 mL). The combined aqueous phase was acidified with 1 N HCl and extracted with EtOAc (3 × 50 mL). The EtOAc layer was washed with brine (50 mL), dried over $MgSO_4$, filtered, and evaporated to provide 500 mg (89%) of acid. ^{1}H NMR (400 MHz, $CDCl_3$) 5.50 (br s, 1H), 4.47 (dq, *J* = 9.6, 6.0 Hz, 1H), 3.43−3.39 (m, 1H), 3.36 (d, *J* = 15.6 Hz, 1H), 3.10 (dd, *J* = 14.0, 2.4 Hz, 1H), 2.91−2.84 (m, 1H), 2.82−2.77 (m, 1H), 2.70 (dd, *J* = 10.6, 4.2 Hz, 1H), 2.69−2.63 (m, 1H), 2.57−2.52 (m, 1H), 2.34−2.29 (m, 1H), 1.53−1.42 (m, 1H), 1.34 (d, *J* = 6.0 Hz, 3H).

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*R*)-Decahydro-1-methyl-3-oxo-3*H*-thiopyrano[3,4-*f*]isobenzofuran-9-carboxylic Acid (13). To a solution of **12** (500 mg, 1.86 mmol) in MeOH (30 mL) was added acetic acid (3 mL) and PtO_2 (250 mg), and the suspension was shaken under 40 psi H_2 in a Parr vessel for 1.5 days. The catalyst was filtered off with a celite pad, the solution was concentrated, and the resultant residue was dissolved in an AcOH−MeOH−CH_2Cl_2 mixture (0.5:2:97.5 v/v/v/) and filtered through a short SiO_2 column to provide 400 mg (79%) of the reduced product as a resin that solidified on standing. ^{1}H NMR (400 MHz, $CDCl_3$) 4.68 (dq, *J* = 9.4, 5.9 Hz, 1H), 2.76−2.69 (m, 2H), 2.60−2.55 (m, 3H), 2.49 (d, *J* = 11.6 Hz, 1H), 2.10 (br s, 1H), 1.93 (ddd, *J* = 13.5, 6.0, 2.7 Hz, 1H), 1.60−1.48 (m, 2H), 1.45−1.19 (m, 3H), 1.33 (d, *J* = 5.6 Hz, 3H).

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Decahydro-1-methyl-3-oxo-3*H*-thiopyrano[3,4-*f*]isobenzofuran-9-carboxaldehyde (14). To a solution of **13** (97 mg, 0.36 mmol) in CH_2Cl_2 (4 mL) was added oxalyl chloride (94 μL) followed by 1 drop of DMF. The solution was stirred for 1 h at rt and concentrated to provide the crude acid chloride, which was dissolved in toluene (3 mL) and cooled to 0 °C. $Pd(PPh_3)_4$ (42 mg, 0.04 mmol, 0.1 equiv) was added, followed by Bu_3SnH (94 μL). The mixture was stirred at 0 °C for 3 h, concentrated, and chromatographed with 25% EtOAc−hexane to provide 73 mg (80%) of the title compound as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) 9.75 (d, *J* = 2.8 Hz, 1H), 4.62 (dq, *J* = 9.7, 6.0 Hz, 1H), 2.8−2.70 (m, 2H), 2.65−2.55 (m, 3H), 2.50 (d, *J* = 7.2 Hz), 2.10 (ddd, *J* = 13.2, 6.4, 3.0 Hz, 1H), 1.94 (ddd, *J* = 13.6, 6.0, 3.0, 1H), 1.69 (dq, *J* = 10.9 Hz, 3.00 Hz, 1H), 1.58−1.48 (m, 1H), 1.42−1.20 (m, 3H), 1.33(d, *J* = 6.4 Hz, 3H).

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Decahydro-1-methyl-9-[(1*E*)-2-[5-[3-(trifluoromethyl)phenyl]-2-pyridinyl]ethenyl]-3*H*-thiopyrano-[3,4-*f*]isobenzofuran-3-one (16). To a solution of **15** (156 mg, 0.42 mmol, 2.0 equiv) in THF (1 mL) at 0 °C was added a 2.5 M solution of BuLi in hexanes (170 μL, 0.42 mmol, 2.0 equiv), and the mixture was stirred for 30 min. To this was added a solution of **14** (53 mg, 0.21 mmol) in THF (1.5 mL), and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of aq NH_4Cl (20 mL), the THF was evaporated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with aq $NaHCO_3$ (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed with 40% EtOAc−hexane to provide 90 mg (91%) of resin. ^{1}H NMR (400 MHz, $CDCl_3$) 8.78 (d, *J* = 2.2 Hz, 1H), 7.85 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.80 (s, 1H), 7.75 (d, *J* = 7.3 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 1H), 6.62−6.53 (m, 2H), 4.78−4.71 (m, 1H), 2.77−2.63 (m, 2H), 2.56−2.34 (m, 5H), 2.17−2.13 (m, 1H), 1.94 (ddd, *J* = 3.3, 6.3, 13.7 Hz, 1H), 1.57−1.48 (m, 1H), 1.43 (d, *J* = 5.9 Hz, 1H), 1.33−1.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.14, 153.72, 147.85, 138.16, 135.93, 134.88, 133.53, 131.00, 129.94, 129.48, 124.58, 124.55, 123.49, 123.45, 121.69, 48.62, 45.34, 41.85, 41.35, 40.47, 34.16, 33.08, 31.33, 28.89, 22.16; HRMS calcd for $C_{26}H_{27}F_3NO_2S$, 474.1715; found, 474.1721.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Decahydro-1-methyl-9-[(1*E*)-2-[5-[3-(trifluoromethyl)phenyl]-2-pyridinyl]ethenyl]-3*H*-thiopyrano-[3,4-*f*]isobenzofuran-3-one-6,6-dioxide (17) and (1*R*,3a*R*,4a*S*,-8a*S*,9*S*,9a*S*)-Decahydro-1-methyl-9-[(1*E*)-2-[5-[3-(trifluoromethyl)phenyl]-2-pyridinyl]ethenyl]-3*H*-thiopyrano[3,4-*f*]isobenzofuran-3-one-6-oxide (18a, 18b). To a solution of **16** (70 mg, 0.15 mmol) in AcOH (2 mL) was added CH_3SO_3H (50 μL, 5 equiv) and $NaBO_3\cdot4H_2O$ (30 mg, 0.19 mmol, 1.3 equiv), and the mixture was stirred overnight at rt. The acetic acid was evaporated, and the resultant residue was taken up in an aq $NaHCO_3$−Na_2SO_3 mixture (25 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, concentrated, and purified by preparative thin layer chromatography using 4% MeOH in dichloromethane to provide 36 mg of **17**, 11 mg of **18a** (isomer 1), and 4 mg of **18b** (isomer 2).

Sulfone 17: ^{1}H NMR (400 MHz, $CDCl_3$) 8.80 (d, *J* = 2.2 Hz, 1H), 7.88 (dd, *J* = 2.6, 8.5 Hz, 1H), 7.81 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.62 (t, *J* = 7.7, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.68−6.58 (m, 2H), 4.77−4.70 (m, 1H), 3.10−3.03 (2H), 2.96 (dt, *J* = 3.4, 13.7 Hz, 1H), 2.82−2.74 (m, 2H), 2.56−2.43 (m, 2H), 2.32−2.26 (m, 1H), 2.12−1.99 (m, 2H), 1.83−1.72 (m, 1H), 1.46 (d, *J* = 5.9 Hz, 3H), 1.45−1.34 (m, 2H); HRMS calcd for $C_{26}H_{27}F_3NO_4S$, 506.1613; found, 506.1612 (MH^+).

Sulfoxide 18a (Isomer 1): ^{1}H NMR (400 MHz, $CDCl_3$) 8.79 (d, *J* = 2.2 Hz, 1H), 8.80 (d, *J* = 2.2, 8.1 Hz, 1H), 7.81 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 7.3 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 6.68−6.58 (m, 2H), 4.79−4.72 (m, 1H), 3.05−2.97 (m, 2H), 2.84−2.77 (m, 1H), 2.62−2.56 (m, 1H), 2.48−2.19 (m, 4H), 2.10−2.00 (m, 1H), 1.95−1.89 (m, 2H), 1.46 (d, *J* = 5.9 Hz, 3H), 1.50−1.34 (m, 2H); HRMS calcd for $C_{26}H_{27}F_3NO_3S$, 490.1664; found, 490.1661 (MH+).

Sulfoxide 18b (Isomer 2): ^{1}H NMR (400 MHz, $CDCl_3$) 8.80 (d, *J* = 2.4 Hz, 1H), 7.87 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.81 (s, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 9.6 Hz, 1H), 6.67−6.55 (m, 2H), 4.78−4.71 (m, 1H), 3.44−3.40 (m, 1H), 3.35 (dt, *J* = 12.1, 2.8 Hz, 1H), 2.78−2.71 (m, 1H), 2.64−2.57 (m, 1H), 2.52−2.36 (m, 3H), 2.26−2.21 (m, 1H), 2.04 (ddd, *J* = 13.5, 6.5, 2.7 Hz, 1H), 1.45 (d, *J* = 6.0 Hz, 3H), 1.60−1.25 (m, 6H).

Enal **19a**[36] was converted to aldehyde **25a** using procedures used for the preparation of **25b** described below.

3-(5,6-Dihydro-2*H*-pyran-3-yl)-2-propenoic Acid (20a). ^{1}H NMR (400 MHz, $CDCl_3$) 7.28 (d, *J* = 16.1 Hz, 1H), 6.34 (t, *J* = 4.2 Hz, 1H), 5.62 (d, *J* = 16.1 Hz, 1H), 4.31 (d, *J* = 2.2 Hz, 2H), 3.80 (t, *J* = 5.5 Hz, 2H), 2.37−2.35 (m, 2H); MS 155.1 (MH^+).

(2*Z*,4*R*)-4-[[(2*E*)-3-(5,6-Dihydro-2*H*-pyran-3-yl)-1-oxo-2-propenyl]oxy]-2-pentenoic Acid, Phenylmethyl Ester (22a). ^{1}H NMR (400 MHz, $CDCl_3$) 7.38−7.35 (m, 5H), 7.23 (d, *J* = 16.6 Hz, 1H), 6.32 (t, *J* = 4.2 Hz, 1H), 5.64−5.59 (m, 1H), 5.60 (d, *J* = 16.4 Hz, 1H), 5.19 (s, 2H), 4.29 (d, *J* = 2 Hz, 1H), 3.78 (t, *J* = 5.3 Hz, 1H), 2.37−2.34 (m, 2H), 1.56 (d, *J* = 7.2 Hz, 3H); MS 341.2 (MH^+).

(1*R*,3a*R*,8a*S*,9*S*,9a*R*)-1,3a,5,7,8,8a,9,9a-Octahydro-1-methyl-3-oxo-3*H*-pyrano[3,4-*f*]isobenzofuran-9-carboxylic Acid, Phenylmethyl Ester (23a). ^{1}H NMR (400 MHz, $CDCl_3$) 7.40−7.26 (m, 5H), 5.49 (s, 1H), 5.16 (ABq, *J* = 12.4 Hz, 2H), 4.50−4.43 (m, 1H), 4.17 (d, *J* = 12.8 Hz, 1H), 3.99 (dd, *J* = 4.4, 11.6 Hz, 1H), 3.95−3.91 (m, 1H), 3.58 (dt, *J* = 2.4, 12.2 Hz, 1H), 3.40−3.36 (m, 1H), 2.78−2.73 (m, 2H), 2.62 (dd, *J* = 11.2, 4.0 Hz, 1H), 1.91−1.87 (m, 1H), 1.37−1.26 (m, 1H), 1.13 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.17, 172.40, 137.39, 134.71, 128.60, 128.57, 128.52, 114.76, 76.40, 71.44, 67.57, 67.13, 44.59, 43.90, 43.77, 32.66, 31.89, 20.07; HRMS 343.1548 (MH^+).

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*R*)-Decahydro-1-methyl-3-oxo-3*H*-pyrano[3,4-*f*]isobenzofuran-9-carboxylic Acid (24a). ^{1}H NMR (400

MHz, $CDCl_3$) 4.73−4.66 (m, 1H), 4.01 (dd, *J* = 3.7, 11.7 Hz, 1H), 3.87 (dd, *J* = 4.0, 11.4 Hz, 1H), 3.48 (dt, *J* = 2.0, 11.9 Hz, 1H), 3.09 (t, *J* = 11.0 Hz, 1H), 2.76−2.70 (m, 1H), 2.63−2.52 (m, 2H), 1.81 (ddd, *J* = 2.0, 6.0, 13.4 Hz, 1H), 1.77−1.73 (m, 1H), 1.65 (dq, *J* = 3.1, 11.1 Hz, 1H), 1.33 (d, *J* = 5.9 Hz, 3H), 1.47−1.24 (m, 2H), 1.08 (q, *J* = 13.0 Hz, 1H); MS 255.1 (MH^+).

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Decahydro-1-methyl-3-oxo-3*H*-pyrano[3,4-*f*]isobenzofuran-9-carboxaldehyde (25a). ^{1}H NMR (400 MHz, $CDCl_3$) 9.79 (d, *J* = 2.2 Hz, 1H), 4.64−4.57 (m, 1H), 3.99 (dd, *J* = 4.4, 11.7 Hz, 1H), 3.87 (dd, *J* = 4.0, 11.4 Hz, 1H), 3.48 (dt, *J* = 2.2, 12.3 Hz, 1H), 3.12 (t, *J* = 11.0 Hz, 1H), 2.78−2.60 (m, 3H), 1.85−1.73 (m, 3H), 1.47−1.38 (m, 1H), 1.34 (d, *J* = 5.9 Hz, 3H), 1.29−1.22 (m, 1H), 1.10 (q, *J* = 12.9 Hz, 1H).

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Decahydro-1-methyl-9-[(e)-2-[5-[3-(trifluoromethyl)phenyl]-2-pyridinyl]ethenyl]-3*H*-furo[3,4-*g*][2]-benzopyran-3-one (27a). To a solution of [5-(3-trifluoromethyl-phenyl)-pyridin-2-ylmethyl]-phosphonic acid diethyl ester (200 mg, 0.536 mmol) in 2 mL of THF at 0 °C was added a 2.5 M solution of BuLi in hexanes (0.21 mL, 0.537 mmol), and this mixture was stirred for 10 min. To this was added Ti(O*i*-Pr)$_4$ (0.16 mL, 0.538 mmol) followed by a solution of aldehyde **25a** in 1 mL of THF (68 mg, 0.285 mmol). The mixture was stirred for 2 h, poured into 20 mL of aq sodium potassium tartrate, and extracted with dichloromethane (3 × 15 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed using 50% ethyl acetate in hexanes to provide 105 mg of product. ^{1}H NMR (400 MHz, $CDCl_3$) 8.78 (d, *J* = 2.2 Hz, 1H), 7.86 (dd *J* = 8.1, 2.2 Hz, 1H), 7.80 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.65−7.57 (m, 2H,), 7.28 (d, *J* = 8.1 Hz, 1H), 6.64−6.55 (m, 2H), 4.79−4.72 (m, 1H), 3.98 (dd, *J* = 3.7, 11.7 Hz, 1H), 3.86 (dd, *J* = 3.3, 11.4 Hz, 1H), 3.40 (dt, *J* = 2.0, 12.1 Hz, 1H), 3.06 (t, *J* = 11.0 Hz, 1H), 2.77−2.70 (m, 1H), 1.83 (dq, *J* = 1.9, 7.0 Hz, 1H), 1.67 (d, *J* = 11.7 Hz, 1H), 1.44 (d, *J* = 5.9 Hz, 3H), 1.48−1.39 (m, 2H), 1.28−1.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.20, 153.75, 147.89, 147.80, 138.16, 135.25, 134.88, 133.53, 131.07, 129.94, 129.47, 124.57, 123.48, 121.63, 76.63, 72.02, 68.43, 48.29, 44.87, 41.50, 39.64, 38.87, 31.24, 26.37, 22.17; $[\alpha]^{20}_D$ = +25.7 (*c* 10 mg/mL, MeOH); HRMS calcd for $C_{26}H_{27}F_3NO_3$ (MH^+), 458.1943; found, 458.1941; Anal. ($C_{26}H_{26}F_3NO_3$·HCl·0.6H_2O) C, H, N.

The following compounds were prepared using a procedure similar to the preparation of **27a** using appropriate phosphonate reagents.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-9-[(*E*)-2-[5-(3-Fluorophenyl)-2-pyridinyl]ethenyl]-decahydro-1-methyl-3*H*-furo[3,4-*g*][2]benzopyran-3-one (27b). ^{1}H NMR (400 MHz, $CDCl_3$) 8.75 (d, *J* = 1.5 Hz, 1H), 7.80 (dd, *J* = 2.9, 8.1 Hz, 1H), 7.45−7.39 (m, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.09−7.05 (m, 1H), 6.61−6.51 (m, 2H), 4.78−4.71 (m, 1H), 3.97 (dd, *J* = 3.6, 11. 7 Hz, 1H), 3.85 (dd, *J* = 3.3, 11.4 Hz, 1H), 3.39 (t, *J* = 11.7 Hz, 1H), 3.05 (t, *J* = 10.6 Hz, 1H), 2.76−2.69 (m, 1H), 2.45−2.36 (m, 1H), 1.84−1.79 (m, 1H), 1.66 (d, *J* = 13.2 Hz, 1H), 1.43 (d, *J* = 5.9 Hz, 3H), 1.47−1.37 (m, 2H), 1.27−1.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.21, 164.17, 161.72, 153.56, 147.87, 147.76, 139.53, 139.46, 134.93, 134.72, 133.68, 131.17, 130.52, 130.44, 122.33, 122.30, 121.54, 114.85, 114.65, 113.70, 113.48, 71.99, 68.42, 48.24, 44.84, 41.42, 39.63, 38.86, 31.21, 26.35, 22.18, 22.13; $[\alpha]^{20}_D$ = +25.9 (*c* 8 mg/mL, MeOH); HRMS calcd for $C_{25}H_{26}FNO_3$ (MH^+), 408.1975; found, 408.1982; Anal. ($C_{25}H_{26}FNO_3$·HCl·0.5H_2O) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-9-[(*E*)-2-[5-(2-Fluorophenyl)-2-pyridinyl]ethenyl]-decahydro-1-methyl-3*H*-furo[3,4-*g*][2]benzopyran-3-one (27c). ^{1}H NMR (400 MHz, $CDCl_3$) 8.74 (s, 1H), 7.85 (d, *J* = 8.1, Hz, 1H), 7.44 (dt, *J* = 1.7, 7.7 Hz, 1H), 7.41−7.35 (m, 1H), 7.28−7.17 (m, 4H), 6.64−6.55 (m, 2H), 4.80−4.74 (m, 1H), 4.00 (dd, *J* = 3.7, 11.7 Hz, 1H), 3.88 (dd, *J* = 4.1, 11.4 Hz, 1H), 3.41 (dt, *J* = 2.0, 12.1 Hz, 1H), 3.07 (t, *J* = 10.7 Hz, 1H), 2.78−2.72 (m, 1H), 2.40−2.38 (m, 2H), 1.85 (ddd, *J* = 2.6, 6.3, 13.2 Hz, 1H), 1.70 (d, *J* = 13. 2 Hz, 1H), 1.46 (d, *J* = 5.9 Hz, 3H), 1.49−1.36 (m, 2H), 1.29−1.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.26, 160.75, 158.29, 153.16, 149.14, 136.70, 136.67, 134.82, 131.24, 129.98, 129.95, 129.74, 129.67, 125.18, 125.05, 124.54, 124.51, 121.21, 116.24, 116.02, 76.65, 71.99, 68.42, 48.20, 44.78, 41.42, 39.59, 38.81, 31.18, 26.33, 22.18; $[\alpha]^{20}_D$ = +23.9 (*c* 10.6 mg/mL, MeOH); HRMS calcd for $C_{25}H_{26}FNO_3$ (MH^+), 408.1975; found, 408.1989; Anal. ($C_{25}H_{26}FNO_3$·HCl·0.5H_2O) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-9-[(*E*)-2-[5-(2,3-Difluorophenyl)-2-pyridinyl]ethenyl]-decahydro-1-methyl-3*H*-furo[3,4-*g*][2]-benzopyran-3-one (27d). ^{1}H NMR (400 MHz, $CDCl_3$) 8.71 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.23−7.14 (m, 3H), 6.65−6.54 (m, 2H), 4.79−4.72 (m, 1H), 3.98 (dd, *J* = 4.1, 11.4 Hz, 1H), 3.86 (dd, *J* = 3.3, 11.4 Hz, 1H), 3.40 (t, *J* = 12.1 Hz, 1H), 3.06 (t, *J* = 10.6 Hz, 1H), 2.77−2.70 (m, 1H), 2.48−2.37 (m, 2H), 1.83 (dd, *J* = 6.3, 11.4 Hz, 1H), 1.67 (d, *J* = 12.5 Hz, 1H),1.44 (d, *J* = 5.9 Hz, 3H), 1.48−1.38 (m, 2H), 1.28−1.01 (m, 2H); $[\alpha]^{20}_D$ = +12.2 (*c* 8 mg/mL, MeOH); HRMS calcd for $C_{25}H_{26}F_2NO_3$ (MH^+), 426.1881; found, 426.1881; Anal. ($C_{25}H_{25}F_2NO_3$·HCl·0.4H_2O) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-9-[(*E*)-2-[5-(3-Chlorophenyl)-2-pyridinyl]ethenyl]-decahydro-1-methyl-3*H*-furo[3,4-*g*][2]benzopyran-3-one (27e). ^{1}H NMR (400 MHz, $CDCl_3$) 8.75 (d, *J* = 1.5 Hz, 1H), 7.81 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.55−7.54 (m, 1H), 7.47−7.35 (m, 3H), 7.25 (d, *J* = 8.1 Hz, 1H), 6.63−6.52 (m, 2H), 4.80−4.72 (m, 1H), 3.99 (dd, *J* = 3.7, 11.7, 1H), 3.87 (dd, *J* = 3.7, 11.0 Hz, 1H), 3.40 (dt, *J* = 2.0, 11.9 Hz, 1H), 3.06 (t, *J* = 10.9 Hz, 1H), 2.77−2.71 (m, 1H), 2.47−2.36 (m, 2H), 1.84 (ddd, *J* = 2.2, 6.6, 13.2 Hz, 1H), 1.68 (d, *J* = 12.5 Hz, 1H), 1.44 (d, *J* = 5.9 Hz, 3H), 1.48−1.38 (m, 2H), 1.28−1.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.27, 153.51, 139.09, 135.06, 134.83, 133.62, 131.10, 130.20, 127.94, 126.79, 124.83, 121.63, 72.04, 68.45, 48.26, 44.87, 41.47, 39.65, 38.86, 31.23, 26.38, 22.20; $[\alpha]^{20}_D$ = −8.2 (*c* 1.7 mg/mL, MeOH); HRMS calcd for $C_{25}H_{27}ClNO_3$ (MH^+), 424.1679; found, 424.1686; Anal. ($C_{25}H_{26}ClNO_3$·HCl·0.8H_2O) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-9-[(*E*)-2-[5-(2-Chlorophenyl)-2-pyridinyl]ethenyl]-decahydro-1-methyl-3*H*-furo[3,4-*g*][2]benzopyran-3-one (27f). ^{1}H NMR (400 MHz, $CDCl_3$) 8.63 (d, *J* = 2.2 Hz, 1H), 7.70 (dd, *J* = 2.9, 8.1 Hz, 1H), 7.52−7.49 (m, 1H), 7.37−7.31 (m, 3H), 7.26 (d, *J* = 7.3 Hz, 1H), 6.64−6.55 (m, 2H), 4.81−4.74 (m, 1H), 4.00 (dd, *J* = 3.7, 11.7 Hz, 1H), 3.88 (dd, *J* = 3.7, 11.0 Hz, 1H), 3.41 (dt, *J* = 2.0, 12.1 Hz, 1H), 3.07 (d, *J* = 10.7 Hz, 1H), 2.78−2.72 (m, 1H), 2.47−2.38 (m, 2H), 1.85 (ddd, *J* = 2.2, 6.6, 13.4 Hz, 1H), 1.70 (d, *J* = 13.2 Hz, 1H), 1.47 (d, *J* = 5.9 Hz, 3H), 1.49−1.39 (m, 2H), 1.30−1.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.24, 153.22, 149.67, 137.31, 136.49, 134.82, 133.43, 132.48, 131.37, 130.93, 130.02, 129.20, 127.01, 120.79, 76.67, 72.04, 68.45, 48.27, 44.88, 41.48, 39.65, 38.90, 31.24, 26.40, 22.25; $[\alpha]^{20}_D$ = +16.9 (*c* 6 mg/mL, MeOH); HRMS calcd for $C_{25}H_{27}ClNO_3$ (MH^+), 424.1679; found, 424.1684; Anal. ($C_{25}H_{26}ClNO_3$·HCl·0.7H_2O) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-9-[(*E*)-2-[5-(2,3-Dichlorophenyl)-2-pyridinyl]ethenyl]-decahydro-1-methyl-3*H*-furo[3,4-*g*][2]-benzopyran-3-one (27g). ^{1}H NMR (400 MHz, $CDCl_3$) 8.60 (d, *J* = 2.2 Hz, 1H), 7.74 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.53 (dd, *J* = 1.9, 7.7 Hz, 1H), 7.31−7.22 (m, 3H), 6.67−6.56 (m, 1H), 4.81−4.74 (m, 1H), 4.00 (dd, *J* = 4.1, 11.4 Hz, 1H), 3.88 (dd, *J* = 3.7, 11.7 Hz, 1H), 3.40 (dt, *J* = 2.2, 11.7 Hz, 1H), 3.07 (t, *J* = 10.7 Hz, 1H), 2.78−2.72 (m, 1H), 2.49−2.38 (m, 2H), 1.84 (ddd, *J* = 2.2, 6.6, 13.6 Hz, 1H), 1.70 (d, *J* = 13.2 Hz, 1H), 1.47 (d, *J* = 5.9 Hz, 3H), 1.44−1.37 (m, 2H), 1.30−1.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.24, 153.58, 149.48, 138.80, 137.25, 135.22, 133.80, 133.34, 131.25, 131.13, 130.08, 129.09, 127.35, 120.85, 76.65, 72.06, 68.46, 48.28, 44.91, 41.50, 39.66, 38.90, 31.25, 26.40, 22.26; $[\alpha]^{20}_D$ = +15.5 (*c* 5 mg/mL, MeOH); HRMS calcd for $C_{25}H_{26}Cl_2NO_3$, 458.1290; found, 458.1299; Anal. ($C_{25}H_{25}Cl_2NO_3$·HCl·1.5H_2O) C, H, N.

3-Formyl-5,6-dihydro-1(2*H*)-pyridinecarboxylic Acid, Ethyl Ester (19b). To a solution of 5,6-dihydro-2*H*-pyridine-1,3-dicarboxylic acid 1-ethyl ester 3-methyl ester[37] (35.4 g, 166 mmol) in CH_2Cl_2 (600 mL) at −78 °C was slowly added a solution of 1 M DIBAL (365 mL, 365 mmol, 2.2 equiv) in CH_2Cl_2, and the mixture was stirred for 1.5 h. The reaction was quenched by the addition of 1 L of satd aq Rochelle's salt, and the organic layer was separated. The aqueous layer was extracted with 2 × 250 mL of CH_2Cl_2, and the combined organic layer was washed with 500 mL of brine, dried over $MgSO_4$, filtered, and concentrated, and the resultant crude was chromatographed with 40% EtOAc−hexane to provide 17 g (55%) of alcohol as an oil.

To a solution of above alcohol (17.0 g, 92 mmol) in 150 mL of CH_2Cl_2 at rt was added $NaHCO_3$ (15.4 g, 183 mmol, 2 equiv) and Dess−Martin reagent (46.7 g, 110 mmol, 1.2 equiv), and the suspension was stirred for 45 min. To this was added 300 mL of Et_2O, and a solution of $Na_2S_2O_3 \cdot 5H_2O$ (70 g, 282 mmol, 2 equiv) and $NaHCO_3$ (15.4 g, 183 mmol, 2 equiv) in 600 mL of H_2O. The mixture was stirred vigorously until the two layers became clear. The organic layer was separated and the aqueous layer was extracted with 2 × 150 mL of Et_2O. The combined organic layer was washed with 300 mL each of aq $Na_2S_2O_3$/$NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated to give 15.3 g (91%) of oil. ^{1}H NMR (400 MHz, $CDCl_3$) 9.43 (s, 1H), 6.93 (s, 1H), 4.15 (q, J = 7. 1 Hz, 2H), 4.14 (s, 2H), 3.58 (t, J = 5.7 Hz, 2H), 2.46 (bs, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 191.40, 155.41, 147.85, 138.68, 61.62, 40.96, 39.71, 26.23, 14.78; HRMS calcd for $C_9H_{13}NO_3$ (MH^+), 184.0974; found, 184.0966.

3-[(1*E*)-2-Carboxyethenyl]-5,6-dihydro-1(2*H*)-pyridinecarboxylic Acid, 1-Ethyl Ester (20b). To a suspension of 60% NaH (4.35 g, 109 mmol, 1.3 equiv) in THF (300 mL) at 0 °C was added dropwise triethyl phosphonoacetate (20 mL, 109 mmol, 1.3 equiv), and the mixture was stirred at 0 °C for 30 min. To this was added a solution of **19b** (15.3 g, 83.5 mmol), and the mixture was stirred for 30 min at 0 °C. The reaction was quenched by the addition of 600 mL of aq NH_4Cl, the THF was evaporated, and the aqueous slurry was extracted with 3 × 200 mL of Et_2O. The combined organic layer was washed with 200 mL of brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed with 15% EtOAc−hexane to provide 19.9 g (94%) of the ester as oil.

To a solution of the above ester (19.9 g, 79 mmol) in 100 mL each of CH_3OH, THF and H_2O was added KOH (13.3 g, 237 mmol, 3 equiv), and the mixture was stirred at rt for 2 h. The mixture was diluted with 200 mL of H_2O, acidified with 1 N HCl to ∼pH 2, and extracted with 3 × 200 mL of EtOAc. The combined organic layer was washed with 200 mL each of H_2O and brine, dried over $MgSO_4$, filtered, and evaporated to give 17.0 g (96%) of **20b** as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) 7.33 (d, J = 16.0 Hz, 1H), 6.33 (s, 1H), 5.80 (d, J = 16.0 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.12 (br, 2H), 3.57 (t, J = 5.8 Hz, 2H), 2.36 (br, 2H), 1.29 (t, J = 7.2 Hz, 3H); HRMS calcd for $C_{11}H_{16}NO_4$ (MH^+), 226.1079; found, 226.1083.

3,6-Dihydro-5-[(1*E*)-3-[[(1*R*)-1-methyl-4-oxo-4-(phenylmethoxy)-2-butynyl]oxy]-3-oxo-1-propenyl]-1(2*H*)-pyridinecarboxylic Acid, Ethyl Ester (22b). To a solution of **20b** (17.0 g, 76 mmol) in 400 mL of CH_2Cl_2 at rt was added oxalyl chloride (13.2 mL, 151 mmol, 2 equiv) and DMF (120 μL, 1.6 mmol, 2 mol %). The mixture was stirred for 1 h, concentrated, and evaporated with 100 mL of anhydrous toluene to provide the acid chloride. To a solution of this acid chloride in 200 mL of CH_2Cl_2 at 0 °C was added DMAP (925 mg, 7.6 mmol, 0.1 equiv), **21** (15.4 g, 75 mmol, 1.0 equiv) in 15 mL of CH_2Cl_2, followed by Et_3N (12.7 mL, 91 mmol, 1.2 equiv). The mixture was stirred for 1.5 h at 0 °C, then diluted with 600 mL of Et_2O. The solution was washed successively with 200 mL of H_2O, 2 × 200 mL 1 N HCl, 200 mL of aq $NaHCO_3$, and 200 mL of brine. It was dried over anhydrous $MgSO_4$, filtered, concentrated, and chromatographed with 20% EtOAc−hexane to provide 20 g (78%) of resin. ^{1}H NMR (400 MHz, $CDCl_3$) 7.38−7.35 (m, 5H), 7.28 (d, J = 16.0 Hz, 1H), 6.31 (s, 1H), 5.77 (d, J = 16.0 Hz, 1H), 5.62 (q, J = 6.8 Hz, 1H), 5.19 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 4.08 (br, 2H), 3.56 (br, 2H), 2.34 (br, 2H), 1.57 (d, J = 6.8 Hz, 3H), 1.28 (t, J = 7. 2 Hz); HRMS calcd for $C_{23}H_{26}NO_6$ (MH^+), 412.1760; found, 412.1764.

(1*R*,3a*R*,8a*S*,9*S*,9a*R*)-1,3a,5,7,8,8a,9,9a-Octahydro-1-methyl-3-oxo-furo[3,4-*g*]isoquinoline-6,9(3*H*)-dicarboxylic Acid, 6-Ethyl 9-(Phenylmethyl) Ester (23b). A suspension **22b** (10 g, 29 mmol), quinoline (700 μL, 5.9 mmol, 0.2 equiv), and Lindlar catalyst (1.0 g, 10 wt %) in 150 mL of THF was stirred under a H_2 balloon for 2.5 h. Another batch of 10 g of **22b** was similarly reduced with Lindlar catalyst. The two batches were combined, filtered through a celite pad, and evaporated, and the residue was redissolved in 600 mL of EtOAc. It was washed with 3 × 200 mL of 1 N HCl and 200 mL of brine, dried over $MgSO_4$, filtered, and evaporated to give 20 g of resin, which was used immediately for the Diels−Alder reaction.

A solution of the above product (20 g) in 500 mL of toluene in a sealed glass vessel was heated at 185 °C for 6 h using an oil bath. The solution was cooled to rt, treated with DBU (1.8 mL, 12 mmol, 0.2 equiv) for 1 h, concentrated, and chromatographed with 25% EtOAc−hexane to provide 11.3 g (56%) of the cyclized *exo*-product **23b**. ^{1}H NMR (400 MHz, $CDCl_3$) 7.39−7.35 (m, 5H), 5.56 (s, 1H), 5.17 (dd, J = 18.4, 12.0 Hz, 2H), 4.53 (br, 1H), 4.47 (dq, J = 9.8, 6.0 Hz, 1H), 4.17 (br, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.42 (d, J = 14.8 Hz, 1H), 3.38−3.34 (m, 1H), 2.93 (t, J = 12.0 Hz, 1H), 2.77−2.72 (m, 1H), 2.65−2.63 (m, 1H), 2.58 (dd, J = 10.8, 4.0 Hz, 1H), 1.93−1.89 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.14 (d, J = 5.6 Hz, 3H); HRMS calcd for $C_{23}H_{28}NO_6$ (MH^+), 414.1917; found, 414.1923.

(1*R*,3a*R*,4a*S*,8a*R*,9*S*,9a*R*)-Decahydro-1-methyl-3-oxo-furo[3,4-*g*]isoquinoline-6,9(3*H*)-dicarboxylic Acid, 6-Ethyl Ester (24 b). A suspension of **23b** (11.2 g, 27 mmol) and 10% Pd−C (1.2 g, 10 wt %) in 200 mL of EtOAc was stirred under a H_2 balloon until the debenzylation was complete. It was filtered through a celite pad, concentrated, and redissolved in 200 mL of CH_3OH. To this was added 900 mg of PtO_2, and the suspension was shaken under 50 atm of H_2 in a Parr vessel. The mixture was filtered through a celite pad and concentrated to provide 8.5 g (96%) of **24b**. ^{1}H NMR (400 MHz, $CDCl_3$) 4.72−4.65 (m, 1H), 4.22−4.09 (m, 2H), 4.12 (q, J = 6.8 Hz, 2H), 2.78 (br, 1H), 2.74−2.68 (m, 1H), 2.59 (dt, J = 10.1, 6.5 Hz, 1H), 2.51−2.46 (m, 1H), 2.43 (br, 1H), 1.94−1.90 (m, 1H), 1.82 (d, J = 10.4 Hz, 1H), 1.64−1.53 (m, 1H), 1.33 (d, J = 5.9 Hz, H), 1.24 (t, J = 7.1 Hz, 3H), 1.39−1.03 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.33, 155.25, 76.22, 61.76, 48.86, 46.18, 44.16, 43.99, 41.20, 37.56, 37.45, 30.00, 27.66, 20.20, 14.74; $[\alpha]^{25}_D$ = −11.5 (*c* 13 mg/mL, MeOH); HRMS calcd for $C_{16}H_{24}NO_6$ (MH^+), 326.1604; found, 326.1600.

(1*R*,3a*R*,4a*S*,8a*R*,9*S*,9a*S*)-9-Formyldecahydro-1-methyl-3-oxo-furo[3,4-*g*]isoquinoline-6(3*H*)-carboxylic Acid, Ethyl Ester (25b). To a solution of **24b** (415 mg, 1.28 mmol) in 10 mL of CH_2Cl_2 at rt was added oxalyl chloride (225 μL, 2.58 mmol, 2 equiv), followed by 1 drop of DMF. The solution was stirred at rt for 1 h, at which time there was no evolution of gas. It was concentrated and evaporated with anhydrous toluene to give the acid chloride. The acid chloride was dissolved in 6 mL of anhydrous toluene and cooled to 0 °C, and $Pd(PPh_3)_4$ (74 mg, 0.064 mmol, 5 mol %) was added, followed by Bu_3SnH (520 μL, 1.93 mmol, 1.5 equiv). The mixture was stirred at 0 °C for 3 h, concentrated, and chromatographed with 50% EtOAc−hexane to provide 360 mg (91%) of **25b** as a resin. ^{1}H NMR (400 MHz, $CDCl_3$) 9.78 (d, J = 2.2 Hz, 1H), 4.62−4.55 (m, 1H), 4.16 (br, 2H), 4.11 (q, J = 7.1 Hz, 2H), 2.79 (br, 1H), 2.75−2.65 (m, 2H), 2.58 (ddd, J = 11.0, 5.1, 2.2. Hz, 1H), 2. 46 (br, 1H), 1.96−1.91 (m, 1H), 1.87−1.83 (m, 1H), 1.67 (dq, J = 3.1, 11.1 Hz, 1H), 1.32 (d, J = 5.9 Hz, 3H), 1.24 (t, J = 7.3 Hz, 3H), 1.42−1.21 (m, 2H), 1.04 (dq, J = 4.0, 12.3 Hz, 1H); MS (ESI) *m/z* 310.1 (MH^+).

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Decahydro-1-methyl-3-oxo-9-[(1*E*)-2-[5-[3-(trifluoromethyl)phenyl]-2-pyridinyl]ethenyl]-furo[3,4-*g*]isoquinoline-6(3*H*)-carboxylic Acid Ethyl Ester (28a). To a solution of [5-(3-trifluoromethyl-phenyl)-pyridin-2-ylmethyl]-phosphonic acid diethyl ester (110 mg, 0.295 mmol, 2.0 equiv) in 1 mL of THF at 0 °C was added 2.5 M solution of BuLi in hexanes (0.11 mL, 0.295 mmol, 2.0 equiv) and stirred for 15 min. To this was added a solution of aldehyde **25b** in 1.5 mL of THF (45 mg, 0.145 mmol). The mixture was stirred for 1 h, diluted with 30 mL of water, and extracted with dichloromethane (3 × 15 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed using 50% ethyl acetate in hexanes to provide 68 mg of (**28a**). ^{1}H NMR (400 MHz, $CDCl_3$)

8.78 (d, $J = 2.2$ Hz, 1H), 7.84 (dd, $J = 2.2$, 8.1 Hz, 1H), 7.80 (s, 1H), 7.75 (d, $J = 7.3$ Hz, 1H), 7.66−7.58 (m, 2H), 7.27 (dd, $J = 8.8$ Hz, 1H), 6.65−6.53 (m, 2H), 4.79−4.72 (m, 1H), 4.18 (br, 2H), 4.11 (q, 7.1 Hz, 2H), 2.76−2.70 (m, 2H), 2.44−2.36 (m, 3H), 1.96 (dd, $J = 6.2$, 12.1 Hz, 1H), 1.77 (d, $J = 13.2$ Hz, 1H), 1.43 (d, $J = 5.9$ Hz, 3H), 1.24 (t, $J = 7.0$ Hz, 3H), 1.34−1.15 (m, 3H), 1.10−1.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.17, 155.10, 153.70, 147.85, 138.17, 135.30, 134.89, 133.59, 131.05, 129.96, 129.49, 124.60, 123.51, 123.48, 121.73, 76.64, 61.39, 49.08, 48.44, 44.94, 44.30, 41.57, 40.36, 38.35, 30.69, 28.15, 22.17, 14.79; HRMS calcd for $C_{29}H_{32}F_3N_2O_4$ (MH^+), 529.2314; found, 529.2313.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Decahydro-1-methyl-3-oxo-9-[(1*E*)-2-[5-(3-fluorophenyl)-2-pyridinyl]ethenyl]-furo[3,4-*g*]isoquinoline-6(3*H*)-carboxylic Acid Ethyl Ester (28b). To a solution of [5-(3-fluorophenyl)-pyridin-2-ylmethyl]-phosphonic acid diethyl ester (660 mg, 2.04 mmol, 1.5 equiv) in 10 mL of THF at 0 °C was added 2.5 M solution of BuLi in hexanes (0.82 mL, 2.04 mmol, 1.5 equiv) and stirred for 15 min. To this was added Ti(O*i*-Pr)$_4$ (0.6 mL, 2.03 mmol, 1.5 equiv), followed by a solution of aldehyde **25b** in 4 mL of THF (420 mg, 1.36 mmol). The mixture was stirred for 1.5 h at rt, diluted with 60 mL of aqueous sodium potassium tartrate solution, and extracted with dichloromethane (3 × 15 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed using 50% ethyl acetate in hexanes to provide 510 mg of (**28b**). ^{1}H NMR (400 MHz, $CDCl_3$) 8.76 (d, $J = 2.0$ Hz, 1H), 7.82 (dd, $J = 2.6$, 8.2 Hz, 1H), 7.43 (dt, $J = 6.1$, 7.6 Hz, 1H), 7.35 (d, 1H, $J = 8.0$ Hz, 1H), 7.28−7.24 (m, 2H), 7.08 (dt, $J = 2.8$, 8.1 Hz, 1H), 6.64−6.52 (m, 2H), 4.78−4.71 (m, 1H), 4.17 (br, 2H), 4.11 (q, $J = 6.9$ Hz, 2H), 2.75−2.69 (m, 2H), 2.43−2.36 (m, 3H), 1.95 (dd, $J = 6.2$, 12.2 Hz, 1H), 1.77 (d, $J = 6.4$ Hz, 1H), 1.43 (d, $J = 6.4$ Hz, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.31−1.14 (m, 3H), 1.10−1.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.10, 164.20, 161.76, 155.09, 153.46, 147.80, 139.43, 135.15, 134.81, 133.78, 131.05, 130.56, 130.47, 122.34, 121.66, 114.92, 114.71, 113.75, 113.53, 76.61, 61.37, 49.09, 48.45, 44.96, 44.31, 41.57, 40.37, 38.38, 30.65, 28.17, 22.19, 14.79; $[\alpha]^{20}_D = -56.1$ (*c* 7.6 mg/mL, MeOH); HRMS calcd for $C_{28}H_{32}FN_2O_4$ (MH^+), 479.2346; found, 479.2348; Anal. ($C_{28}H_{31}FN_2O_4$•HCl•1.5H_2O) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Ethyl Decahydro-1-methyl-3-oxo-9-[(e)-2-[5-(2-fluorophenyl)-2-pyridinyl]ethenyl]furo[3,4-*g*]isoquinoline-6(3*H*)-carboxylate (28c). ^{1}H NMR (400 MHz, $CDCl_3$) 8.73 (s, 1H), 7.84 (dt, $J = 8.1$, 1.9 Hz, 1H), 7.42 (dt, $J = 1.7$, 7.7 Hz, 1H), 7.39−7.34 (m, 1H), 7.27−7.15 (m, 3H), 6.64−6.53 (m, 2H), 4.77−4.71 (m, 1H), 4.20 (br, 2H), 4.11 (q, $J = 7.0$ Hz, 2H), 2.75−2.69 (m, 2H), 2.42−2.37 (m, 3H), 1.95 (dd, $J = 5.9$, 12.5 Hz, 1H), 1.77 (d, $J = 12.5$ Hz, 1H), 1.44 (d, $J = 5.9$ Hz, 3H), 1.24 (t, $J = 7.0$ Hz, 3H), 1.34−1.17 (m, 3H), 1.09−1.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.19, 160.81, 158.34, 155.10, 153.06, 136.83, 135.10, 131.13, 130.06, 130.02, 129.99, 129.83, 129.75, 124.59, 124.55, 121.35, 116.31, 116.08, 61.38, 49.07, 48.42, 44.92, 44.29, 41.57, 40.35, 38.35, 30.64, 28.15, 22.22, 14.79; $[\alpha]^{25}_D = -58.7$ (*c* 7.3 mg/mL, MeOH); HRMS calcd for $C_{28}H_{32}FN_2O_4$ (MH^+), 479.2346; found, 479.2339; Anal. ($C_{28}H_{31}FN_2O_4$•HCl•0.6H_2O) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Ethyl 9-[(e)-2-[[2,3′-Bipyridin]-6′-yl]-ethenyl]-decahydro-1-methyl-3-oxofuro[3,4-*g*]isoquinoline-6(3*H*)-carboxylate (28d). To a solution of **29** (100 mg, 0.22 mmol) in toluene (5 mL) was added Pd(OAc)$_2$ (5 mg, 0.022 mmol, 0.1 equiv), (*S*)-(−)-2,2′-bis(diphenylphoshphino)-1,1′-binaphthyl (13 mg, 0.022 mmol, 0.1 equiv), and 2-tributylstannyl pyridine (119 mg, 0.32 mmol, 1.5 equiv). The mixture was bubbled with N_2 for 5 min, then heated to 100 °C in a pressure tube. After 16 h, the mixture was poured onto aqueous NH_4Cl (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. Purification by silica gel chromatography, eluting with 2% $CH_3OH-CH_2Cl_2$, followed by silica gel chromatography, eluting with 60% EtOAc−hexane, yielded 30 mg of **28d**. ^{1}H NMR (400 MHz, $CDCl_3$) 9.12 (d, $J = 2.2$ Hz, 1H), 8.70 (d, $J = 6.6$ Hz, 1H), 9.8.29 (dd, $J = 2.2$ Hz, 8.1 Hz 1H), 7.74−7.80 (m, 3H), 7.25−7.30 (m, 3H), 6.57−6.66 (m, 3H), 4.71−4.78 (m, 1H), 4.05−4.3 (m, 4H), 2.68−2.76 (m, 2H), 2.36−2.44 (m, 3H), 1.96 (dd, $J = 5.9$ Hz, 11.7 Hz, 1H), 1.78 (d, 12.4 Hz, 1H), 1.43 (d, 5.9 Hz, 3H), 2.24 (t, 7.3 Hz, 3H), 1.00−1.36 (m, 5H); HRMS calcd for $C_{27}H_{32}N_3O_4$ (MH^+), 462.2393; found, 462.2401.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-9-[(1*E*)-2-(5-Bromo-2-pyridinyl)-ethenyl]decahydro-1-methyl-3-oxo-furo[3,4-*g*]isoquinoline-6(3*H*)-carboxylic Acid, Ethyl Ester (29). To a solution of the phosphonate **32** (3.49 g, 11.3 mmol, 2 equiv) in THF (50 mL) at 0 °C was added a 1 M solution of LHMDS in THF (11.3 mL, 11.3 mmol, 2 equiv). After stirring for 10 min, Ti(O*i*-Pr)$_4$ (3.4 mL, 11.3 mmol, 2 equiv) was added, followed by a solution of **25b** (1.75 g, 5.7 mmol, 1 equiv) in THF (10 mL), and the mixture was stirred for 1 h under N_2. The reaction mixture was poured into saturated aqueous sodium potassium tartrate solution (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and evaporated to dryness. Purification by silica gel chromatography, eluting with 5% $CH_3OH-CH_2Cl_2$, yielded 1.80 g (70%) of the title compound as a pale yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) 8.59 (d, $J = 4.8$ Hz, 1H), 7.76 (dd, $J = 3$ Hz, 8.4 Hz, 1H), 7.06 (d, $J = 8.4$ Hz, 1H), 6.56 (dd, $J = 9.6$ Hz, 15.2 Hz, 1H), 6.45 (d, $J = 15.2$ Hz, 1H), 4.73 (m, 1H), 4.35−4.05 (m, 2H), 4.12 (q, $J = 6.8$ Hz, 2H), 2.73−2.69 (m, 2H), 2.47−2.35(m, 3H), 1.96 (q, 6.0 Hz, 1H), 1.74 (d, $J = 12.8$ Hz, 1H), 1.41 (d, $J = 6.0$ Hz, 3H), 1.35−1.18 (m, 7H), 1.10−0.98 (m, 1H).

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Decahydro-1-methyl-9-[(e)-2-[5-[3-(trifluoromethyl)phenyl]-2-pyridinyl]ethenyl]furo[3,4-*g*]isoquinolin-3(1*H*)-one (30a). A solution of **28a** (250 mg, 0.473 mmol) and iodotrimethylsilane (0.34 mL, 2.39 mmol, 5 equiv) in 5 mL of dichloromethane was heated at reflux for 3 h. The reaction mixture was cooled to rt, quenched by the addition of aq $NaHCO_3$, and stirred for 15 min at rt, and the mixture was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide 240 mg of **30a**. ^{1}H NMR (400 MHz, $CDCl_3$) 8.79 (d, $J = 2.2$ Hz, 1H), 7.85 (dd, $J = 2.2$, 8.1 Hz, 1H), 7.81 (s, 1H), 7.70 (d, $J = 8.1$ Hz, 1H), 7.67−7.59 (m, 2H), 7.29 (d, $J = 8.1$ Hz, 1H), 6.65−6.55 (m, 2H), 4.80−4.73 (m, 1H), 3.12 (br, 2H), 2.77−2.71 (m, 1H), 2.65 (br, 1H), 2.48−2.36 (m, 3H), 1.91 (dd, $J = 6.2$, 12.8 Hz, 1H), 1.80 (br, 2H), 1.44 (d, $J = 5.9$ Hz, 3H), 1.47−1.08 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.56, 153.66, 147.78, 138.08, 134.88, 134.62, 133.55, 131.58, 131.43, 131.11, 129.92, 129.43, 124.50, 123.42, 121.77, 76.99, 49.79, 48.19, 45.55, 44.44, 41.36, 38.81, 37.08, 28.93, 28.09, 22.12; HRMS calcd for $C_{26}H_{28}F_3N_2O_2$ (MH^+), 457.2103; found, 457.2093

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Decahydro-6-methyl-1-methyl-9-[(e)-2-[5-[3-(trifluoromethyl)phenyl]-2-pyridinyl]ethenyl]furo-[3,4-*g*]isoquinolin-3(1*H*)-one (30b). A mixture of **30a** (62 mg, 0.136 mmol), sodium cyanoborohydride (100 mg), and excess paraformaldehyde in 2 mL of dichloromethane was stirred overnight at rt and quenched with aq NH_4Cl. The mixture was extracted with dichloromethane, the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give residue. The residue was purified by preparative TLC using 5% MeOH−dichloromethane as eluent to provide 31 mg of **30b**. ^{1}H NMR (400 MHz, $CDCl_3$) 8.78 (d, $J = 2.2$ Hz, 1H), 7.84 (dd, $J = 2.2$, 8.1 Hz, 1H), 7.80 (s, 1H), 7.76 (d, $J = 7.3$ Hz, 1H), 7.66−7.57 (m, 2H), 7.27 (d, $J = 8.1$ Hz, 1H), 6.65−6.54 (m, 2H), 4.77−4.70 (m, 1H), 2.90 (d, $J = 11.7$ H, 1H), 2.85 (dd, $J = 2.9$, 11.7 Hz, 1H), 2.76−2.70 (m, 1H), 2.45−2.36 (m, 2H), 2.28 (s, 3H), 1.95−1.88 (m, 2H), 1.77 (dd, $J = 2.6$, 12.8 Hz, H), 1.69 (t, $J = 11.0$ Hz, 1H), 1.43 (d, $J = 6.6$ Hz, 3H), 1.50−1.42 (m, 1H), 1.27−1.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.48, 153.87, 147.98, 147.85, 138.22, 135.70, 134.86, 133.50, 131.52, 131.19, 130.82, 129.95, 129.48, 124.58, 124.54, 123.52, 123.48, 121.73, 76.72, 61.47, 56.02, 48.66, 46.19, 44.97, 41.76, 39.67, 38.53, 30.85, 28.86, 22.19; $[\alpha]^{20}_D = +3.3$ (*c* 3.0 mg/mL, MeOH); HRMS calcd for $C_{27}H_{30}F_3N_2O_2$ (MH^+), 471.2259; found, 471.2255; Anal. ($C_{27}H_{29}F_3N_2O_2$•2HCl•0.8H_2O) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-6-Acetyl-decahydro-1-methyl-9-[(e)-2-[5-[3-(trifluoromethyl)phenyl]-2-pyridinyl]ethenyl]furo[3,4-*g*]-

isoquinolin-3(1*H*)-one (30c). To a solution of **30a** (26 mg, 0.057 mmol) in 1 mL of dichloromethane was added acetic anhydride (27 μL, 0.286 mmol, 5 equiv), followed by triethyl amine (24 μL, 0.172 mmol, 3 equiv). The mixture was stirred overnight at rt, diluted with ethyl acetate, and washed with aq $NaHCO_3$, followed by brine. It was dried over $MgSO_4$, filtered, and concentrated to give 21 mg of **30c**. ^{1}H NMR (400 MHz, $CDCl_3$) 8.79 (s, 1H), 7.86 (dt, J = 2.2, 8.1 Hz, 1H), 7.81 (s, 1H), 7.76 (d, J = 7.3 Hz, 1H), 7.67−7.59 (m, 2H), 7.28 (d, J = 9.5 Hz, 1H), 6.67−6.54 (m, 2H), 4.79−4.64 (m, 2H), 3.86−3.74 (m, 1H), 3.07−2.27 (m, 2H), 2.48−2.37 (m, 2H), 2.23−1.96 (m, 5H), 1.89−1.73 (m, 2H), 1.46−1.02 (m, 6H); HRMS calcd for $C_{28}H_{30}F_3N_2O_3$ (MH$^+$), 499.2209; found, 499.2209; Anal. ($C_{28}H_{29}F_3N_2O_3$·HCl), H, N, C: calcd, 62.86; found, 63.64.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Decahydro-1-methyl-6-(2-methyl-1-oxopropyl)-9-[(e)-2-[5-[3-(trifluoromethyl)phenyl]-2-pyridinyl]-ethenyl]furo[3,4-*g*]isoquinolin-3(1*H*)-one (30d). ^{1}H NMR (400 MHz, $CDCl_3$) 8.79 (s, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.81 (s, 1H), 7.76 (d, J = 7.3 Hz, 1H), 7.69−7.59 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 6.67−6.55 (m, 2H), 4.78−4.67 (m, 2H), 3.99−3.90 (m, 1H), 3.04−3.71 (m, 3H), 2.41−2.17 (m, 3H), 2.04−1.95 (m, 1H), 1.86 (t, J = 15.4 Hz, 1H), 1.72 (br, 1H), 1.49−1.41 (m, 4H), 1.27−1.05 (m, 8H); HRMS calcd for $C_{30}H_{34}F_3N_2O_3$ (MH$^+$), 527.2522; found, 527.2517; Anal. ($C_{30}H_{33}F_3N_2O_3$·HCl·1.5H_2O) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-6-(Cyclopropylcarbonyl)-decahydro-1-methyl-9-[(e)-2-[5-[3-(trifluoromethyl)phenyl]-2-pyridinyl]-ethenyl]furo[3,4-*g*]isoquinolin-3(1*H*)-one (30e). ^{1}H NMR (400 MHz, $CDCl_3$) 8.80 (d, J = 2.2 Hz, 1H), 7.85 (dd, J = 2.9, 8.1 Hz, 1H), 7.81 (s, 1H), 7.77 (d, J = 7.3 Hz, 1H), 7.68−7.59 (m, 2H), 7.27 (d, J = 8.1 Hz, 1H), 6.68−6.55 (m, 2H), 4.79−4.63 (m, 2H), 4.28−4.17 (m, 1H), 3.11−2.74 (m, 2H), 2.53−2.26 (m, 2H), 2.00 (dd, J = 6.2, 11. 4 Hz, 1H), 1.93−1.73 (m, 2H), 1.46 (d, J = 5.9 Hz, 3H), 1.5−1.09 (m, 4H), 1.01−0.96 (m, 2H), 0.76 (br, 2H); HRMS calcd for $C_{30}H_{32}F_3N_2O_3$ (MH$^+$), 525.2365; found, 525.2372; Anal. ($C_{30}H_{31}F_3N_2O_3$·HCl) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-6-(Cyclopropylcarbonyl)-9-[(e)-2-[5-(3-fluorophenyl)-2-pyridinyl]ethenyl]-decahydro-1-methylfuro-[3,4-*g*]isoquinolin-3(1*H*)-one (30f). ^{1}H NMR (400 MHz, $CDCl_3$) 8.74 (s, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.40 (dd, J = 8.1, 13.9 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.25 (s, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.05 (t, J = 8.4 Hz, 1H), 6.62−6.51 (m, 2H), 4.78−4.58 (m, 2H), 4.24−4.13 (m, 1H), 3.07−2.67 (m, 3H), 2.51−2.19 (m, 3H), 1.94 (dd, J = 6.2, 11.4 Hz, 1H), 1.87−1.69 (m, 2H), 1.42 (d, J = 5.9 Hz, 3H), 1.46−1.07 (m, 4H), 0.98−0.82 (m, 2H), 0.72 (br, 2H); HRMS calcd for $C_{29}H_{32}FN_2O_3$ (MH$^+$), 475.2397; found, 475.2406; $[\alpha]^{25}_D$ = −77.4 (c 3.5 mg/mL, MeOH); Anal. ($C_{29}H_{31}FN_2O_3$·HCl·0.3H_2O), C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-6-(Cyclopropylcarbonyl)-9-[(e)-2-[5-(2-fluorophenyl)-2-pyridinyl]ethenyl]-decahydro-1-methylfuro-[3,4-*g*]isoquinolin-3(1*H*)-one (30g). ^{1}H NMR (400 MHz, $CDCl_3$) 8.72 (s, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.42 (t, J = 8.7 Hz, 1H), 7.38−7.33 (m, 1H), 7.26−7.14 (m, 3H), 6.64−6.53 (m, 2H), 4.77−4.40 (m, 2H), 4.26−4.15 (m, 1H), 3.08−2.69 (m, 2H), 2.53−2.21 (m, 3H), 1.97 (dd, J = 6.6, 11.0 Hz, 1H), 1.44 (d, J = 5.9 Hz, 3H), 1.47−1.09 (m, 4H), 1.06−0.84 (m, 2H), 0.73 (br, 2H); HRMS calcd for $C_{29}H_{32}FN_2O_3$ (MH$^+$), 475.2397; found, 475.2411; $[\alpha]^{25}_D$ = −145.7 (c 3.2 mg/mL, MeOH); Anal. ($C_{29}H_{31}FN_2O_3$·HCl) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Dodecahydro-1-methyl-3-oxo-9-[(e)-2-[5-(3-fluorophenyl)-2-pyridinyl]ethenyl]furo[3,4-*g*]isoquinoline-6-carboxamide (30h). ^{1}H NMR (400 MHz, $CDCl_3$) 8.77 (d, J = 2.2 Hz, 1H), 7.83 (dd, J = 2.9, 8.1 Hz, 1H), 7.45 (dt, J = 5.9, 8.1 Hz, 1H), 7.37−7.34 (m, 1H), 7.28−7.24 (m, 2H), 7.10 (dt, J = 2.9, 8.4 Hz, 1H), 6.64−6.53 (m, 2H), 4.79−4.72 (m, 1H), 4.55 (s, 2H), 3.98 (d, J = 13.2 Hz, 1H), 3.92 (d, J = 13.9 Hz, 1H), 2.81 (dt, J = 2.9, 13.2 Hz, 1H), 2.75−2.71 (m, 1H), 2.51−2.37 (m, 3H), 1.96 (dd, J = 5.9, 11.7 Hz, 1H), 1.81 (dd, J = 2.2, 13.2 Hz, 1H), 1.44 (d, J = 5.9 Hz, 1H), 1.37−1.31 (m, 2H), 1.26−1.07 (m, 2H); HRMS calcd for $C_{26}H_{29}FN_3O_3$ (MH$^+$), 450.2193; found, 450.2187; Anal. ($C_{26}H_{28}FN_3O_3$·HCl·1.8H_2O), C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-*N*-Ethyl-dodecahydro-1-methyl-3-oxo-9-[(e)-2-[5-(3-fluorophenyl)-2-pyridinyl]ethenyl]furo[3,4-*g*]-isoquinoline-6-carboxamide (30i). ^{1}H NMR (400 MHz, $CDCl_3$) 8.72 (d, J = 2.2 Hz, 1H), 7.78 (dd, J = 2.2, 8.1 Hz, 1H), 7.92−7.36 (m, 1H), 7.31 (d, J = 7.3 Hz, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.04 (dt, J = 2.2, 8.1 Hz, 1H), 6.59−6.49 (m, 2H), 4.84 (t, J = 5.1 Hz, 1H), 4.74−4.68 (m, 1H), 3.95 (d, J = 9.5 Hz, 2H), 3.23−3.13 (m, 2H), 2.71−2.65 (m, 2H), 2.40−2.32 (m, 3H), 1.89 (dd, J = 5.9, 12.5 Hz, 1H), 1.73 (d, J = 13.2 Hz, 1H), 1.38 (d, J = 5.9 Hz, 3H), 1.29−1.26 (m, 2H), 1.07 (t, J = 7.0 Hz, 3H), 1.19−1.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.21, 164.02, 161.57, 157.16, 153.37, 147.71, 139.37, 139.29, 134.93, 134.67, 133.58, 130.99, 130.45, 130.37, 122.25, 121.55, 114.76, 114.55, 113.56, 113.34, 76.60, 49.23, 48.25, 44.72, 44.43, 41.45, 40.28, 38.09, 35.67, 30.45, 28.09, 22.04, 15.55; HRMS calcd for $C_{28}H_{33}FN_3O_3$ (MH$^+$), 478.2506; found, 478.2515; $[\alpha]^{20}_D$ = −64.4 (c 3.4 mg/mL, MeOH); Anal. ($C_{28}H_{32}FN_3O_3$·HCl·1.5H_2O), C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-9-[(*E*)-2-[5-(3-Fluorophenyl)-2-pyridinyl]ethenyl]-decahydro-1-methyl-6-(methylsulfonyl)furo[3,4-*g*]isoquinolin-3(1*H*)-one (30j). ^{1}H NMR (400 MHz, $CDCl_3$) 8.77 (d, J = 2.2 Hz, 1H), 7.83 (dd, J = 2.2, 8.1 Hz, 1H), 7.14 (dt, J = 5.9, 8.1 Hz, 1H), 7.36−7.34 (m, 1H), 7.28−7.24 (m, 2H), 7.09 (dt, J = 3.3, 8.4 Hz, 1H), 6.65−6.55 (m, 2H), 4.76−4.70 (m, 1H), 3.84 (d, J = 11.7 Hz, 1H), 3.78 (dd, J = 4.4, 11.4 Hz, 1H), 2.78 (s, 3H), 2.79−2.73 (m, 1H), 2.65−2.59 (m, 1H), 2.49−2.32 (m, 3H), 1.97 (ddd, J = 2.9, 6.1, 13.5 Hz, 1H), 1.90 (d, J = 10.3 Hz, 1H), 1.53−1.47 (m, 1H), 1.44 (d, J = 5.9 Hz, 3H), 1.30−1.16 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 176.92, 164.19, 161.74, 153.23, 147.75, 139.46, 139.38, 134.89, 134.54, 133.89, 131.27, 130.59, 130.51, 122.38, 122.36, 121.99, 114.98, 114.76, 113.75, 113.53, 76.60, 50.95, 48.34, 46.44, 44.62, 41.39, 39.85, 38.25, 34.92, 30.43, 28.13, 22.11; HRMS calcd for $C_{26}H_{30}FN_2O_4S$ (MH$^+$), 485.1910; found, 485.1901; Anal. ($C_{26}H_{29}FN_2O_4S$·HCl·0.5H_2O) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-9-[(*E*)-2-[5-(3-Fluorophenyl)-2-pyridinyl]ethenyl]-decahydro-1-methyl-6-(propylsulfonyl)furo[3,4-*g*]isoquinolin-3(1*H*)-one (30k). ^{1}H NMR (400 MHz, $CDCl_3$) 8.77 (d, J = 2.2 Hz, 1H), 7.83 (dd, J = 2.2, 8.1 Hz, 1H), 7.44 (dt, J = 5.9, 7.7 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.28−7.24 (m, 2H), 7.10 (dt, J = 2.4, 8.4 Hz, 1H), 6.65−6.54 (m, 2H), 4.77−4.70 (m, 1H), 3.84 (d, J = 12.5, 1H), 3.78 (dd, J = 4.0, 12.1 Hz, 1H), 2.89−2.85 (m, 2H), 2.79−2.69 (m, 3H), 2.49−2.38 (m, 3H), 1.96 (ddd, J = 2.9, 6.6, 13.2 Hz, 1H), 1.89−1.80 (m, 3H), 1.45 (d, J = 5.9 Hz, 3H), 1.50−1.44 (m, 1H), 1.31−1.51 (m, 3H), 1.05 (t, J = 7.3 Hz, 3H); HRMS calcd for $C_{28}H_{34}FN_2O_4S$ (MH$^+$), 513.2223; found, 513.2227; Anal. ($C_{28}H_{33}FN_2O_4S$·HCl·0.5H_2O) C, H, N.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-Phenylmethyl Decahydro-1-methyl-3-oxo-9-[(e)-2-[5-[3-(trifluoromethyl)phenyl]-2-pyridinyl] ethenyl]furo[3,4-*g*]isoquinoline-6(3*H*)-carboxylate (30l). ^{1}H NMR (400 MHz, $CDCl_3$) 8.79 (d, J = 2.2 Hz, 1H), 7.85 (dd, J = 2.2, 8.1 Hz, 1H), 7.81 (s, 1H), 7.75 (d, J = 7.3 Hz, 1H), 7.67−7.59 (m, 2H), 7.35 (br, 5H), 7.27 (d, J = 9.5 Hz, 1H), 6.66−6.54 (m, 2H), 5.12 (s, 2H), 4.79−4.72 (m, 1H), 4.23 (br, 2H), 2.76−2.70 (m, 2H), 2.52−2.37 (m, 3H), 1.97 (br, 1H), 1.80 (d, J = 12.5, 1H), 1.46 (d, J = 5.9 Hz, 3H), 1.35−1.19 (m, 3H), 1.13−1.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.04, 154.73, 153.62, 147.75, 138.09, 136.42, 135.19, 134.81, 133.47, 131.38, 131.06, 130.99, 129.90, 129.42, 128.24, 127.77, 127.61, 124.47, 123.41, 123.37, 121.66, 76.53, 67.02, 49.11, 48.32, 44.80, 44.39, 41.45, 40.20, 38.24, 28.03, 22.08; HRMS calcd for $C_{34}H_{34}F_3N_2O_4$ (MH$^+$), 591.2471; found, 591.2464; Anal. ($C_{34}H_{33}F_3N_2O_4$·HCl) H, N, C: calcd, 65.12; found, 67.79.

(1*R*,3a*R*,4a*S*,8a*S*,9*S*,9a*S*)-2-Methoxyethyl 9-[(e)-2-[5-(3-Fluorophenyl)-2-pyridinyl]ethenyl]-decahydro-1-methyl-3-oxo-furo-[3,4-*g*]isoquinoline-6(3*H*)-carboxylate (30m). To a solution of **29** (0.270 g, 0.58 mmol) in CH_2Cl_2 (15 mL) was added TMSI (624 μL, 4.4 mmol, 7.5 equiv), and the mixture was heated to reflux. After 6 h, the mixture was poured onto aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and evaporated to dryness resulting in 209 mg of amine (92%). To this product in CH_2Cl_2 (15 mL) at 0 °C was added Et_3N (97 μL, 0.69

mmol, 1.3 equiv) and chloroformic acid 2-methoxyethyl ester (68 μL, 5.9 mmol, 1.1 equiv), and the mixture was allowed to slowly warm to rt while stirring under N_2. After 1 h, the mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. Purification by silica gel chromatography, eluting with 3% CH_3-$OH-CH_2Cl_2$, yielded 183 mg of the carbamate analog as a solid (69%). ^1H NMR (400 MHz, $CDCl_3$) 8.59 (d, J = 2.4 Hz, 1H), 7.76 (dd, J = 2.4, 8.2 Hz, 1H), 7.06 (d, J = 8.3 Hz, 1H) 6.56 (dd, J = 9.6, 15.4 Hz, 1H), 6.45 (d, J = 15.4 Hz, 1H), 4.72 (m, 1H), 4.1−4.28 (m, 4H), 3.59 (t, J = 4.49 Hz, 2H), 3.38 (s, 3H), 2,75−2.68 (m, 2H), 2.32−2.51 (m, 3H), 1.96 (dd, J = 6.3, 12.8 Hz, 1H), 1.73 (d, J = 12.5 Hz, 1H), 1.41 (d, J = 5.95 Hz, 3H), 1.37−1.00 (m, 4H).

To 65 mg of the above product dissolved in toluene (2 mL)/H_2O (1 mL)/EtOH (0.5 mL) was added 3-fluorobenzene boronic acid (28 mg, 1.5 equiv), K_2CO_3 (73 mg, 4 equiv), and tetrakis-(triphenylphosphine)palladium (8 mg, 5 mol %). After bubbling with nitrogen for 2−3 min, the mixture was heated to 100 °C in a sealed tube for 4 h. The mixture was poured onto aq 1 N NaOH and extracted with diethyl ether. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtered, and evaporated to dryness. Purification by flash chromatography yielded 62 mg of **30m**. ^1H NMR (400 MHz, $CDCl_3$) 8.77 (d, J = 2.2 Hz, 1H), 7.82 (dd, J = 2.2 Hz, 8.1 Hz, 1H), 7.42−7.47 (m, 2H), 7.24−7.29 (m, 3H), 6.53−6.64 (m, 2H), 4.72−4.79 (m, 1H), 4.16−4.26 (m, 5H), 3.59 (t, J = 4.4 Hz, 2H), 3.38 (s, 3H), 2.68−2.78 (m, 2H), 2.36−2.44 (m, 2H), 1.98 (dd, J = 5.9, 12.4 Hz, 1H), 1.80 (d, J = 12.4 Hz, 1H), 1.45 (d, J = 5.9 Hz, 3H), 1.10−1.38 (m, 4H); HRMS calcd for $C_{29}H_{34}FN_2O_5$ (MH^+), 509.2452; found, 509.2448; Anal. ($C_{29}H_{33}FN_2O_5$·HCl) C, H, N.

5-Bromo-2-pyridinemethanol (31). To a solution of 2,5-dibromopyridine (10 g, 84.4 mmol) in 1 L toluene at −78 °C was added 2.5 M solution of *n*-butyl lithium in hexanes (40.5 mL, 101.3 mmol, 1.2 equiv) drop by drop over a period of 15 min, stirred for 2 h, and then DMF (13.1 mL, 169.2 mmol) was added. The mixture was stirred for 1 h at −78 °C, 30 min at 0 °C then warmed to rt using a warm water bath. To the reaction mixture was added 100 mL of methanol, followed by $NaBH_4$ (3.2 g, 84.6 mmol, 1 equiv), and stirred for 30 min at rt. It was quenched by the addition of aq NH_4Cl and stirred vigorously for 10 min, and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, concentrated, and evaporated to dryness to give the crude product. Another batch of the same reaction was carried out, and the crude products from both of these batches were combined and recrystallized from ethyl acetate−hexanes to provide 11.9 g of solid. The filtrate was concentrated and recrystallized from ether−hexanes to provide another 4.29 g of solid (51% combined yield). ^1H NMR (400 MHz, $CDCl_3$) 8.64 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 2.0, 8.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 4.74 (s, 2H).

[(5-Bromo-2-pyridinyl)methyl]-phosphonic Acid, Diethyl Ester (32). To a solution of alcohol **31** (20 g, 106 mmol) and Et_3N (17.8 mL, 128 mmol, 1.2 equiv) in CH_2Cl_2 (300 mL) kept at ∼−30 °C was slowly added methanesulfonyl chloride (9.1 mL, 118 mmol, 1.1 equiv). The slurry was stirred for 1 h while it warmed up to 0 °C. The reaction mixture was diluted with aq $NaHCO_3$ (500 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 200 mL), and the combined organic layers were washed with aq $NaHCO_3$ (2 × 300 mL) and brine (300 mL). The solution was dried over $MgSO_4$, filtered, and evaporated to give the crude mesylate, which was used as such for the next step. ^1H NMR (400 MHz, $CDCl_3$) 8.67 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 8.4, 2.4 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 5.28 (s, 2H), 3.10 (s, 3H).

To a suspension of 60% NaH (8.5 g, 212 mmol 2.0 equiv) in THF (500 mL) at rt was added diethylphosphite (27.4 mL, 213 mmol, 2 equiv) drop by drop, and the mixture was stirred for 1 h. To this cloudy solution was added a solution of the above mesylate in THF (125 mL), and the mixture was stirred at rt for 1 h. The reaction was quenched by the addition of H_2O (500 mL), the THF was evaporated, and the aq layer was extracted with EtOAc (4 × 150 mL). The combined organic layers were washed with aq K_2-CO_3 (2 × 300 mL) and brine (300 mL), dried over $MgSO_4$, filtered, and evaporated, and the crude product was chromatographed with 5:95 $MeOH-CH_2Cl_2$ to give 31.7 g (97%) of oil. ^1H NMR (400 MHz, $CDCl_3$) 8.59 (d, J = 2.0 Hz, 1H), 7.76 (dd, J = 8.2, 2.1 Hz, 1H), 7.29 (dd, J = 8.2, 2.2 Hz, 1H), 4.12−4.05 (m, 4 H), 3.36 (d, J = 22.0 Hz, 2H), 1.27 (t, J = 7.0 Hz, 6H).

2-Oxopiperidine-1-carboxylic Acid Ethyl Ester (33). δ-Valerolactam (6.7 g, 0.0675 mol) was dissolved in THF (250 mL) and cooled to −78 °C. *n*-BuLi (28.44 mL, 1.1 equiv, 2.5 M solution in hexanes) was added dropwise. The mixture was stirred for 30 min, then ethyl chloroformate (6.49 mL, 1.05 equiv) was added, and the mixture allowed to warm to rt. Water was added, and the organic layer was extracted with EtOAc. The combined organic layers were dried and concentrated to give 11.57 g of **1A** (99%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (q, J = 7.2 Hz, 2H), 3.71 (br t, J = 5.6 Hz, 2H), 2.50 (br t, J = 6.8 Hz, 2H), 1.83 (br s, 4H), 1.33 (t, J = 7.2 Hz, 3H).

6-Trifluoromethanesulfonyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Ethyl Ester (34). Compound **33** (11.15 g, 65 mmol) was dissolved in THF (250 mL), and the solution was cooled to −78 °C. LHMDS (65 mL, 1 equiv, 1 M solution in THF) was added dropwise, and the resulting mixture stirred for 30 min. A solution of 2-[*N*,*N*-bis(trifluoromethylsulfonyl)-amino]-5-chloropyridine in THF (73 mL) was added dropwise. The resulting mixture was stirred for 10 min and allowed to warm to rt. Water was added, and the organic layer was extracted with EtOAc. The combined organic layers were dried and concentrated. Chromatography (5−10% EtOAc in hexane) gave 12.0 g of **34** (61%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.32 (t, J = 3.6 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.66 (m, 2H), 2.27 (m, 2H), 1.78 (m, 2H), 1.30 (J = 7.2 Hz, 3H).

(2*E*)-3-(Diethoxyboryl)-2-propenoic Acid Ethyl Ester (35). Borane dimethylsulfide complex (5.82 mL, 1.05 equiv) was dissolved in THF and cooled to 0 °C. (1*R*)-(+)-α-Pinene (22.56 mL, 2.32 equiv) was added dropwise, and the mixture was stirred at 0 °C for 1 h and at rt for 2 h. The mixture was cooled to −35 °C and ethyl propiolate (6.2 mL, 1 equiv) was added dropwise; the mixture was stirred at −35 °C for 45 min and rt for 3 h. Acetaldehyde (48 mL) was added, and the mixture was heated at 40−41 °C overnight. The volatile organic components were carefully removed under reduced pressure to give 29 g of a mixture of the product and α-pinene (1:2.3 by NMR). ^1H NMR (400 MHz, $CDCl_3$) δ characteristic peaks for the product include, 6.95 (d, J = 18.0 Hz, 1H), 6.48 (d, J = 18.0 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.60 (q, J = 7.2 Hz, 4H).

6-((*E*)-2-Ethoxycarbonylvinyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Ethyl Ester (36). $Pd(OAc)_2$ (592 mg, 10%) and 2-(di-*t*-butylphosphino)biphenyl (1.57 g, 20%) were dissolved in THF (100 mL). The mixture was stirred for 10 min under N_2, and then a mixture of compound **34** (8 g, 26 mmol) and compound **35** (20 g, 1.5 equiv) in THF (32 mL) was added. KF (4.6 g) was then added, and the mixture was heated at 55 °C overnight. The mixture was allowed to cool to rt and diluted with EtOAc. The mixture was washed with $NaHCO_3$ (satd), NH_4Cl (satd), water, and finally dried over $MgSO_4$. Removal of solvents under reduced pressure followed by column chromatography (10% EtOAc in hexane) gave 6 g (89%) of colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 15.6 Hz, 1H), 5.88 (d, J = 15.6 Hz, 1H), 5.69 (t, J = 4.0 Hz, 1H), 4.15 (m, 4H), 3.59 (m, 2H), 2.26 (m, 2H), 1.82 (m, 2H), 1.25 (m, 6H).

6-((*E*)-2-Carboxyvinyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Ethyl Ester (37). Compound **36** (6 g, 23.6 mmol) was dissolved in a 1:1 mixture of MeOH and THF (66 mL). A solution of 1 N NaOH (52 mL) was added, and the mixture was stirred for 2.5 h until no starting material remained. The mixture was acidified to pH 1 with 2 N HCl and extracted with EtOAc. The extracts were washed with NH_4Cl (satd), dried, and concentrated under reduced pressure to give 5 g of **37** (93.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 15.2 Hz, 1H), 5.87 (d, J = 15.2 Hz, 1H), 5.73 (m, 1 H), 4.14 (m, 2H), 3.60 (m, 2H), 2.70 (m, 2H), 1.82 (m, 2H), 1.23 (m, 3H).

6-[(*E*)-2-((*Z*)-3-Benzyloxycarbonyl-1(*R*)-methylallyloxycarbonyl)vinyl]-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid Ethyl Ester (38). Compound **37** (3.06 g, 13.6 mmol) and 4-pyrollidinopyridine (201.6 mg, 10%) were dissolved in CH_2Cl_2 (70 mL) and stirred at 0 °C. DCC (2.81 g, 1 equiv) was added, and after stirring for 10 min, a solution of alcohol **8** (3.36 g, 1.2 equiv) was added. The resulting mixture was stirred for 2 h. The mixture was filtered, concentrated under reduced pressure, and finally purified by silica gel chromatography (5:1 hexane/EtOAc) to give 3.7 g of **38** (66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.2 Hz, 3H), 1.40 (d, J = 6.6 Hz, 3H), 1.78−1.88 (m, 2H), 2.23−2.3 (m, 2H), 3.58−3.61 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 5.19 (br s, 3H), 5.7 (t, J = 4 Hz, 1H), 5.82−5.9 (m, 2H), 6.2 (dd, J = 11.7, 7.3 Hz, 1H), 6.29−6.38 (m, 1H), 7.32−7.4 (m, 5H).

(4a*S*,5*S*,5a*S*,6*R*,8a*R*)-6-Methyl-8-oxo-3,4,4a,5,5a,6,8,8a-octahydro-2*H*-furo[3,4-*g*]quinoline-1,5-dicarboxylic Acid 5-Benzyl Ester 1-Ethyl Ester (39). Compound **38** (3.7 g, 8.96 mmol) was dissolved in *m*-xylene (400 mL), the mixture was degassed and heated in a sealed tube at 150 °C for 45 min. The solvent was removed under reduced pressure. The residue was filtered through a silica gel pad (eluting with hexane/EtOAc 4:1). After concentration under reduced pressure, the residue (1.7 g) was taken up in THF (30 mL), and DBU (0.615 mL, 4.11 mmol) was added, After stirring for 1 h, $NH_4Cl_{(satd)}$ was added, and the mixture was extracted with EtOAc. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give 1.7 g of **39** (46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 5.86 Hz, 3H), 1.18 (t, J = 7.3 Hz, 3H), 1.57−1.73 (m, 3H), 2.02−2.07 (m, 1H), 2.55 (m, 1H), 2.63−2.82 (m, 3H), 3.39−3.43 (m, 1H), 4.04 (q, J = 7.3 Hz, 2H), 4.31 (br d, J = 12.5 Hz, 1H), 4.55−4.62 (m, 1H), 5.17 (m, 2H), 5.48 (s, 1H), 7.34−7.39 (m, 5H).

(4a*S*,5*S*,5a*S*,6*R*,8a*R*,9a*S*)-6-Methyl-8-oxodecahydrofuro[3,4-*g*]quinoline-1,5-dicarboxylic Acid 1-Ethyl Ester (40). Compound **39** (1.7 g, 4.11 mmol) was dissolved in EtOAc, palladium on carbon (10 wt %, 170 mg) was added, and the mixture was stirred under 1 atm of H_2 for 2 h. The mixture was filtered through celite, and the solvent was removed under reduced pressure. The resulting residue (1.4 g) was taken up in MeOH (25 mL), and PtO_2 (140 mg) was added. The mixture was shaken using a parr apparatus under 50 psi of H_2 for 48 h. The catalyst was removed by filtration, and the solvent was removed under reduced pressure to give 1.36 g of **40** (98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (m, 1H), 1.26 (t, J = 7.3 Hz, 3H), 1.35 (d, J = 5.86 Hz, 3H), 1.57−1.74 (m, 3H), 1.81−1.92 (m, 2H), 1.95−2.04 (m, 1H), 2.41−2.46 (m, 1H), 2.53−2.63 (m, 2H), 2.84 (quintet, J = 6.6 Hz, 1H), 3.14−3.28 (m, 2H), 3.77−3.83 (m, 1H), 4.14 (q, J = 7.3 Hz, 2H), 4.70−4.77 (m, 1H).

(4a*S*,5*S*,5a*S*,6*R*,8a*R*,9a*S*)-5-Formyl-6-methyl-8-oxodecahydrofuro[3,4-*g*]quinoline-1-carboxylic Acid Ethyl Ester (41). Compound **40** (1 g, 3.076 mmol) was suspended in CH_2Cl_2 (17 mL), and $(COCl)_2$ (0404 mL, 1.5 equiv) was added, followed by a drop of DMF. The mixture was stirred for 1 h and then concentrated under reduced pressure. The resulting residue was dissolved in PhMe (15 mL) and cooled to 0 °C. $Pd(Ph_3P)_4$ (355.5 mg, 10 mol %) was added followed by dropwise addition of Bu_3SnH (1.24 mL, 1.5 equiv). The mixture was stirred at 0 °C for 30 min followed by 1 h at room temperature. The reaction mixture was purified by silica gel chromatography (hexane/EtOAc 10:1−2:1) to give 570 mg of **41** (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.3 Hz, 3H), 1.35 (d, J = 5.86 Hz, 3H), 1.62−1.73 (m, 3H), 1.80−1.93 (m, 2H), 2.10 (m, 1H), 2.42−2.48 (m, 1H), 2.60−2.68 (m, 2H), 2.85 (quintet, J = 6.6 Hz, 1H), 3.13−3.27 (m, 2H), 3.73−3.78 (m, 1H), 4.14 (q, J = 7.3 Hz, 2H), 4.61−4.67 (m, 1H), 9.76 (d, J = 2.2 Hz, 1H).

(4a*S*,5*S*,5a*S*,6*R*,8a*R*,9a*S*)-5-[(*E*)-2-(5-Bromopyridin-2-yl)vinyl]-6-methyl-8-oxodecahydrofuro[3,4-*g*]quinoline-1-carboxylic Acid Ethyl Ester (42). Compound **32** (896 mg, 2.91 mmol, 2 equiv) was dissolved in THF (4 mL) and cooled to 0 °C. LiHMDS (2.91 mL of a 1.0 M solution in THF, 2.91 mmol, 2 equiv) was added. After stirring for 30 min, the mixture was allowed to warm to rt, and $Ti(OiPr)_4$ (0.859 g, 2.91 mmol, 2 equiv) was added. After 5 min, a solution of compound **41** (450 mg, 1.455 mmol, 1 equiv) in THF (4 mL) was added, and after stirring for 1.5 h, a saturated solution of potassium sodium tartrate was added, the THF was removed under reduced pressure, and the mixture was extracted with EtOAc. The organic layers were dried ($MgSO_4$), concentrated, and purified by silica gel chromatography (hexane/EtOAc 2:1) to give 500 mg of compound **42** (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.3 Hz, 3H), 1.39 (d, J = 5.86 Hz, 3H), 1.55−1.65 (m, 2H), 1.67−1.88 (m, 3H), 2.29−2.35 (m, 1H), 2.41−2.50 (m, 2H), 2.83 (quintet, J = 6.6 Hz, 1H), 3.07−3.14 (m, 1H), 3.25−3.32 (m, 1H), 3.76−3.82 (m, 1H), 4.07−4.13 (m, 2H), 4.71−4.78 (m, 1H), 6.43 (d, J = 15.4 Hz, 1H), 6.55 (dd, J = 15.4, 10.2 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 7.75 (dd, J = 8.8, 2.2 Hz, 1H), 8.58 (d, J = 2.2 HZ, 1H).

Ethyl (4a*S*,5*S*,5a*S*,6*R*,8a*R*,9a*S*)-5-[(*E*)-2-[5-(3-Fluorophenyl)-2-pyridinyl]ethenyl]-decahydro-6-methyl-8-oxofuro[3,4-*g*]quinoline-1(2*H*)-carboxylate (43a). Compound **42** (90 mg, 0.194 mmol) was dissolved in PhMe/EtOH/H_2O (0.3 mL, 0.03 mL, 0.1 mL), K_2CO_3 (80.4 mg, 3 equiv), $Pd(Ph_3P)_4$ (22 mg, 10 mol %), and 3-fluorobenzeneboronic acid (33 mg, 1.2 equiv) were added. The mixture was heated at 100 °C for 3 h. The mixture was extracted with Et_2O, and the extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by silica gel chromatography (hexane/EtOAc 2:1) gave 60 mg of **43a** (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00−1.09 (m, 1H), 1.27 (t, J = 7.3 Hz, 3H), 1.44 (d, J = 5.86 Hz, 3H), 1.56−1.89 (m, 5H), 2.33−2.39 (m, 1H), 2.43−2.54 (m, 2H), 2.86 (quintet, J = 6.6 Hz, 1H), 3.08−3.16 (m, 1H), 3.32 (td, J = 11, 2.9 Hz, 1H), 3.78−3.84 (m, 1H), 4.15 (q, J = 7.3 Hz, 2H), 4.75−4.82 (m, 1H), 6.52−6.63 (m, 2H), 7.09 (td, J = 8.0, 2.2 Hz, 1H), 7.25−7.29 (m, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.41−7.47 (m, 1H), 7.82 (dd, J = 8.0, 2.2 Hz, 1H), 8.77 (d, J = 2.2 Hz, 1H), MS (CI) *m*/*z* 479 (MH^+, 100%); HRMS calcd for $C_{28}H_{31}FN_2O_4$ (MH^+), 479.2346; found, 479.2350; Anal. ($C_{28}H_{31}FN_2O_4$·HCl·1.5H_2O) C, H, N.

Ethyl (4a*S*,5*S*,5a*S*,6*R*,8a*R*,9a*S*)-5-[(*E*)-2-[5-(2-Fluorophenyl)-2-pyridinyl]ethenyl]-decahydro-6-methyl-8-oxofuro[3,4-*g*]quinoline-1(2*H*)-carboxylate (43b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00−1.09 (m, 1H), 1.26 (t, J = 7.3 Hz, 3H), 1.45 (d, J = 5.86 Hz, 3H), 1.57−1.87 (m, 5H), 2.34−2.39 (m, 1H), 2.43−2.54 (m, 2H), 2.86 (quintet, J = 6.6 Hz, 1H), 3.08−3.16 (m, 1H), 3.31 (td, J = 11.7, 2.2 Hz, 1H), 3.78−3.84 (m, 1H), 4.14 (q, J = 7.3 Hz, 2H), 4.75−4.82 (m, 1H), 6.53−6.63 (m, 2H), 7.16−7.23 (m, 1H), 7.25−7.27 (m, 2H), 7.35−7.46 (m, 2H), 7.84 (d, J = 8.05 Hz, 1H), 8.74 (s, 1H); MS (CI) *m*/*z* 479 (MH^+, 100%); HRMS calcd for $C_{28}H_{31}FN_2O_4$ (MH^+), 479.2346; found, 479.2350; Anal. ($C_{28}H_{31}$-FN_2O_4·HCl·1.5H_2O) C, H, N.

Ethyl (4a*S*,5*S*,5a*S*,6*R*,8a*R*,9a*S*)-5-[(*E*)-2-[5-(2-Methylphenyl)-2-pyridinyl]ethenyl]-decahydro-6-methyl-8-oxofuro[3,4-*g*]quinoline-1(2*H*)-carboxylate (43c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00−1.08 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.46 (d, J = 6.04 Hz, 3H), 1.56−1.91 (m, 5H), 2.30 (s, 3H), 2.33−2.56 (m, 3H), 2.86 (quintet, J = 6.04 Hz, 1H), 3.07−3.17 (m, 1H), 3.32 (td, J = 11.5, 2.2 Hz, 1H), 3.77−3.85 (m, 1H), 4.15 (q, J = 7.2 Hz, 2H), 4.75−4.84 (m, 1H), 6.56−6.58 (m, 2H), 7.18−7.32 (m, 5H), 7.61 (dd, J = 8.2, 2.2 Hz, 1H), 8.54 (d, J = 2.2 Hz, 1H); MS (CI) *m*/*z* 475 (MH^+, 100%); HRMS calcd for $C_{29}H_{34}N_2O_4$ (MH^+), 475.2597; found, 475.2591; Anal. ($C_{29}H_{34}N_2O_4$·HCl·1.5H_2O) C, H, N.

Ethyl (4a*S*,5*S*,5a*S*,6*R*,8a*R*,9a*S*)-5-[(*E*)-2-[5-(3-Cyanophenyl)-2-pyridinyl]ethenyl]-decahydro-6-methyl-8-oxofuro[3,4-*g*]quinoline-1(2*H*)-carboxylate (43d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98−1.09 (m, 1H), 1.25 (t, J = 7.3 Hz, 3H), 1.43 (d, J = 5.8 Hz, 3H), 1.58−1.89 (m, 5H), 2.33−2.39 (m, 1H), 2.43−2.55 (m, 2H), 2.86 (quintet, J = 6.6 Hz, 1H), 3.09−3.17 (m, 1H), 3.31 (td, J = 11.7, 2.2 Hz, 1H), 3.77−3.83 (m, 1H), 4.08−4.17 (m, 2H), 4.75−4.82 (m, 1H), 6.54−6.66 (m, 2H), 7.28 (d, J = 8.05 Hz, 1H), 7.43−7.47 (m, 1H), 7.52−7.69 (m, 2H), 7.79−7.84 (s, 2H), 8.75 (s, 1H);

MS (CI) *m*/*z* 486 (MH^+, 100%); HRMS calcd for $C_{29}H_{31}N_3O_4$ (MH^+), 486.2393; found, 486.2399; Anal. ($C_{29}H_{31}N_3O_4$•HCl) C, H, N.

Ethyl (4a*S*,5*S*,5a*S*,6*R*,8a*R*,9a*S*)-5-[(*E*)-2-[3,3′-Bipyridin]-6-ylethenyl]decahydro-6-methyl-8-oxo-furo[3,4-*g*]quinoline-1(2*H*)-carboxylate (43e). ^1H NMR (400 MHz, $CDCl_3$) δ 1.00−1.07 (m, 1H), 1.27 (t, $J = 7.3$ Hz, 3H), 1.44 (d, $J = 6.6$ Hz, 3H), 1.56−1.89 (m, 5H), 2.33−2.40 (m, 1H), 2.43−2.55 (m, 2H), 2.86 (quintet, $J = 5.9$ Hz, 1H), 3.08−3.16 (m, 1H), 3.31 (td, $J = 10.9$, 2.9 Hz, 1H), 3.78−3.83 (m, 1H), 4.14 (q, $J = 7.3$ Hz, 2H), 4.75−4.82 (m, 1H), 6.53−6.65 (m, 2H), 7.29 (d, $J = 8.05$ Hz, 1H), 7.39−7.42 (m, 1H), 7.83−7.89 (m, 2H), 8.64 (d, $J = 4.4$ Hz, 1H), 8.78 (s, 1H), 8.84 (s, 1H); MS (CI) *m*/*z* 462 (MH^+, 100%); HRMS calcd for $C_{27}H_{31}N_3O_4$ (MH^+), 462.2393; found, 462.2387.

Acknowledgment. The authors like to thank Drs. Catherine Strader, John Piwinski, Ashit Ganguly, Paul Mcnamara, Michael Graziano, Richard Morrison, and Ronald White for helpful discussions, Drs. Birendra Pramanik and Pradip Das for mass spectral data, and Wenqing Feng and Dr. Mohindar Puar for NMR data.

Supporting Information Available: Results of elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Davie, E. W.; Fujikawa, K.; Kisiel, W. The coagulation cascade: Initiation, maintenance, and regulation. *Biochemistry* **1991**, *30*, 10363−10370.
(2) Reiter, R. A.; Jilma, B. Platelets and new antiplatelet drugs. *Therapy* **2005**, *2* (3), 465−502.
(3) Volturo, G. A.; Mazzola, J. L.; Przyklenk, K. The role of antiplatelet therapy in the management of acute coronary syndromes. *Expert Opin. Drug Saf.* **2005**, *4* (3), 541−556.
(4) Jackson, S. P.; Schoenwaelder, S. M. Antiplatelet therapy: In search of the “magic bullet”. *Nat. Rev. Drug Discovery* **2003**, *2* (10), 775−789.
(5) Bhatt, D. L.; Topol, E. J. Scientific and therapeutic advances in antiplatelet therapy. *Nat. Rev. Drug Discovery* **2003**, *2*, 15−28.
(6) Newby, L. K.; Califf, R. M.; White, H. D.; Harrington, R. A.; Van de Werf, F.; Granger, C. B.; Simes, R. J.; Hasselblad, V.; Armstrong, P. W. The failure of orally administered glycoprotein IIb/IIIa inhibitors to prevent recurrent cardiac events. *Am. J. Med*. **2002**, *112* (8), 647−658.
(7) Coughlin, S. R. Protease-activated receptors. In *Handbook of Cell Signaling*; Bradshaw, R. A., Dennis, E. A., Eds.; Elsevier: San Diego, CA, 2004; Vol. 1, pp 167−171.
(8) Coughlin, S. R. Protease-activated receptors in the cardiovascular system. *Cold Spring Harbor Symp. Quant. Biol.* **2002**, *67*, 197−208.
(9) Coughlin, S. R. Protease-activated receptors in vascular biology. *Thromb. Haemostasis* **2001**, *86*, 298−307.
(10) Chackalamannil, S. Thrombin receptor (protease activated receptor-1) antagonists as potent antithrombotic agents with strong antiplatelet effects. *J. Med. Chem.* **2006**, *49*, 5389−5403.
(11) Grand, R. J. A.; Turnell, A. S.; Grabham, P. W. Cellular consequences of thrombin-receptor activation. *Biochem. J.* **1996**, *313*, 353−368.
(12) Coughlin, S. R. Protease-activated receptors in hemostasis, thrombosis, and vascular biology. *J. Thromb. Haemostasis.* **2005**, *3*, 1800−1814.
(13) Coughlin, S. R. How the protease thrombin talks to cells. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 11023−11027.
(14) Vu, T.-K. H.; Hung, D. T.; Wheaton, V. I.; Coughlin, S. R. Molecular cloning of a functional thrombin receptor reveals a novel proteolytic mechanism of receptor activation. *Cell* **1991**, *64*, 1057−1068.
(15) Hung, D. T.; Vu, T.-H.; Nelken, N. A.; Coughlin, S. R. Thrombin-induced events in non-platelet cells are mediated by the unique proteolytic mechanism established for the cloned platelet thrombin receptor. *J. Cell Biol.* **1992**, *116*, 827−832.
(16) Vu, T.-K. H.; Wheaton, V. I.; Hung, D. T.; Charo, I.; Coughlin, S. R. Domains specifying thrombin-receptor interaction. *Nature* **1991**, *353*, 674−677.
(17) Chackalamannil, S.; Xia, Y.; Greenlee, W. J.; Clasby, M.; Doller, D.; Tsai, H.; Asberom, T.; Czarniecki, M.; Ahn, H.-S.; Boykow, G.; Foster, C.; Agans-Fantuzzi, J.; Bryant, M.; Lau, J.; Chintala, M. Discovery of potent orally active thrombin receptor (protease activated receptor 1) antagonists as novel antithrombotic agents. *J. Med. Chem.* **2005**, *48*, 5884−5887.
(18) Clasby, M. C.; Chackalamannil, S.; Czarniecki, M.; Doller, D.; Eagen, K.; Greenlee, W.; Kao, G.; Lin, Y.; Tsai, H.; Xia, Y.; Ahn, H.-S.; Agans-Fantuzzi, J.; Boykow, G.; Chintala, M.; Foster, C.; Smith-Torhan, A.; Alton, K.; Bryant, M.; Hsieh, Y.; Lau, J.; Palamanda, J. Metabolism-based identification of a potent thrombin receptor antagonist. *J. Med. Chem.* **2007**, *50*, 129−138.
(19) Andrade-Gordon, P.; Maryanoff, B. E.; Derian, C. K.; Zhang, H.-C.; Addo, M. F.; Darrow, A. L.; Eckardt, A. J.; Hoekstra, W. J.; McComsey, D. F.; Oksenberg, D.; Reynolds, E. E.; Santulli, R. J.; Scarborough, R. M.; Smith, C. E.; White, K. B. Design, synthesis, and biological characterization of a peptide-mimetic antagonist for a tethered-ligand receptor. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96* (22), 12257−12262.
(20) Zhang, H.-C.; Derian, C. K.; Andrade-Gordon, P.; Hoekstra, W. J.; McComsey, D. F.; White, K. B.; Poulter, B. L.; Addo, M. F.; Cheung, W.-M.; Damiano, B. P.; Oksenberg, D.; Reynolds, E. E.; Pandey, A.; Scarborough, R. M.; Maryanoff, B. E. Discovery and optimization of a novel series of thrombin receptor (PAR-1) antagonists: Potent, selective peptide mimetics based on indole and indazole templates. *J. Med. Chem*. **2001**, *44* (7), 1021−1024.
(21) Zhang, H.-C.; White, K. B.; McComsey, D. F.; Addo, M. F.; Andrade-Gordon, P.; Derian, C. K.; Oksenberg, D.; Maryanoff, B. E. High-affinity thrombin receptor (PAR-1) ligands: A new generation of indole−Based peptide mimetic antagonists with a basic amine at the C-terminus. *Bioorg. Med. Chem. Lett.* **2003**, *13* (13), 2199−2203.
(22) Ahn, H.-S.; Arik, L.; Boykow, G.; Burnett, D. A.; Caplen, M. A.; Czarniecki, M.; Domalski, M. S.; Foster, C.; Manna, M.; Stamford, A. W.; Wu, Y. Structure−activity relationships of pyrroloquinazolines as thrombin receptor antagonists. *Bioorg. Med. Chem. Lett.* **1999**, *9* (14), 2073−2078.
(23) Ahn, H.-S.; Foster, C.; Boykow, G.; Stamford, A.; Manna, M.; Graziano, M. Inhibition of cellular action of thrombin by *N*3-cyclopropyl-7-{[4-(1-methylethyl)phenyl]methyl}-7*H*-pyrrolo[3,2-*f*]-quinazoline-1,3-diamine (SCH 79797), a nonpeptide thrombin receptor antagonist. *Biochem. Pharmacol.* **2000**, *60* (10), 1425−1434.
(24) Chackalamannil, S.; Doller, D.; Eagen, K.; Czarniecki, M.; Ahn, H. S.; Foster, C. J.; Boykow, G. Potent, low molecular weight thrombin receptor antagonists. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2851−2853.
(25) After intravenous administration of a radiolabeled sample of **2** in cynomolgus monkey, recovery of the radioactivity required more than ten days.
(26) McGinnis, N. A.; Robinson, R. Synthesis of substances related to the sterols. XXXIV. Some thiopyranophenanthrene derivatives. *J. Chem. Soc.* **1941**, 404−408.
(27) (*R*)-3-Butyn-2-ol (ee > 97%) was purchased from DSM Fine Chemicals, 217 Rt. 46W., Saddle Brook, NJ.
(28) Chackalamannil, S.; Davies, R. J.; Asberom, T.; Doller, D.; Leone, D. A Highly efficient total synthesis of (+)-himbacine. *J. Am. Chem. Soc.* **1996**, *118*, 9812−9813.
(29) Four, P.; Guibe, F. Palladium-catalyzed reaction of tributyltin hydride with acyl chlorides. A mild, selective, and general route to aldehydes. *J. Org. Chem*. **1981**, *46*, 4439−4445.
(30) Wang, X.; Rabbat, P.; O’Shea, P.; Tillyer, R.; Grabowski, E. J. J.; Reider P. J. Selective monolithiation of 2,5-dibromopyridine with butyllithium. *Tetrahedron Lett.* **2000**, *41* (22), 4335−4338.
(31) For the use of KF as a base in Suzuki couplings, see: Fu, G. C.; Dai, C.; Littke, A. F. Versatile catalysts for the Suzuki cross-coupling of arylboronic acids with aryl and vinyl halides and triflates under mild conditions. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028 and references cited therein.
(32) Ahn, H.-S.; Foster, C.; Boykow, G.; Arik, L.; Smith-Torhan, A.; Hesk, D.; Chatterjee, M. Binding of a thrombin receptor tethered ligand analog to human platelet thrombin receptor. *Mol. Pharm.* **1997**, *51*, 350−356.
(33) Following 3 mg/kg oral dose (0.4% methylcellulose) of **27c** in c. monkey, $AUC_{0-24\ hr}$ for parent = 7394 ng•hr/ml; $AUC_{0-24\ hr}$ for (M + 16) metabolites = 2384 ng•hr/ml.
(34) Analytical data not shown for **44** and **45**.
(35) Tritium-labeled **28b** was prepared by heating **28b** with freshly prepared platinum and tritiated water (530 mCi, 0.9 Ci/mmol) at 110 °C for 48 hours. A total batch of 4.9 mCi was isolated after HPLC purification.
(36) Eckhardt, H.; Halbritter, K.; Goetz, N.; Heilen, G.; Preparation of 3-formyl-5,6-dihydro-2*H*-pyran. U.S. Patent 4532337, 1985.
(37) Kratzel, M.; Weigl, A. 5-(Alk-1-enyl)-1,2,3,6-tetrahydropyridines as congeners of streptazolin. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1009−1012.

JM070704K