Potent and Selective Non-Peptidic Inhibitors of Endothelin-Converting Enzyme-1 with Sustained Duration of Action

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Potent and selective non-peptidic inhibitors of human endothelin-converting enzyme-1 (ECE-1) have been designed as potential modulators of endothelin (ET-1) production in vivo. Because of its unique structural characteristics and long duration of action in vivo, the dual ECE-1 and neutral endopeptidase 24.11 (NEP) inhibitor, CGS 26303, was selected as an attractive lead for further optimization of potency and selectivity. Replacement of the P_1' biphenyl substituent of CGS 26303 by a conformationally restricted 3-dibenzofuranyl group led to more potent and more selective ECE-1 inhibitors, such as the tetrazole **27**. The remarkable effect of this P_1' modification allowed for the first time phosphonomethylcarboxylic acids, such as **29**, to display *both* potent ($IC_{50} = 22$ nM) and selective (104-fold vs NEP) ECE-1 inhibition. Chemoenzymatic syntheses of the new α-amino acid *(S)*-3-dibenzofuran-3-ylalanine intermediate were developed, and improved procedures to generate substituted α-aminoalkylphosphonic acids were devised to support the production of various analogues. Although additional gains in intrinsic ECE-1 inhibitory potency could occasionally be achieved by addition of a P_1 side chain, these compounds (e.g. **43a**) showed poor functional activity in vivo in the big ET-1 pressor test. Phosphonoalkyl dipeptides featuring 3-dibenzofuranyl groups in both the P_1' and P_2' positions were also very potent ECE-1 inhibitors, albeit lacking the desired selectivity against NEP. Functionally, **27** and **29** were the two most efficacious compounds from this study, producing sustained inhibition of ECE-1 activity in rats, as measured by their ability to block the hypertensive effects induced by big ET-1. This profile was similar to that of a potent ET_A/ET_B dual receptor antagonist, SB 209670. Due to their favorable in vitro and in vivo profiles, **27** (CGS 34043) and **29** (CGS 35066) constitute new pharmacological tools useful in assessing the role of ECE-1 in pathological conditions.

Introduction

Since its initial characterization as an exceedingly potent vasoconstrictive peptide, endothelin-1 (ET-1) has been the target of an intense research effort aimed at elucidating its potential significance in health and diseases.[1] From these studies, ET-1 has emerged as an important regulatory element during fetal development, while its overproduction, resulting in abnormally high plasma or tissue levels, has been implicated in a heterogeneous list of diseases encompassing systemic and pulmonary hypertension, cerebral vasospasm and stroke, asthma, cardiac and renal failure, atherosclerosis, preeclampsia, benign prostatic hyperplasia, and carcinogenesis.[2−5] Among several conceptual therapeutic approaches to block the biological effects of ET-1, the antagonism of its G-protein-coupled receptors, ET_A and/or ET_B, is currently the most advanced. Indeed, several potent peptidic and non-peptidic ET-1 receptor antagonists, such as SB 209670, have been described,[6] and several members of this class of compounds are presently undergoing clinical trials.[7]

By contrast, the discovery of potent and selective inhibitors of ET-1 biosynthesis has apparently represented a more challenging task.[8] Endothelin-converting enzyme-1 (ECE-1) is a zinc metalloprotease catalyzing the posttranslational conversion of big ET-1 to ET-1 in a rate-limiting fashion[9] and, therefore, constitutes a prime therapeutic target for the regulation of ET-1 production in vivo.[10] It is ubiquitously distributed in the human vascular endothelium, where both big ET-1 and mature ET-1 have been observed.[11] In addition, ECE-1 activity has been detected in brain tissues. Until now, three isoforms, ECE-1a, ECE-1b, and ECE-1c, differing only in their N-terminal regions as a result of alternative splicing of a single gene, have been identified in human tissues.[11−13] Recent supporting evidence for the significance of ECE-1 in ET-1 biosynthesis includes the observation that disruption of the ECE-1 gene in mice results in term embryos exhibiting phenotypes similar to those lacking the ET-1 or ET_A receptor genes.[14] Although ECE-1 emerges as a critical player in the biosynthesis of ET-1, it still remains possible that other enzymes could partially contribute to the proteolytic cleavage of big ET-1 under physiological or pathological conditions, or even under chronic ECE-1 inhibition in vivo. Selective inhibitors of ECE-1 with good in vivo efficacy would represent novel pharmacological tools to address this question. Until recently, the most potent ECE-1 inhibitors reported have also demonstrated inhibitory activity against other zinc metalloproteases,

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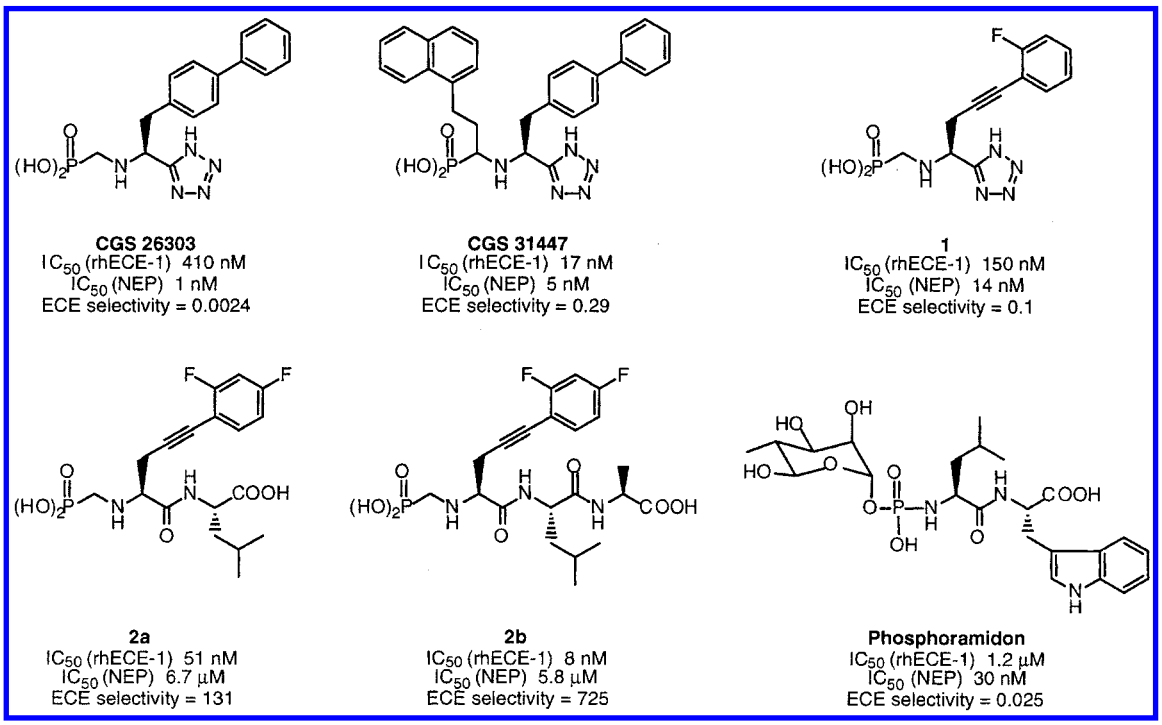
Chart 1

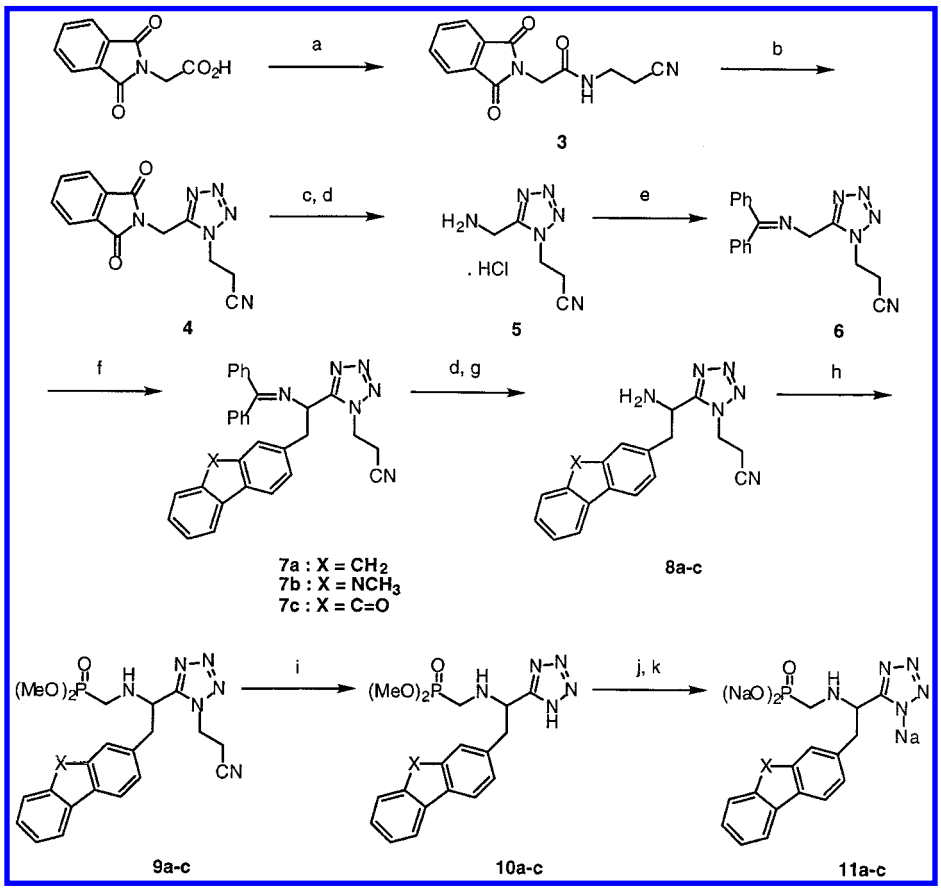


in particular neutral endopeptidase 24.11 (NEP), an enzyme involved in the degradation of several vasoactive peptides including atrial natriuretic peptide (ANP).[8] From an efficacy point of view, we and others[15,16] have favored the rationale that dual ECE/NEP inhibitors could exhibit a superior therapeutic profile in the treatment of various cardiovascular and renal disorders, by depressing the effects of ET-1 while concomitantly potentiating those of ANP. In parallel, we have also searched for agents able to selectively inhibit ECE-1 because inhibition of NEP may not always be necessary or even desirable under some pathological conditions such as asthma.[17] Several attempts to obtain selective ECE-1 inhibitors by systematic structural modification of the dipeptidic metalloprotease inhibitor phosphoramidon[18,19] or by screening compound and natural product libraries have been reported.[8,20−22] Although moderate success has been reported occasionally, the identification of potent and selective ECE-1 inhibitors that possess sustained functional activity in vivo still remains a challenge. Consequently, the in vivo characterization of ECE inhibitors remains scarce.[23,24]

Discovered several years ago, CGS 26303 (Chart 1) is a structurally unique non-peptidic dual ECE/NEP inhibitor characterized by a long duration of action in vivo.[25] As such, this compound produced therapeutic benefits in preclinical models of hypertension[25] and cerebral vasospasm following subarachnoid hemorrhage,[26−28] a condition linked to a local overproduction of ET-1. Although CGS 26303 represented an attractive lead toward the rational design of more potent and, possibly, more selective ECE inhibitors, preliminary structure−activity relationship investigations indicated that even minor structural alterations of the core template generally resulted in a dramatic loss of ECE inhibitory activity. One successful approach, however, consisted in adding a lipophilic P_1 side chain, as in CGS 31447, thereby increasing the in vitro potency significantly.[29] However, this compound, and other related analogues, retained potent NEP inhibitory activity.[30] More recently, our search for surrogates of the biphenyl group has led to the discovery of 2-fluorophenylacetylene derivatives (e.g. **1**) which showed enhanced inhibitory potency *and* selectivity (defined as the ratio of IC_{50} NEP to IC_{50} ECE) relative to CGS 26303, without the need for a P_1 substituent.[31] Di- and tripeptide derivatives (e.g. **2a** and **2b**) displayed an even superior profile in vitro, although they departed from our major focus of designing truly non-peptidic inhibitors. When administered intravenously to anesthetized rats, **2a** and **2b** inhibited by 51% and 64%, respectively, the pressor response induced by big ET-1 for at least 15 min.[31] Unfortunately, possibly because of their peptidic nature, these highly selective ECE inhibitors failed to maintain their inhibitory effects when big ET-1 was administered 90 min post-dosing. At this time point, the levels of pressor response inhibition by **2a** and **2b** had been reduced to 12% and 13%, respectively (results not shown). In addition, we noted that, despite their higher ECE-1 inhibitory potency and selectivity in vitro, these two compounds were less effective in vivo than the intrinsically weaker ECE inhibitor, phosphoramidon.

Remarkably, despite weak potency and poor ECE selectivity, the non-peptidic inhibitors CGS 26303 and its 2-fluoroacetylene tetrazole analogue **1** were characterized by a strong and sustained functional inhibition in vivo (50% and 83% inhibition of the pressor response at 90 min, respectively). Since **1** was a more potent and more selective ECE inhibitor than CGS 26303, we aimed for further structural optimization of the P_1' substituent. Toward that goal, and considering the narrow structural tolerance in that region of the inhibitors, we focused on altering the conformation of the distal phenyl ring at the P_1' position as a possible means to enhance the potency and selectivity of these non-peptidic inhibitors toward ECE. In this article, we describe a new series of

Scheme 1[a]



[a] (a) $H_2N(CH_2)_2CN$, EDC; (b) $(CF_3SO)_2O$, NaN_3; (c) H_2NNH_2; (d) HCl; (e) $Ph_2C{=}NH$; (f) NaHMDS, RBr; (g) $NaHCO_3$; (h) $(EtO)_2P(O)CH_2OSO_2CF_3$, $EtN(^iPr)_2$; (i) DBU; (j) TMSBr; (k) NaOH then CHP-20.

ECE-1 inhibitors featuring coplanar biphenyl surrogates at the P_1' position.

Chemistry

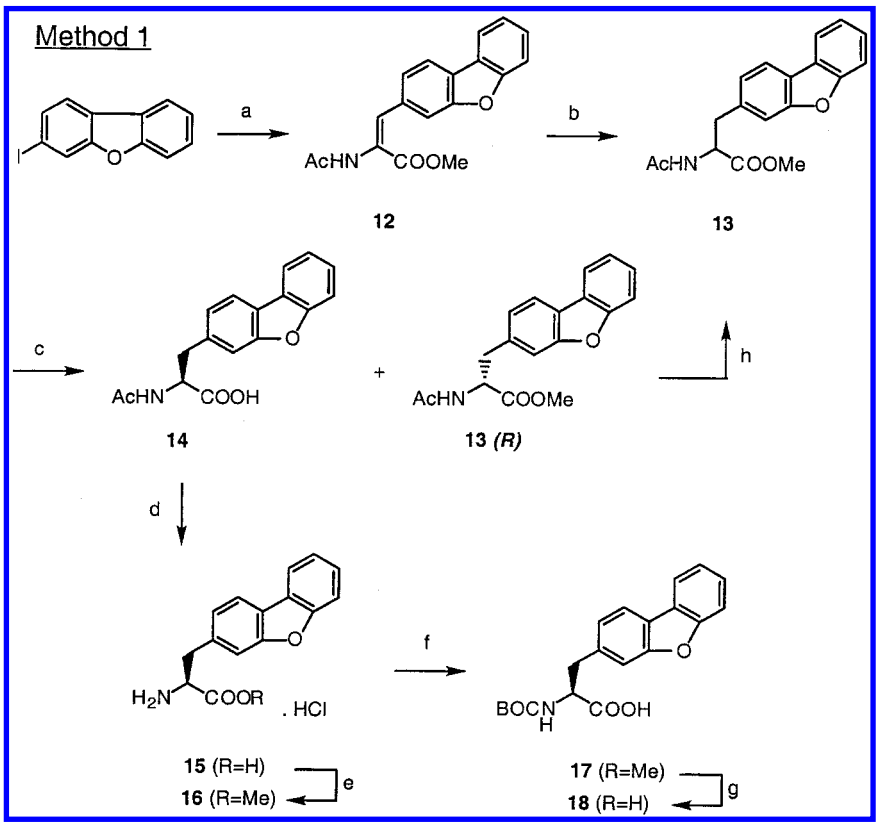
The synthesis of **11a** (X = CH_2), **11b** (X = NCH_3), and **11c** (X = C=O), the fluorene, 9-methylcarbazole, and fluorenone analogues of CGS 26303, respectively, exploits a modification of the alkylation protocol of tetrazole benzophenone imines reported previously (Scheme 1).[32]

In the current variation, the 2-cyanoethyl group was chosen as the N^1-protecting group of the tetrazole instead of the originally prescribed 4-methoxybenzyl, because the conditions for its removal were milder and chemically more compatible. When the alkylation step was carried out at −78 °C, the loss of the 2-cyanoethyl group by *β*-elimination was minimized, allowing the reaction to proceed with moderate yields. After acid hydrolysis of the imines **7a**−**c**, the target aminophosphonic acids were elaborated by alkylation of the corresponding amines **8a**−**c** with dimethylphosphonomethyl triflate, as described previously.[31,33] The final compounds were usually converted to their trisodium salts **11a**−**c** to maximize water solubility. When necessary, these salts were purified by chromatography on a CHP-20P resin[34] (see Experimental Section).

The novel α-amino acid, *(S)*-3-dibenzofuran-3-ylalanine (**15**), was selected as a common building block for the preparation of various derivatives and was obtained by two alternative methods (Schemes 2 and 3). In method 1, Heck coupling between 3-iododibenzofuran and methyl 2-acetamidoacrylate afforded the α,*β*-unsaturated α-amido ester **12** which was hydrogenated to yield the racemic ester **13**. Incubation of **13** with alcalase led to the enantiospecific hydrolysis of the *S* enantiomer, giving the carboxylic acid **14**. The unreacted *R* enantiomer **13*(R)*** was recycled by a sequence of epimerization/resolution to provide an additional amount of acid **14**. On larger scale, this recycling protocol could be repeated several times. The latter compound was eventually converted in four straightforward steps to the BOC-protected α-amino acid **18** (Scheme 2).

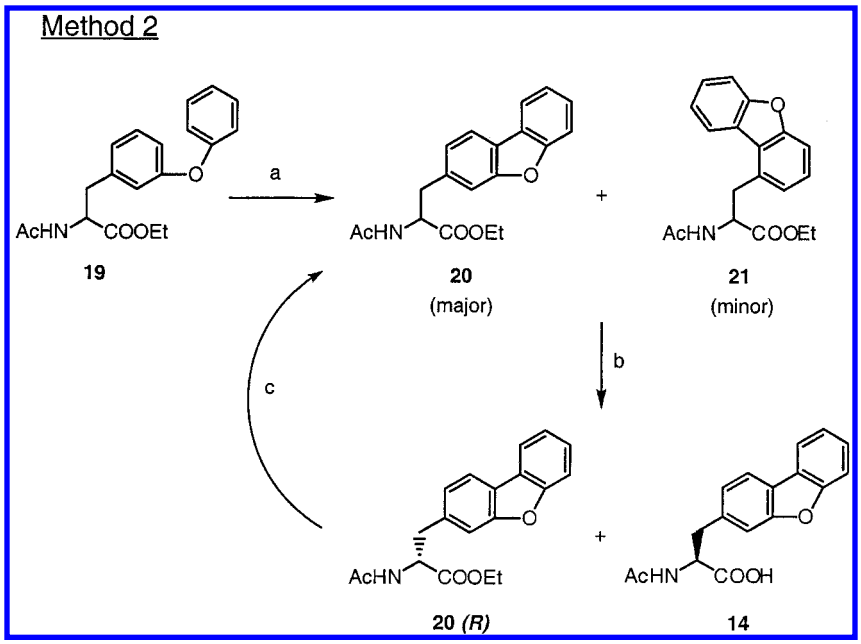
Method 2 relies on a biaryl formation via ortho palladation[35] of the readily available diaryl ether **19**[36] and provided a more direct access to the acid intermediate **14**. Besides the desired product **20**, a small amount (14%) of regioisomer **21** was also formed when the reaction was carried out in acetic acid. The reaction proceeded faster in trifluoroacetic acid (3 h at reflux), but a larger amount of undesired isomer **21** was formed under these conditions. Although the latter compound could not be easily separated from **20**, a small amount was eventually obtained for characterization purposes by successive triturations in ether. It was also determined that **21** was not a substrate to alcalase. Therefore, subsequent enzymatic digestion of the mixture of ethyl esters **20** and **21** provided both an efficient separation and a resolution method, affording the key carboxylic acid intermediate **14** in high chemical and enantiomeric purity (Scheme 3). Recycling of the enan-

Scheme 2[a]



[a] (a) Methyl 2-acetamidoacrylate, $Pd(OAc)_2$, $^nBu_4NCl$, DMF; (b) Pd−C, H_2; (c) alcalase, $NaHCO_3$, MeCN; (d) HCl; (e) HCl, MeOH; (f) BOC_2O; (g) LiOH, MeOH; (h) DBU.

Scheme 3[a]



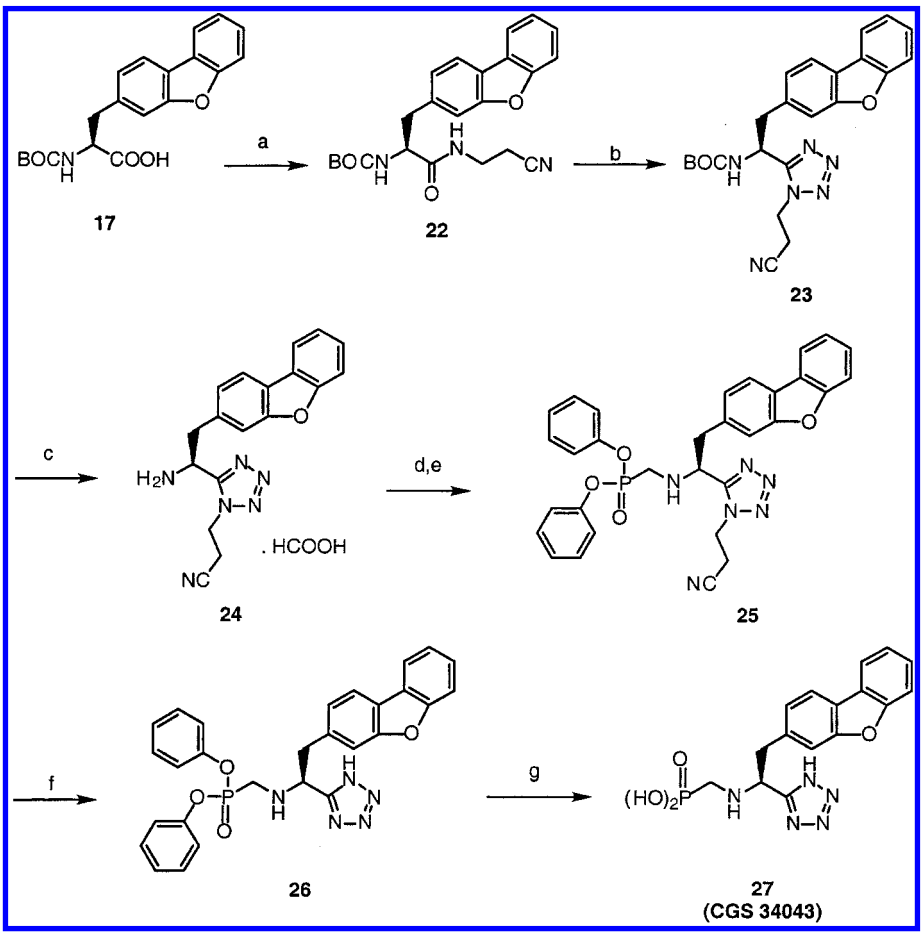
[a] (a) $Pd(OAc)_2$, AcOH; (b) alcalase, $NaHCO_3$, MeCN; (c) DBU or EtOH, EtONa(cat.).

tiomer **20**(*R*) was performed as described above, but the number of cycles was limited by the accumulation of regioisomer **21** which hindered the crystallization of **14**.

For the synthesis of **27**, the elaboration of the tetrazole ring and the introduction of the phosphonomethyl group followed procedures specifically developed earlier for the preparation of CGS 26303 (Scheme 4).[37] Particularly noteworthy is the use of the diphenyl phosphonate **26** (CGS 34753) which serves both as a chemical precusor and as a potential orally bioavailable prodrug of **27**.

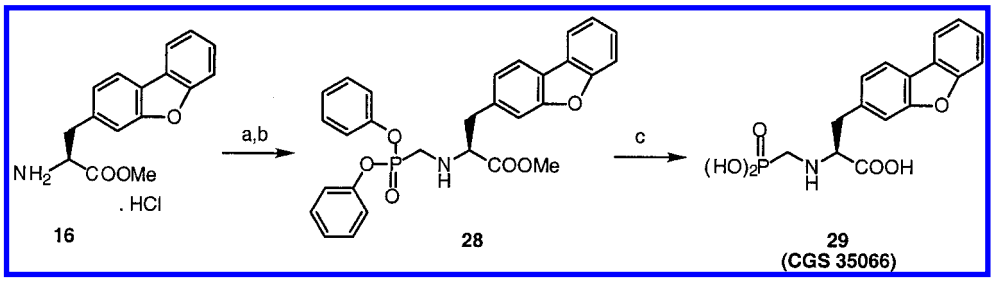
Starting from the α-amino ester **16**, a similar synthetic approach was used to prepare the corresponding *N*-phosphonomethyl α-amino acid analogue **29**. In this case, an exhaustive acid hydrolysis of the diphenyl phosphonate intermediate **28** afforded **29** directly (Scheme 5). The high enantiopurity (>96%) of this compound was confirmed by NMR analysis.[38]

Scheme 4[a]



[a] (a) $H_2N(CH_2)_2CN$, BOP; (b) $TMSN_3$, DIAD, PPh_3; (c) HCOOH; (d) HCHO(aq), $NaHCO_3$; (e) $PO(OPh)_2$; (f) DBU; (g) $NaHCO_3$.

Scheme 5[a]

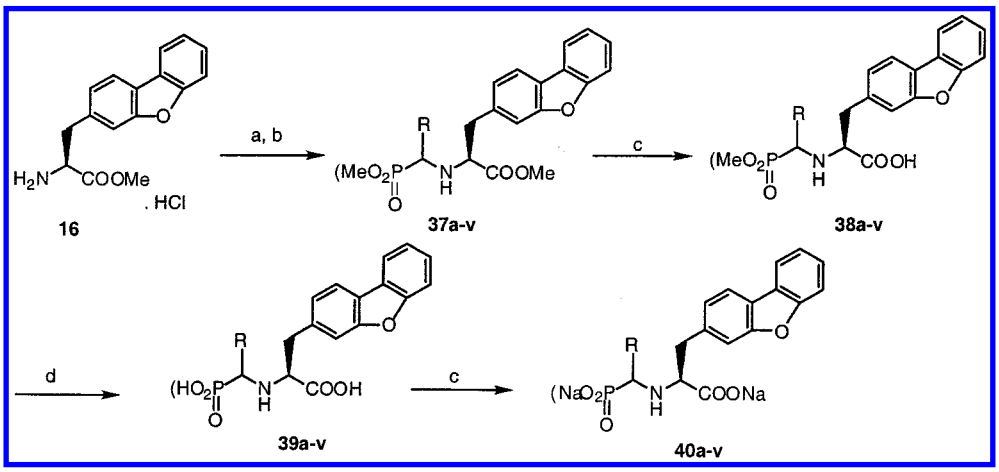


[a] (a) HCHO(aq), $NaHCO_3$; (b) $PO(OPh)_2$; (c) HCl(aq), 100 °C.

C-Terminal amide derivatives (**30, 31**) and dipeptides (**32**−**36**) (Table 2) were obtained readily according to the methods already described for the biphenyl and phenylacetylene analogues.[31,39,40]

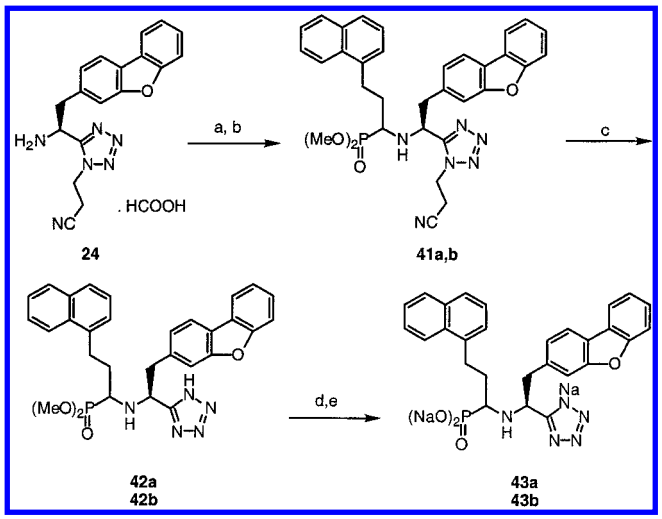
Introduction of various substituents at the P_1 position required a convergent access to α-substituted α-aminophosphonic acids. Since the published procedures afforded low yields of the expected products,[30] a synthetic optimization effort was devoted to address this issue. We found that the desired substituted α-aminophosphonates could be conveniently obtained using a Lewis acid-promoted addition of trimethyl phosphite to a preformed imine intermediate[41,42] generated from the condensation of *(S)*-3-dibenzofuran-3-ylalanine methyl ester hydrochloride (**16**) with an aldehyde. The use of $BF_3{\cdot}Et_2O$ turned out to be particularly advantageous in this case, readily affording dimethyl α-aminophosphonates in satisfactory yields under mild conditions (Scheme 6). Compounds **37a**−**v** were generally obtained as mixtures of two diastereoisomers (A and B), which could often be separated by chromatography on SiO_2. If the resolution was poor, the mixtures were then converted to the corresponding acids **38a**−**v** and separated on Lichroprep DIOL columns. However, because the saponification of **37a**−**v** often resulted in some hydrolysis of the dimethyl phosphonate, the mixture of products, containing mainly **38a**−**v**, was typically used directly in the final deprotection step with HBr or TMSBr. The phosphonic acids **39a**−**v** were usually converted to their sodium salts **40a**−**v** to allow their solubilization in water (Table 3). When necessary, these salts could be purified by chromatography on a CHP-20P resin[34] (see Experimental Section). For our purpose, the lack of a stereoselectivity of the α-aminophosphonate synthesis was advantageous since the absolute configuration required for the P_1 side chain was not

Scheme 6[a]



[a] (a) RCHO (see Table 3 for definitions of R), NEt_3, Na_2SO_4; (b) $BF_3{\cdot}OEt_2$, $P(OMe)_3$; (c) NaOH; (d) HBr or TMSBr.

Scheme 7[a]



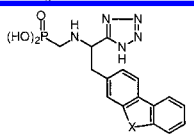
[a] (a) 1-Naphthyl-CHO, NEt_3, Na_2SO_4; (b) $BF_3{\cdot}OEt_2$, $P(OMe)_3$; (c) DBU then separate diastereomers on Lichroprep DIOL; (d) HBr, AcOH; (e) NaOH then CHP-20.

known a priori. Unfortunately, in these diastereomers, we were unable to unambiguously assign the configuration of the α-aminophosphonate carbon. This α-aminophosphonate synthesis could also be carried out with the cyanoethyl-protected tetrazole analogue **24**, providing an access to the two diastereomers **43a** and **43b** (Scheme 7).

Results and Discussion

In Vitro Activity. The incorporation of a local conformational constraint into a ligand can be a successful strategy to increase its binding and selectivity toward a particular molecular target. We have applied this approach to the biphenyl group of CGS 26303, aiming for a minimal yet significant alteration of the original inhibitor core structure. The replacement of the biphenyl group of CGS 26303 by a fluorene moiety provided early support to this strategy (Table 1), assuming that the inhibitory activities (ECE and NEP) of the phosphonic acids reside essentially in a single *S* enantiomer, as suggested from previous SAR studies in this series. Indeed, not only was **11a**, as a racemate, a slightly more potent ECE inhibitor than racemic CGS 26303, but its intrinsic NEP affinity was substantially

Table 1. In Vitro ECE and NEP Inhibitory Potencies of Phosphonomethyl Aminoalkyl Tetrazoles

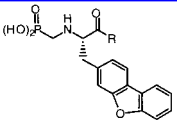


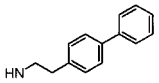
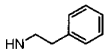
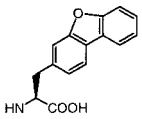
Cpd	conf.	X	IC_{50} (nM)		ECE
			rhECE-1	NEP	Selectivity[a]
11a	(R/S)	CH_2	520 ± 15	450 ± 17	0.9
11b	(R/S)	NCH_3	> 4000 nM	140 ± 7	< 0.03
11c	(R/S)	C=O	30 ± 2	230 ± 3	7.7
27	(S)	O	6 ± 0.4	114 ± 5	19
CGS 26303	(S)	none	410	1	0.0024

[a] ECE selectivity is defined as the ratio IC_{50} NEP/IC_{50} ECE.

decreased (about 225-fold). Since forcing coplanarity of the aryl rings not only was tolerated but even appeared to increase the ECE selectivity and, to a lesser extent, the ECE inhibition, we have concentrated on incorporating structural attributes that could potentially enhance the inhibitory activity of the phosphonic acids. Although the 9-methylcarbazole **11b** displayed much weaker activities than CGS 26303, the fluorenone **11c** and, especially, the dibenzofuran **27** were both potent and moderately selective ECE inhibitors. The potency-enhancing effect of a dibenzofuran at the P_1' position was even more dramatically demonstrated in a series of carboxylic acids. We have reported that the replacement of the tetrazole heterocycle of CGS 26303 with a carboxyl group resulted in a substantial loss of ECE inhibition.[30] By contrast, the dibenzofuran analogue **29** maintained potent ECE inhibitory activity while its NEP activity was only in the micromolar range, leading to an ECE selectivity of about 104, i.e. a 43000-fold improvement over CGS 26303 (Table 2). Terminal amides **30** and **31** were found to be weak ECE inhibitors, a remarkable observation considering that similar derivatives bearing a 2-fluorophenylacetylene P_1' substituent maintained significant ECE inhibitory activity. Little emphasis was devoted to dipeptide analogues, but among the few compounds prepared, such as **32**−**36**, those featuring large hydrophobic P_2' substituents, including the 3-dibenzofuranyl group itself, produced

Table 2. In Vitro ECE and NEP Inhibitory Potencies of Phosphonomethyl 3-Dibenzofuranyl Alanine Derivatives



Cpd	R	%I[a]	IC_{50} (nM)		ECE
			rhECE-1	NEP	Selectivity[d]
29	OH	92	22 ± 0.9	2,300 ± 33	104
30[b]		5	ND[c]	ND[c]	ND[c]
31[b]		29	ND[c]	ND[c]	ND[c]
32[b]	(S)-Phe-OH	91	23	12 ± 1.2	0.5
33	(S)-Leu-OH	92	13	31 ± 0.2	2.3
34[b]	β-Ala-OH	35	ND[c]	1,640 ± 140	ND[c]
35	Gly-OH	43	ND[c]	>10,000	ND[c]
36[b]		95	6.4	2.7 ± 0.004	0.42

[a] % Inhibition of ECE activity at a concentration of 1 μM of test compound. [b] Sodium salt. [c] ND, not determined. [d] ECE selectivity is defined as the ratio IC_{50} NEP/IC_{50} ECE.

potent ECE inhibition. Interestingly, the presence of this second amino acid residue, as in **36**, also restored NEP inhibition, thereby imparting mediocre selectivity to these compounds (Table 2). By contrast, it is worth noting the weak NEP inhibitory activity, or even lack thereof, of the dipeptides **34** and **35**, considering that structurally very close analogues, differing only by the absence of a bridging oxygen in the biaryl P_1' group, potently inhibited NEP at low nanomolar concentration.[39]

Since addition of a lipophilic P_1 substituent had resulted in an increase of ECE inhibitory activity in a related biphenyl series (e.g. CGS 31447), substituted derivatives of **27** were prepared (Table 3). A naphthylethyl substituent was originally selected for direct comparison with CGS 31447. Although this modification failed to provide a compound **(40a)** with enhanced potency, the selectivity toward ECE was increased. Other substituents, potentially acting as naphthyl surrogates but conferring lower lipophilicity and possibly enhanced water solubility at physiological pH, were selected from methoxy-substituted phenyl groups and quinolyl moieties (**40c**−**n**). In general, one of the diastereomers produced was a potent (14−40 nM) and highly selective ECE inhibitor. Methyl, isobutyl, aminopropyl, and aminobutyl side chains, albeit tolerated, were not optimal for ECE inhibition (**40o**−**v**). On the basis of previous SAR considerations, the combination of a 1-naphthylethyl P_1 side chain with a 3-dibenzofuranyl substituent in P_1' and a terminal tetrazole group was expected to be a very potent ECE inhibitor. Indeed, the diastereomer **43a** was the most potent inhibitor of the recombinant human ECE-1 reported to date.

In Vivo Activity. The functional activity of the selective ECE inhibitors was evaluated according to their ability to inhibit the big ET-1-induced pressor response in anesthetized, ganglion-blocked rats. Animals were challenged with big ET-1 (1 nmol/kg, iv) 15 and 90 min after intravenous administration of the inhibitor (10 mg/kg). It had been demonstrated previously that, in the absence of ECE inhibitor, the pressor response lasted for about 1 h and that the mean arterial pressure had returned to control levels by 90 min. Many peptidic ECE inhibitors, including the recently described phenylacetylene di- and tripeptides **2a** and **2b**, while functionally active at early time points (15 min), were unable to block the pressor response substantially at 90 min (results not shown). Even the potent nonpeptidic inhibitor CGS 31447 was also plagued with a short duration of action (Figure 1). Considering that, under testing conditions, the rat plasma levels of CGS 31447 were extremely high (about 20 μg/mL),[43] we suspect an exceedingly high plasma protein binding at the equilibrium state (> 99%)[43] to be responsible for limiting the access of the inhibitors to the target enzyme. Similarly, among the new, potent ECE inhibitors described in this work, those featuring a P_1 lipophilic side chain also typically displayed weak or short-lasting in vivo activity (Table 4).

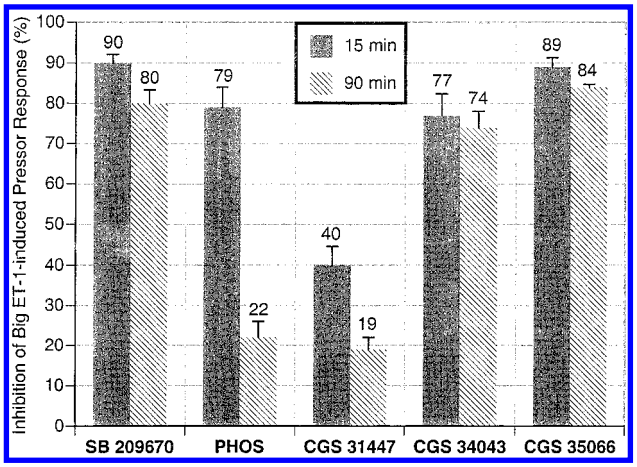


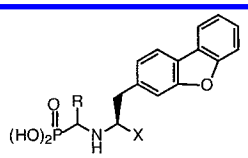
Figure 1. Inhibition of the increase in mean arterial pressure elicited by big ET-1 in anesthetized, ganglion-blocked rats. Rats were injected intravenously with the test compounds (10 mg/kg) or the vehicle (0.05 N NaOH, 1 mL/kg), then challenged with big ET-1 (1 nmol/kg, iv) 15 and 90 min later. SB 209670, phosphoramidon (PHOS), CGS 31447, CGS 34043 (**27**), and CGS 35066 (**29**) attenuated the increase in mean arterial pressure when compared to vehicle. Results are expressed as percent inhibition of the big ET-1-induced pressor response and listed on top of bars. Values are the mean ± SEM ($n = 4$).

However, compounds lacking these structural attributes fared much better in this in vivo test. In particular, after a single intravenous administration of a 10 mg/kg dose to rats, **27** and **29** significantly prevented the big ET-1-induced pressor response at both 15 and 90 min and compared favorably with the potent ET_A/ET_B receptor antagonist SB 209670 (Figure 1). It is worthwhile noting that, even at this dose, a complete blockade of the pressor response was never achieved (maximum 90%) with either the selective ECE inhibitors, the ECE/NEP inhibitors, or the ET receptor antagonist.

Conclusion

In the present study, we have demonstrated that replacement of the P_1' biphenyl substituent of CGS 26303 by a conformationally restricted 3-dibenzofuranyl

Table 3. In Vitro ECE and NEP Inhibitory Potencies of Phosphonoalkyl 3-Dibenzofuranyl Alanine Derivatives and Tetrazole Analogues



Cpd	X	Diast[a]	R	Yield[b]	%i[c]	IC_{50} (nM)		ECE
						rhECE-1	NEP	Selectivity[m]
40a[l]	COOH	A	(1-naphthyl)ethyl	31	95	24 ± 0.9	13,770 ± 1,776	574
40b[l]		B		47	34	1,800 ± 200	ND[g]	ND[g]
40c	COOH	A	(2,3-dimethoxy)phenethyl	60	95	19 ± 0.9	24,000 ± 1,000	1263
40d[l]		B		38	85	110 ± 3	6,400 ± 150	58
40e[l]	COOH	A	(3,4-dimethoxy)phenethyl	56	93	29 ± 3.5	> 10,000	> 345
40f[l]		B		23	58	890[d]	ND[g]	ND[g]
40g[l]	COOH	A	(3,4,5-trimethoxy)phenethyl	48	92	22 ± 3	18,000 ± 330	818
40h[f]		B		17[e]	NA[f]	NA[f]	NA[f]	ND[g]
40i[l]	COOH	A	(3,4,6-trimethoxy)phenethyl	61	91	40 ± 1.2	> 10,000	> 250
40j[l]		B		29	38	ND[g]	ND[g]	ND[g]
40k[l]	COOH	A	(2,3,4-trimethoxy)phenethyl	43	91	35 ± 1.2	15,000 ± 120	428
40l[l]		B		34	64	520 ± 42	ND[g]	ND[g]
40m[l]	COOH	A	(8-quinolyl)ethyl	44	94	14 ± 0.6	59,000 ± 1,300	4214
40n[l]		B		48	78	200 ± 17	48,000 ± 3,500	240
40o[l]	COOH	A	4-aminobutyl	68[h]	84	97± 0.6	> 100,000	> 1031
40p[l]		B		23[h]	19	ND[g]	ND[g]	ND[g]
40q[l]	COOH	A	3-aminopropyl	41[h]	73	ND[g]	ND[g]	ND[g]
40r[l]		B		40[h]	29	ND[g]	ND[g]	ND[g]
40s[l]	COOH	A	4-methylpentyl	49	89	65 ± 5.5	> 16,000	> 286
40t[f]		B		6[e]	NA[f]	NA[f]	NA[f]	ND[g]
40u	COOH	A	methyl	35	88	96 ± 12	28,000 ± 330	292
40v		B		42[i]	81[j]	180 ± 10	47,000 ± 330	261
43a[l]		A	(1-naphthyl)ethyl	38[k]	98	2.6 ± 0.8	210 ± 13	81
43b[l]		B		40[k]	73	440 ± 40	13,000 ± 410	29
Phosphoramidon					47	1200 ± 70	30 ± 2	0.025
Thiorphan					9	> 100,000	4.8 ± 2	< 0.00005

[a] Diastereomer A is obtained from the least polar aminophosphonate **37** (highest R_f by TLC) according to Scheme 6. [b] Chemical yield, after separation by flash chromatography, of aminophosphonate diastereomer **37** according to Scheme 6. [c] % Inhibition of ECE activity at a concentration of 1 μM of test compound. [d] Single determination. [e] Due to a low recovery yield, this aminophosphonate was not converted to the final aminophosphonic acid. [f] NA, not available. [g] ND, not determined. [h] Yield of *N*-phthalimido-protected aminophosphonate precursor. [i] Contains 43% of diastereomer **37u**. [j] Contains 43% of diastereomer **40u**. [k] Chemical yield, after separation on Lichroprep DIOL, of aminophosphonate diastereomers **42a** and **42b** according to Scheme 7. [l] Sodium salt. [m] ECE selectivity is defined as the ratio IC_{50} NEP/IC_{50} ECE.

group leads to more potent and more selective ECE inhibitors, such as **27.** The remarkable effect of this P_1' modification allowed for the first time phosphonomethylcarboxylic acids, such as **29**, to display *both* potent (IC_{50} = 22 nM) and selective (104-fold vs NEP) ECE inhibition. Although additional gains in intrinsic potency could occasionally be achieved by addition of a P_1 side chain, these analogues (e.g. **43a**) showed poor functional activity in vivo in the big ET-1 pressor test. Phosphonoalkyl dipeptides featuring 3-dibenzofuranyl groups in both the P_1' and P_2' positions were also very potent ECE-1 inhibitors, albeit lacking the desired selectivity against NEP. On the basis of the unique binding mode of CGS 26303 to ECE, relative to other dipeptidic congeners, it remains possible that the non-peptidic compounds presented in this study share a common SAR which differs from that of the dipeptide analogues.[44] Functionally, **27** and **29** turned out to be the two most efficacious compounds from this study, producing sustained inhibition of ECE-1 activity in rats, as measured by their ability to block the hypertensive effects induced by big ET-1. This profile was similar to that of a potent ET_A/ET_B dual receptor antagonist, SB 209670. At this time, due to their favorable in vitro and in vivo profiles, **27** and **29** constitute new pharmacological tools useful in assessing the role of ECE-1 in pathological conditions. Additional pharmacological char-

Table 4. Inhibition of the Big ET-1-Induced Pressor Response by Phosphonoalkyl 3-Dibenzofuranyl Alanine Derivatives

Cpd	Inhibition of big ET-1-induced pressor response (%)[a]		Cpd	Inhibition of big ET-1-induced pressor response (%)[a]	
	at 15 min	at 90 min		at 15 min	at 90 min
40a	7	2	**40m**	52	29
40c	18	0	**40n**	22	21
40d	8	24	**40o**	85	73
40e	51	19	**40q**	77	65
40g	59	77	**40s**	11	0
40i	9	0	**40u**	87	81
40k	18	0	**40v**	82	80
40l	27	14	**43a**	19	10
			PHOS[b]	79	22

[a] Results are expressed as percent inhibition of the maximum increase in mean arterial pressure produced by intravenous administration of big ET-1 at 1 nmol/kg iv, relative to vehicle (NaOH). Big ET-1 was administered 15 and 90 min after iv bolus injection of the inhibitor (10 mg/kg). [b] Phosphoramidon tested at 30 mg/kg iv.

acterization of **27** (CGS 34043), **29** (CGS 35066), and their diphenyl phosphonate prodrugs will be reported elsewhere.

Experimental Section

Melting points were determined on either a Thomas-Hoover or Mel-Temp II melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet 5SXB FTIR spectrometer. ^{1}H NMR spectra were recorded on either a Bruker AC-250 or Bruker AC-300 using $CDCl_3$, D_2O, or DMSO-d_6 as internal standard. When needed, a few drops of trifluoroacetic acid was used to solubilize the phosphonic acids in DMSO-d_6. ^{31}P NMR spectra were recorded on a Bruker AC-300 spectrometer. ^{31}P chemical shifts are reported relative to 85% aqueous phosphoric acid as external standard. Optical rotations were measured with a Jasco DIP-370 instrument. Mass spectra were obtained on a MicroMass Platform II spectrometer. Microanalyses were performed at Robertson Laboratory, Inc., Madison, NJ. All organic solvents were of anhydrous grade. Chromatographic separations were performed on either SiO_2 60 (flash grade), LiChroprep Diol (E. Merck), or copolymeric hydrophobic resin CHP-20P (Mitsubishi Chemical Industries). Some chromatographic separations were performed on a Biotage Flash40 apparatus with SiO_2. Alcalase (food grade) was acquired from Novo Nordisk (Franklinton, NC).

Enzyme Assays. The ECE-1 (from membranes of CHO cells expressing human recombinant ECE-1a) and NEP 24.11 (from rat kidney cortex membrane homogenates) assays were performed as described previously.[31,40]

Big ET-1-Induced Pressor Responses in Anesthetized Rats. Male Sprague−Dawley rats (275−450 g) were anesthetized with Inactin (100 mg/kg ip) and instrumented with catheters in the femoral artery and vein to measure mean arterial pressure (MAP) and administer compounds, respectively. A tracheotomy was performed and a cannula inserted into the trachea to ensure airway patency. The body temperature of the animals was maintained at 37 °C by means of a heating blanket. Following surgery, MAP was allowed to stabilize for 15 min before interrupting autonomic neurotransmission with chlorisondamine (3 mg/kg iv). The rats were given an additional 30 min to stabilize under the conditions of autonomic blockade. Animals were then treated with a test compound at 10 mg/kg iv or vehicle (0.05−0.1 NaOH at 1 mL/kg iv) and challenged with big ET-1 (1 nmol/kg iv) 15 and 90 min later. The maximum increase in MAP produced by big ET-1 in rats treated with test compounds or vehicle was determined at each time point. Results are expressed as percent inhibition of the big ET-1-induced pressor response in animals treated with ECE inhibitors as compared to vehicle.

***N*-(2-Cyanoethyl)-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)acetamide (3).** To a stirred solution of 3-aminopropionitrile (0.89 mL, 12.1 mmol) in DMF (27 mL) was added *N*-phthaloylglycine (1.86 g, 9.06 mmol) followed by HOBt (1.26 g, 9.3 mmol). The reaction mixture was cooled to 0 °C with an ice bath and EDC (2.1 g, 10.9 mmol) was added. After stirring for 1 h at 0 °C then for 1.5 h at ambient temperature, the reaction mixture was poured into ice-cold H_2O and extracted with EtOAc. The combined organic extracts were washed successively with 1 N HCl, H_2O, 8% $NaHCO_3$ solution, H_2O, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give **3** as a white solid (62%): mp 187−189 °C; IR (Nujol) 3302, 2243, 1776, 1720, 1657, 1566, 956, 716 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.63 (2H, t, J = 6.5 Hz), 3.30 (2H, q, J = 6.3 Hz), 4.20 (2H, s), 7.85−7.93 (4H, m), 8.62 (1H, t, J = 5.4 Hz); MS (ES^{1+}) m/z 458 (M + 1). Anal. ($C_{13}H_{11}N_3O_3$) C, H, N.

3-[5-(1,3-Dioxo-1,3-dihydroisoindol-2-ylmethyl)tetrazol-1-yl]propionitrile (4). Triflic anhydride (31.7 mL, 188 mmol) was added to a stirred slurry of **3** (44.0 g, 171 mmol) and sodium azide (12.2 g, 188 mmol) in MeCN (800 mL) at 0 °C under N_2. The mixture rapidly dissolved resulting in a clear solution. After 16 h, the reaction mixture was poured into 8% $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extracts were washed with 8% $NaHCO_3$ solution and H_2O, then dried over Na_2SO_4 and concentrated to give a solid. Recrystallization from MeOH gave **4** as colorless crystals: mp 165−167 °C (67%); IR (Nujol) 2250, 1772, 1725, 1395, 937, 713 cm^{-1}; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 3.27 (2H, t, J = 6.6 Hz), 4.84 (2H, t, J = 6.6 Hz), 5.23 (2H, s), 7.86−7.96 (4H, m); MS (DCI) m/z 283 (M + 1). Anal. ($C_{13}H_{10}N_6O_2$) C, H, N.

3-(5-Aminomethyltetrazol-1-yl)propionitrile Hydrochloride (5). A mixture of **4** (4.51 g, 16 mmol) and anhydrous hydrazine (1.0 mL, 32 mmol) in MeOH (100 mL) was stirred at reflux for 16 h. The reaction mixture was cooled to ambient temperature and filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and filtered. The filtrate was concentrated under reduced pressure to give a yellow oil. The oil was dissolved in MeCN and 4.5 mL of 3.4 N HCl in Et_2O were added. The white precipitate was collected by filtration, washed with MeCN, and dried in vacuo (99%): mp 157−159 °C; IR (Nujol) 2900 (vs), 2259, 1611 cm^{-1}; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 3.24 (2H, t, J = 6.7 Hz), 4.51 (2H, s), 4.81 (2H, t, J = 6.6 Hz), 9.04 (3H, s). Anal. ($C_5H_8N_6$·HCl) C, H, N.

3-{5-[Benzhydrylideneaminomethyl]tetrazol-1-yl}propionitrile (6). Benzophenone imine (2.51 mL, 15.0 mmol) was added to a stirred slurry of **5** (1.75 g, 9.31 mmol) in CH_2Cl_2 under N_2. After stirring for 16 h, the reaction mixture was filtered and the filtrate concentrated under reduced pressure to give an oil. The oil was triturated with hot hexanes (50 mL) and the resulting residue suspended in hexanes:Et_2O (1:1, 100 mL) until a solid formed. The solid was collected by filtration and dried in vacuo (1.6 g, 55%): mp 108−110 °C; IR (Nujol) 2243, 1626, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.16 (2H, t, J = 7.0 Hz), 4.93 (2H, s), 5.05 (2H, t, J = 7.1 Hz), 7.20−7.60 (10 H, m); MS (DCI) m/z 317 (M + 1). Anal. ($C_{18}H_{16}N_6$) C, H, N.

3-{5-[1-(Benzhydrylideneamino)-2-(9*H*-fluoren-2-yl)-ethyl]tetrazol-1-yl}propionitrile (7a). Sodium bis(trimethylsilyl)amide (1.0 M solution in THF) was added slowly over 5 min to a stirred solution of **6** (0.56 g, 1.77 mmol) and 2-(bromomethyl)-9*H*-fluorene (0.47 g, 1.77 mmol) in THF (10 mL) at −78 °C under an argon atmosphere. After 1 h of stirring at −78 °C, the reaction mixture was quenched by the addition of MeOH, then warmed to ambient temperature. The reaction mixture was diluted with EtOAc and washed with saturated NH_4Cl and brine. The aqueous layer was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$

and concentrated under reduced pressure. Flash chromatography of the residue on SiO_2 (hexanes:EtOAc, 3:1) afforded recovered starting materials **6** and 2-(bromomethyl)-9*H*-fluorene in 29% and 31% yield, respectively, as well as the desired product **7a** as an oil (0.27 g, 30 %): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.73−2.89 (2H, m), 3.19−3.30 (2H, m), 3.78 (2H, s), 4.69 (1H, dt, J = 14.3, 7.5 Hz), 4.95 (1H, dt, J = 14.3, 7.5 Hz), 5.58 (1H, t, J = 7.5 Hz), 6.68 (2H, d, J = 7.1 Hz), 6.69 (1H, d, J = 8.3 Hz), 7.08 (1H, s), 7.25−7.68 (11H, m), 7.73−7.81 (2H, m).

3-{5-[1-Amino-2-(9*H*-fluoren-2-yl)ethyl]tetrazol-1-yl}-propionitrile (8a). To a stirred slurry of **7a** (0.42 g, 0.85 mmol) in Et_2O:EtOAc (1:1, 10 mL) was added 1 N HCl (5 mL). The reaction mixture was stirred 16 h then diluted with Et_2O, and the organic solvents were decanted. The remaining residue was triturated with Et_2O. The resulting white solid was dried in vacuo. The hydrochloride salt was diluted with 8% $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure to give **8a** as an oil (0.18 g, 80%): ^{1}H NMR (DMSO-d_6, 250 MHz) δ 2.52−2.61 (1H, m), 2.63−2.87 (1H, m), 3.24−3.28 (1H, m), 3.50 (1H, dd, J = 13.3, 5.9 Hz), 3.84 (2H, s), 4.38−4.53 (2H, m), 5.27 (1H, t, J = 7.7 Hz), 7.08 (1H, d, J = 7.6 Hz), 7.27−7.39 (3H, m), 7.56 (1H, d, J = 6.7 Hz), 7.80 (1H, d, J = 7.9 Hz), 7.85 (1H, d, J = 7.1 Hz), 8.93 (2H, bs).

{[1-[1-(2-Cyanoethyl)-1*H*-tetrazol-5-yl]-2-(9*H*-fluoren-2-yl)ethylamino]methyl}phosphonic Acid Dimethyl Ester (9a). A solution of dimethylphosphonomethyl triflate (0.18 g, 0.68 mmol) in CH_2Cl_2 (2 mL) was added to a stirred solution of **8a** (0.18 g, 0.54 mmol) and EtN(^{i}Pr)$_2$ (0.12 mL, 0.68 mmol) in CH_2Cl_2 at 0 °C under an atmosphere of N_2. The reaction mixture was slowly warmed to ambient temperature and stirred for 64 h. The reaction mixture was then diluted with EtOAc, washed with brine, dried over $MgSO_4$, and then concentrated under reduced pressure. Flash chromatography of the residue on SiO_2 (CH_2Cl_2:MeOH, 95:5) gave **9a** as an oil (0.2 g, 81%): IR (thin film) 3053 (b), 2986, 1422, 1264, 1054 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.62 (1H, dt, J = 16.9, 6.8 Hz), 2.76−2.88 (2H, m), 3.00 (1H, t, J = 14.7 Hz), 3.20 (1H, dd, J = 13.3, 8.7 Hz), 3.42 (1H, dd, J = 13.3, 6.6 Hz), 3.68 (3H, d, J = 10.7 Hz), 3.76 (3H, d, J = 10.7 Hz), 3.85 (2H, s), 4.27 (2H, t, J = 7.0 Hz), 4.68 (1H, t, J = 7.4 Hz), 7.06 (1H, d, J = 7.7 Hz), 7.23 (1H, s), 7.35 (3H, dt, J = 19.5, 7.2 Hz), 7.54 (1H, d, J = 7.2 Hz), 7.69 (1H, d, J = 7.7 Hz), 7.76 (1H, d, J = 7.4 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 27.10; MS (DCI) m/z 453 (M + 1). Anal. ($C_{22}H_{25}N_6O_3P$) C, H, N.

{[2-(9*H*-Fluoren-2-yl)-1-(1*H*-tetrazol-5-yl)ethylamino]-methyl}phosphonic Acid Dimethyl Ester (10a). To a stirred solution of **9a** (0.17 g, 0.39 mmol) in CH_2Cl_2 (2 mL) was added DBU (0.14 mL, 0.97 mmol). After 2 h, the reaction mixture was diluted with EtOAc and washed with pH 4 buffer (0.5 M NaH_2PO_4·H_2O) and brine. The organic layer was dried over $MgSO_4$, then concentrated under reduced pressure to give **10a** as a white solid (0.14 g, 92%): IR (thin film) 2900, 1608, 1260, 1040, 825, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.92 (2H, t, J = 11.6 Hz), 3.13 (1H, dd, J = 13.7, 8.6 Hz), 3.40 (1H, dd, J = 14.0, 5.5 Hz), 3.64 (3H, d, J = 11.0 Hz), 3.69 (3H, d, J = 10.7 Hz), 3.81 (2H, s), 4.59 (1H, dd, J = 8.6, 5.5 Hz), 7.10 (1H, d, J = 7.9 Hz), 7.28−7.38 (3H, m), 7.51 (1H, d, J = 6.4 Hz), 7.63 (1H, d, J = 7.9 Hz), 7.71 (1H, d, J = 7.0 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 28.43 (92%), 27.23 (8%); MS (DCI) m/z 400 (M + 1).

{[2-(9*H*-Fluoren-2-yl)-1-(1*H*-tetrazol-5-yl)ethylamino]-methyl}phosphonic Acid Trisodium Salt (11a). Trimethylsilyl bromide (0.28 mL, 2.10 mmol) was added to a suspension of **10a** (0.140 g, 0.351 mmol) in CH_2Cl_2 (6 mL). After 1 h, the reaction mixture was concentrated under reduced pressure to give a tan solid. The solid was diluted with H_2O (15 mL) and stirred for 0.5 h. The resulting white solid was collected by filtration, washed with Et_2O and CH_2Cl_2, and dried in vacuo. The phosphonic acid was then dissolved in a minimal amount of 1 N NaOH and the sodium salt was purified by chromatography on CHP-20P gel[34] (gradient: 100% H_2O to 1:1 H_2O:MeOH in 5% intervals) to give, after lyophilization, **11a** as a fluffy white solid (0.074 g, 57 %): mp 255 °C dec; IR (KBr) 3400 (s), 1625, 1129, 1089, 981, 769, 738 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 2.65 (1H, t, J = 12.8 Hz), 2.85 (1H, t, J = 12.9 Hz), 3.33−3.43 (1H, m), 3.54−3.58 (1H, m), 3.62 (2H, d, J = 3.8 Hz), 4.91 (1H, dd, J = 10.9, 4.8 Hz), 6.97 (1H, d, J = 7.8 Hz), 7.13 (1H, s), 7.24 (2H, dt, J = 15.9, 7.1 Hz), 7.44 (1H, d, J = 7.2 Hz), 7.52 (1H, d, J = 7.8 Hz), 7.62 (1H, d, J = 7.3 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 8.25. Anal. ($C_{17}H_{15}N_5Na_3O_3P$·3/2H_2O) C; H: calcd, 3.91; found, 4.49; N: calcd, 15.08; found, 14.45.

{[2-(9-Methyl-9*H*-carbazol-2-yl)-1-(1*H*-tetrazol-5-yl)ethylamino]methyl}phosphonic acid trisodium salt (11b) was prepared according to the synthesis of **11a**, using 2-bromomethyl-9-methyl-9*H*-carbazole: mp > 280 °C; ^{1}H NMR (D_2O, 300 MHz) δ 2.20 (1H, t, J = 13.2 Hz), 2.45 (1H, t, J = 13.8 Hz), 3.17−3.24 (1H, m), 3.30 (3H, d, J = 10.3 Hz), 3.56 (3H, s), 4.32 (1H, dd, J = 9.6, 5.5 Hz), 6.86 (1H, d, J = 8.1 Hz), 6.96 (1H, s), 7.09 (1H, t, J = 7.0 Hz), 7.34 (2H, t, J = 7.4 Hz), 7.82 (1H, d, J = 7.7 Hz), 7.91 (1H, d, J = 7.7 Hz); ^{31}P NMR (D_2O, 121 MHz) δ 23.13; MS (ES^{1-}) m/z 385 (M − 1). Anal. ($C_{17}H_{16}N_6Na_3O_3P$·5H_2O) C; H: calcd, 3.91; found, 4.49; N: calcd, 15.08; found, 14.45.

{[2-(9-Oxo-9*H*-fluoren-2-yl)-1-(1*H*-tetrazol-5-yl)ethylamino]methyl}phosphonic acid (11c) was prepared according to the synthesis of **11a**, using 2-bromomethylfluoren-9-one: mp 234−235 °C; IR (KBr) 3350, 2770 (vs), 1715, 1608, 1168, 1107, 1056, 945, 741 cm^{-1}; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 3.21 (1H, t, J = 14.3 Hz), 3.36 (2H, t, J = 13.4 Hz), 3.68 (1H, dd, J = 13.3, 4.1 Hz), 5.22 (1H, dd, J = 11.4, 4.4 Hz), 7.16 (1H, d, J = 7.7 Hz), 7.32 (1H, t, J = 7.7 Hz), 7.37 (1H, s), 7.52−7.61 (3H, m), 7.69 (1H, d, J = 7.7 Hz); ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 12.39; MS (ES^{1-}) m/z 384 (M − 1). Anal. ($C_{17}H_{16}N_5O_4P$·5/4H_2O) C, H, N.

2-Acetylamino-3-dibenzofuran-3-yl Acrylic Acid Methyl Ester (12). To a stirred solution of 3-iododibenzofuran (10.0 g, 34 mmol) in anhydrous DMF (260 mL) was added methyl 2-acetamidoacrylate (6.8 g, 47.26 mmol), followed by $Pd(OAc)_2$ (0.30 g, 1.36 mmol), n-Bu_4NCl (9.45 g, 34 mmol), and triethylamine (4.7 mL, 34 mmol). The brown solution was placed in a preheated oil bath (85 °C) and stirred for 15 h. The dark reaction mixture was cooled to ambient temperature and poured into ice-cold H_2O (300 mL) and 1 N HCl (60 mL) and stirred for 30 min. The precipitate was collected and rinsed with H_2O. The filtrate was diluted with Et_2O, stirred, and filtered. The tan solid was dried under high vacuum at 50 °C for 1 h and at ambient temperature overnight (8.78 g, 84%): mp 217−218 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.05 (3H, s), 3.34 (1H, s), 3.73 (3H, s), 7.34 (1H, s), 7.42 (1H, t, J = 7.5 Hz), 7.53−7.58 (1H, m), 7.66−7.73 (2H, m), 8.00 (1H, s), 8.17 (2H, d, J = 8.1 Hz); IR (KBr) 1715, 1656, 1523, 1243, 1204, 755 cm^{-1}. Anal. ($C_{18}H_{15}NO_4$) C, H, N.

2-Acetylamino-3-dibenzofuran-3-ylpropionic Acid Methyl Ester (13). To a solution of **12** (8.72 g, 28.19 mmol) in MeOH (350 mL) and toluene (310 mL) was added 10% Pd/C (5.5 g) under N_2 atmosphere. The reaction mixture was shaken under 50 psi H_2 for 18 h. The reaction mixture was filtered through a bed of Celite and rinsed with 25% MeOH:CH_2Cl_2 and concentrated in vacuo. The residue was triturated with Et_2O hexanes (1:1). The light tan solid was filtered and dried under high vacuum at 50 °C (7.12 g, 81%): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.99 (3H, s), 3.2−3.35 (2H, m), 3.73 (3H, s), 4.90−4.98 (1H, m), 5.98−6.02 (1H, m), 7.04−7.08 (1H, m), 7.28−7.35 (2H, m), 7.40−7.46 (1H, m), 7.52−7.55 (1H, m), 7.83−7.91 (2H, m).

***(S)*-2-Acetylamino-3-dibenzofuran-3-ylpropionic Acid (14).** To a mechanically stirred solution of **13** (11.5 g, 30.50 mmol) in MeCN (385 mL) and 0.2 M $NaHCO_3$ (510 mL) was added alcalase (1.2 mL) and the reaction was monitored by HPLC (column: YMC ODS-A C_{18}; eluent: 70% MeCN:30% H_3PO_4; isocratic; flowrate = 1.5 mL/min). After 2 h, the reaction mixture was diluted with CH_2Cl_2 and stirred for 10 min; then the layers were separated. The organic layer was washed once with H_2O. The combined aqueous layers were washed several times with CH_2Cl_2. The combined organic layers were dried

over $MgSO_4$, then concentrated to give an orange solid corresponding to *(R)*-2-acetylamino-3-dibenzofuran-3-ylpropionic acid methyl ester **13*(R)*** (6.64 g). This compound could be racemized with NaOMe in MeOH (16 h at ambient temperature) and resubmitted to the enzyme resolution (see below for the recycling procedure of the corresponding ethyl ester). The aqueous layer was acidified (pH = 1) with 1 N HCl; the precipitate was filtered and dried under high vacuum at 50 °C for 4 h to give a white solid (4.51 g, 99.5%): mp 247−249 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.77 (3H, s), 2.96−3.04 (1H, m), 3.22 (1H, dd, J = 4.8, 13.7 Hz), 4.46−4.54 (1H, m), 7.27 (1H, d, J = 8.0 Hz), 7.35−7.40 (1H, m), 7.46−7.52 (1H, m), 7.56 (1H, s), 7.67 (1H, d, J = 8.2 Hz), 8.03 (1H, d, J = 7.91 Hz), 8.09 (1H, d, J = 7.5 Hz), 8.26 (1H, d, J = 8.1 Hz); $[\alpha]^{25}_D$ = +25.102 (c = 0.8, DMSO).

The method of Shapiro et al.[38] was used to estimate the enantiomeric purity of **14**: acid **14** (14.5 mg) in DMSO-d_6 (0.5 mL) was mixed with (*R*)-(+)-1-(1-naphthyl)ethylamine (31 μL) for 2 min. NMR spectra were recorded at 500 MHz. Upon spiking the solution of **14** with the racemate **13** (0.6 mg), a new distinct set of peaks (dd) centered at 7.227 ppm was observed next to the initial set (dd) centered at 7.234 ppm. By comparing the relative peak heights of these signals, an enantiomeric purity of at least 97% was determined.

***(S)*-2-Amino-3-dibenzofuran-3-ylpropionic Acid Hydrochloride (15)**. A mechanically stirred suspension of **14** (6.27 g, 21.09 mmol) in concentrated HCl (211 mL) and AcOH (71 mL) was heated at 115 °C for 16 h. The white slurry was cooled to ambient temperature, then cooled in an ice bath. The white solid was filtered and dried under high vacuum at 55 °C for 4 h (5.2 g, 85%): mp 280−281 °C; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 3.23−3.37 (2H, m), 4.3−4.31 (1H, m), 7.29−7.32 (1H, m), 7.36−7.42 (1H, m), 7.48−7.53 (1H, m), 7.62 (1H, s), 7.69 (1H, d, J = 8.1 Hz), 8.1−8.13 (2H, m), 8.35−8.5 (1H, m); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 39.7, 62.5, 117.6, 117.8, 121.9, 122.1, 122.7, 125.4, 127.1, 127.2, 137.4, 155.0, 155.1, 177.0; $[\alpha]^{25}_D$ = +15.09 (c = 0.8, DMSO + 2% TFA). Anal. ($C_{15}H_{13}NO_3$) C, H, N.

***(S)*-2-Amino-3-dibenzofuran-3-ylpropionic Acid Methyl Ester Hydrochloride (16).** Through a stirred solution of **15** (2.58 g, 8.84 mmol) in MeOH (90 mL) at 0 °C was bubbled HCl(g) until saturation. The solution was warmed to ambient temperature and then placed in a preheated oil bath (70 °C) for 2 h, cooled to ambient temperature, and stirred overnight. The mixture containing some precipitate was concentrated in vacuo. The solid residue was triturated with Et_2O, filtered, and dried under high vacuum at 60 °C for 1 h (2.78 g, 100%): $[\alpha]^{25}_D$ = +13.982 (c = 0.8, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 3.3−3.37 (1H, m), 3.46 (1H, dd, J = 6.0, 14.4 Hz), 3.83 (3H, s), 4.43 (1H, dd, J = 6.0, 7.5 Hz), 7.26−7.29 (1H, m), 7.34−7.47 (1H, m), 7.49−7.6 (3H, m), 8.02−8.05 (2H, m).

***(S)*-2-*tert*-Butoxycarbonylamino-3-dibenzofuran-3-ylpropionic Acid Methyl Ester (17).** To a stirred solution of **16** (15.7 g, 51.4 mmol) in CH_2Cl_2 (300 mL) was added triethylamine (9.7 mL, 69 mmol), followed by a solution of di-*tert*-butyl dicarbonate (14 g, 64 mmol) in CH_2Cl_2 (40 mL). A clear solution resulted after 20 min, and the reaction mixture was stirred for 18 h at ambient temperature. The solution was washed with ice-cold H_2O (2 × 100 mL), pH 4 (0.5 M) NaH_2PO_4 buffer (100 mL), and H_2O (100 mL), dried over Na_2SO_4, filtered through a plug of SiO_2, and rinsed with EtOAc:hexanes (1:1, 500 mL). The filtrate was concentrated in vacuo, taken up in CH_2Cl_2, and concentrated again. The oil slowly crystallized (21 g, 100%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (9H, s), 3.2−3.33 (2H, m), 3.74 (3H, s), 4.66 (1H, m), 5.05 (1H, m), 7.3−7.38 (2H, m), 7.45 (1H, m), 7.57 (1H, m), 7.87 (1H, d), 7.92 (1H, d).

***(S)*-2-*tert*-Butoxycarbonylamino-3-dibenzofuran-3-ylpropionic Acid (18)**. To a stirred solution of **17** (8.3 g, 22 mmol) in MeOH (100 mL) was added a solution of lithium hydroxide monohydrate (1.85 g, 44 mmol) in H_2O (40 mL) with adequate cooling to prevent the reaction temperature from rising above 20 °C. After 75 min, ice-cold 1 N HCl (1 mL) was added and the solution was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallized from Et_2O:hexanes (1:2) and dried at 50 °C under high vacuum for 2 h then at ambient temperature for 12 h (8.8 g): mp 138−140 °C; IR (CH_2Cl_2) 1726, 1652, 1233, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (9H, s), 3.12 (2H, ABX), 4.41 (1H, m), 5.14 (1H, m), 7.02 (1H, dd), 7.15 (1H, m), 7.21−7.31 (2H, m), 7.38 (1H, m), 7.70 (1H, d), 7.75 (1H, d); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.22, 38.17, 54.45, 79.40, 111.43, 112.44, 120.26, 120.42, 122.64, 122.71, 123.93, 124.30, 126.85, 136.30, 155.09, 156.06, 156.14, 173.34; $[\alpha]^{25}_D$ = +47.56 (c = 1, CH_2Cl_2); MS (ES^{1-}) m/z 354 (M − 1). Anal. ($C_{20}H_{21}NO_5$) C, H, N.

2-Acetylamino-3-(3-phenoxybenzyl)propionic Acid Ethyl Ester (19). To a mechanically stirred solution of 2-acetylamino-2-(3-phenoxybenzyl)malonic acid diethyl ester[36] (363.86 g, 0.91 mol) in DMF (1.8 L) were added LiBr (79 g, 0.91 mol) and H_2O (33 mL, 1.82 mol). The solution was heated to 138 °C (internal temperature) and stirred for 16 h. The heterogeneous mixture was cooled to 60 °C and concentrated in vacuo at 70 °C. The residue was partitioned between Et_2O (1 L), EtOAc (500 mL), and ice-cold H_2O (500 mL). The insoluble material was filtered. The organic layer was washed with H_2O (2 × 500 mL) and brine (300 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was crystallized from *tert*-butyl methyl ether:hexanes. The white crystalline solid was filtered and dried under high vacuum at 40 °C (254 g, 85%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (3H, t), 1.97 (3H, s), 3.01−3.18 (2H, m), 4.02−4.21 (2H, m), 4.84 (1H, m), 6.0 (1H, d), 6.71 (1H, m), 6.84 (1H, d), 6.92 (1H, dd), 6.94−7.02 (2H, m), 7.11 (1H, m), 7.25 (1H, m), 7.30−7.39 (2H, m).

2-Acetylamino-3-dibenzofuran-3-ylpropionic Acid Ethyl Ester (20). To a stirred solution of **19** (50 g, 153 mmol) in AcOH (500 mL) was added $Pd(OAc)_2$ (51.4 g, 230 mmol). The reaction mixture was heated to reflux temperature (130 °C internal) for 19 h. The black solution was cooled to ambient temperature, then filtered through Celite. The filtrate was concentrated under reduced pressure. The black residue was dissolved in CH_2Cl_2 (50 mL) and diluted with Et_2O (500 mL). The insoluble material was removed by filtration and washed again with Et_2O. The filtrate was concentrated in vacuo. Acetic acid was removed by coevaporation with toluene. The black oily residue was purified by flash chromatography on SiO_2 (900 g) with a gradient of EtOAc in hexanes (40% to 50%). The pure fractions, according to HPLC analysis (column: Waters symmetry C8; eluent: 50% MeCN:50% pH 2.4 buffer; isocratic; flowrate: 1.5 mL/min; t_R = 10 min) were combined and concentrated under reduced pressure. The residue was recrystallized from EtOAc:hexanes and dried at 40 °C under high vacuum to give **20** (27 g) contaminated with a minor amount of regioisomeric ester **21** (14%). **20**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.26 (3H, t, J = 7.0 Hz), 2.00 (3H, s), 3.23−3.37 (2H, m), 4.2 (2H, q, J = 7.0, 14.4 Hz), 4.90−4.97 (1H, m), 5.97 (1H, d, J = 7.63 Hz), 7.09 (1H, dd, J = 1.22, 7.63 Hz), 7.31−7.36 (2H, m), 7.41−7.48 (1H, m), 7.55 (1H, d, J = 8.24 Hz), 7.86 (1H, d, J = 7.94 Hz), 7.92 (1H, d, J = 7.33 Hz).

(S)*-2-Acetylamino-3-dibenzofuran-3-ylpropionic Acid (14).** To a stirred solution of **20** (25 g, 77 mmol) containing 14% of **21** (this byproduct was not enzymatically hydrolyzed) in MeCN (990 mL) was added 0.2 M $NaHCO_3$ (1.3 L), followed by alcalase (2.6 mL). After 3 h, EtOAc (1.75 L) and H_2O (750 mL) were added. The organic layer was washed with H_2O (500 mL) and set aside for subsequent optional epimerization (see below). The aqueous layer was acidified with 2 N HCl (140 mL) under stirring. The white precipitate was filtered, washed with H_2O (2 × 500 mL), and dried under high vacuum at 60 °C for 3 h and at ambient temperature for 15 h (9.28 g). The above organic layer was dried over Na_2SO_4 and concentrated in vacuo to give mostly *(R)*-2-acetylamino-3-dibenzofuran-3-ylpropionic acid ethyl ester (**20*(R)) as a white solid (13 g).

(R)-2-Acetylamino-3-dibenzofuran-3-ylpropionic acid ethyl ester (**20(*R*)**) containing the racemic regioisomer **21** (53 g, 160 mmol) was dried by azeotropic removal of H_2O with toluene−ethanol then dissolved in dry ethanol (450 mL). A solution of sodium ethoxide, freshly prepared from sodium (0.2 g, 8 mmol)

and ethanol (50 mL), was added slowly at ambient temperature. The reaction mixture was stirred at 60 °C for 3 h, then at ambient temperature for 12 h. The solution was saturated with HCl(g) and stirred for 1.5 h at ambient temperature. Ethanol was removed by evaporation under reduced pressure. The residue was partitioned between EtOAc (500 mL) and H_2O (500 mL). The organic layer was separated, washed successively with saturated $NaHCO_3$ (250 mL), H_2O (250 mL), and brine (250 mL), and then dried over Na_2SO_4. The solution was concentrated in vacuo and the residue was recrystallized from EtOAc:hexanes to give racemic **20**, which could be resubmitted to the above-mentioned enzymatic resolution.

***(S)*-2-*tert*-Butoxycarbonylamino-*N*-(2-cyanoethyl)-3-dibenzofuran-3-ylpropionamide (22)**. To a stirred solution of **18** (17.3 g, 48.7 mmol) in anhydrous DMF (300 mL) under N_2 atmosphere was added a solution of 3-aminopropionitrile (3.93 g, 56 mmol) in anhydrous DMF (50 mL) followed by BOP reagent (26.9 g, 60.9 mmol) and triethylamine (17 mL, 121.8 mmol). The reaction was monitored by HPLC (column: YMC ODS; 70% MeCN:30% 0.1% H_3PO_4 in 0.1 M $NaClO_4$; isocratic; flowrate = 1.5 mL/min). After 2 h, the reaction mixture was diluted with EtOAc (1 L) and added to ice−H_2O (500 mL). The aqueous layer was extracted with EtOAc (2 × 400 mL); the combined organic layers were washed successively with H_2O (250 mL), 0.5 M pH 4 buffer (300 mL), saturated NaCl (300 mL), ice-cold saturated $NaHCO_3$ (300 mL), and saturated NaCl (300 mL), then dried over Na_2SO_4, and filtered through a plug of SiO_2 (washed with EtOAc:hexanes, 3:1, 1.5 L). The filtrate was concentrated to give a gelatinous solid, which was treated with *tert*-butyl methyl ether (200 mL), then heated to reflux. After slow addition of hexanes (75 mL), a white solid formed upon cooling (18.26 g, 92%): mp 165−166 °C; IR (KBr) 2245, 1673, 1658, 1528, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38 (9H, s), 2.38−2.6 (2H, m), 3.17−3.27 (2H, m), 3.36−3.48 (2H, m), 4.43 (1H, m), 5.21 (1H, m), 6.74 (1H, m), 7.17 (1H, dd), 7.32 (1H, m), 7.38−7.48 (2H, m), 7.54 (1H, m), 7.87 (1H, d), 7.91 (1H, d); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.18, 28.25, 35.58, 38.75, 55.99, 80.63, 111.68, 112.35, 117.82, 120.58, 120.78, 122.82, 123.25, 123.91, 123.97, 127.15, 135.97, 155.55, 156.33, 156.43, 172.06; $[\alpha]^{25}_D = +6.2778$ ($c = 1$, $CHCl_3$). Anal. ($C_{23}H_{25}N_3O_4$) C, H, N.

***(S)*-3-[5-(1-*tert*-Butoxycarbonylamino-2-dibenzofuran-3-ylethyl)tetrazol-1-yl]propionitrile (23)**. To a mechanically stirred suspension of **22** (18.2 g, 44.7 mmol) and triphenylphosphine (29.3 g, 112 mmol) in ice-cold anhydrous MeCN (350 mL) were added from two separate addition funnels, first, diisopropyl azodicarboxylate (22 mL, 11.2 mmol) and, 2 min later, trimethylsilyl azide (16 mL, 11.8 mmol) over 20 min. The heterogeneous reaction mixture was allowed to warm to ambient temperature over 30 min then stirred for 14 h. To the mixture cooled to 0 °C was added, under stirring, a solution of $NaNO_2$ (3.1 g, 45 mmol) in H_2O (15 mL). After 30 min, a solution of ceric ammonium nitrate (25 g, 45 mmol) in H_2O (70 mL) was added over 10 min and the mixture was stirred for 20 min. The mixture was added to ice-cold H_2O (300 mL) and extracted with CH_2Cl_2 (1 L then 2 × 250 mL). The combined organic layers were washed with H_2O (2 × 250 mL), dried over $MgSO_4$, and concentrated in vacuo. The yellow solid residue was recrystallized from 2-propanol (350 mL). The solid was filtered, washed successively with cold 2-propanol (100 mL) and Et_2O:hexanes (1:1, 200 mL), and dried under high vacuum at 60 °C (15.67 g, 81%): mp 201−202 °C; IR (KBr) 2203, 1680, 1508, 1249, 1233, 1163 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 1.22 (9H, s), 2.97−3.18 (2H, m), 3.35−3.51 (2H, m), 4.62−4.72 (2H, m), 5.30 (1H, m), 7.29−7.42 (2H, m), 7.50 (1H, m), 7.62−7.71 (2H, m), 7.92 (1H, d), 8.05 (1H, d), 8.11 (1H, d); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 17.76, 27.91, 42.33, 45.81, 78.86, 111.6, 112.52, 117.63, 120.67, 120.98, 122.14, 123.03, 123.46, 124.62, 127.31, 136.97, 155.36, 155.51, 155.57, 156.29; $[\alpha]^{25}_D = -5.41$ ($c = 1$, DMSO). Anal. ($C_{23}H_{24}N_6O_3$) C, H, N.

***(S)*-3-[5-(1-Amino-2-dibenzofuran-3-ylethyl)tetrazol-1-yl]propionitrile Formate Salt (24).** A solution of **23** (15.6 g, 36.1 mmol) in formic acid (200 mL) was stirred at 48 °C for 50 min. The reaction mixture was concentrated in vacuo to remove most of the formic acid. The oil crystallized upon addition of Et_2O. More Et_2O was added and the mixture was cooled in an ice bath. The solid was filtered and dried under high vacuum at 50 °C to give **24** (13.46 g, 98%): mp 173−174 °C; IR (KBr) 2203, 1632, 1557, 1190 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.0−3.21 (2H, m), 4.58−4.73 (3H, m), 7.24 (1H, DD, $J = 0.99$, 7.9 Hz), 7.37 (1H, m), 7.48 (1H, m), 7.58 (1H, s), 7.66 (1H, d, $J = 8.1$ Hz), 8.02 (1H, d, $J = 7.9$ Hz), 8.09 (1H, d, $J = 7.0$ Hz), 8.15 (1H, s); $[\alpha]^{25}_D = +11.850$ ($c = 1$, DMSO). Anal. ($C_{19}H_{18}N_6O_3$) H, N; C: calcd, 60.31; found, 59.55.

***(S)*-1-[2-Dibenzofuran-3-yl-1-(1-(2-cyanoethyl)-1*H*-tetrazol-5-yl)ethylamino]methylphosphonic Acid Diphenyl Ester (25)**. To a mixture of **24** (11.7 g, 35 mmol) in EtOAc (200 mL) and CH_2Cl_2 (100 mL) cooled in an ice bath was added formaldehyde (37% aqueous; 5.2 mL, 68.5 mmol). The mixture was warmed to ambient temperature and stirred for 18 h, to give a homogeneous solution. EtOAc (200 mL) was added and the mixture was washed with H_2O (2 × 50 mL). The organic layer was dried over $MgSO_4$, concentrated, and dried under high vacuum to give the intermediate hexahydrotriazine 3-{5-[1-(3,5-bis{1-[1-(2-cyanoethyl)-1*H*-tetrazol-5-yl]-2-dibenzofuran-3-ylethyl}-[1,3,5]triazinan-1-yl)-2-dibenzofuran-3-ylethyl]tetrazol-1-yl}propionitrile as a glassy solid: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.64 (1H, m), 2.83 (1H, m), 3.18−3.5 (2H, m), 3.97−4.2 (2H, m), 4.48 (1H, m), 4.93 (1H, m), 6.85 (1H, d), 7.12 (1H, s), 7.29 (1H, m), 7.36−7.5 (2H, m), 7.68 (1H, d), 7.82 (1H, d).

To a stirred suspension of the above hexahydrotriazine (35 mmol) in a mixture of toluene (150 mL) and THF (75 mL) under N_2 atmosphere was added diphenyl phosphite (75% pure, 12 g, 39 mmol). The mixture was heated in an oil bath at 65 °C to dissolve most of the solids. The reaction was monitored by HPLC (column: YMC ODS; eluent: 70% MeCN: 30% 0.1% H_3PO_4 in 0.1 M $NaClO_4$; isocratic; flowrate = 1.5 mL/min). Some solid precipitated out of the reaction solution after 35 min of heating. After 70 min of stirring, the reaction mixture was cooled to ambient temperature and diluted with Et_2O (100 mL) and hexanes (100 mL). The precipitate was filtered and rinsed with Et_2O:hexanes (1:1). The solid was dried under high vacuum at 45 °C for 2 h to give **25** (13.07 g, 64%): mp 177−179 °C; IR (KBr) 2245, 1587, 1264, 1186, 947, 769 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.95−3.1 (1H, m), 3.12−3.52 (5H, m), 4.59−4.7 (2H, m), 4.76 (1H, m), 6.93−7.08 (4H, m), 7.09−7.2 (2H, m), 7.2−7.31 (6H, m), 7.37 (1H, m), 7.48 (1H, m), 7.6−7.7 (2H, m), 7.98 (1H, d), 8.08 (1H, d); ^{31}P NMR (DMSO-d_6, 121 MHz) δ 20.75; $[\alpha]^{25}_D = -3.8$ ($c = 1$, DMSO). Anal. ($C_{31}H_{27}N_6O_4P$) C, H, N.

***(S)*-1-[2-Dibenzofuran-3-yl-1-(1*H*-tetrazol-5-yl)ethylamino]methylphosphonic Acid Diphenyl Ester (26).** To a slurry of **25** (13 g, 24.5 mmol) in CH_2Cl_2 (300 mL) was added DBU (24.2 mL, 161 mmol). After 5.5 h, the clear solution was poured into a mixture of ice (100 g) and 1 N HCl (125 mL); then CH_2Cl_2 (200 mL) was added. The mixture was filtered through Celite to remove solid impurities. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. The solid residue was triturated with Et_2O: hexanes (2:1), filtered, and dried under high vacuum at 45 °C for 2 h then at ambient temperature for 16 h to give **26** (8.5 g, 66%): mp 141−142 °C; IR (KBr) 1589, 1205, 1185, 1160, 947, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.02−3.23 (3H, m), 3.30 (1H, m), 4.62 (1H, dd, $J = 5.5$, 8.7 Hz), 6.43 (2H, m), 6.98−7.21 (7H, m), 7.22 (2H, m), 7.43 (1H, m), 7.51 (1H, m), 7.79 (1H, d, $J = 7.9$ Hz), 7.88 (1H, d, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.37, 42.68 (d), 56.34 (d), 111.68, 112.34, 120.33, 120.39, 120.59, 120.83, 122.88, 123.35, 123.84, 125.86, 125.95, 127.24, 129.99, 130.12, 135.74, 149.33, 149.46, 149.66, 149.79, 156.32, 156.36, 157.63; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 19.43; $[\alpha]^{25}_D = -41.81$ ($c = 1$, $CHCl_3$); MS (ES^{1+}) m/z 526 (M + 1). Anal. ($C_{28}H_{24}N_5O_4P$) C, H, N.

***(S)*-1-[2-Dibenzofuran-3-yl-1-(1*H*-tetrazol-5-yl)ethylamino]methylphosphonic Acid (27)**. To a slurry of **26** (6.4 g, 12.2 mmol) in MeCN (60 mL) was added 1 N $NaHCO_3$ (115 mL). The solution was heated at 50 °C for 2 h while H_2O was added periodically to maintain homogeneity (up to 50 mL). The

solution was cooled to ambient temperature and extracted with EtOAc (3 × 75 mL). The aqueous layer was carefully acidified with 2 N HCl. The precipitate was filtered, washed with H_2O (2 × 50 mL), and dried under high vacuum at 50 °C for 2 h to give **27**: mp 260−261 °C dec; IR (KBr) 1605, 1498, 1207, 1149, 1084, 1020, 942, 753 cm^{-1}; ^1H NMR (DMSO-d_6, TFA, 300 MHz) δ 3.11−3.53 (3H, m), 3.82 (1H, dd, J = 4.0, 13.1 Hz), 5.26 (1H, dd, J = 5.5, 8.7 Hz), 7.00 (1H, d, J = 8.04 Hz), 7.27−7.39 (2H, m), 7.47 (1H, m), 7.64 (1H, d, J = 8.2 Hz), 7.96 (1H, d, J = 7.9 Hz), 8.05 (1H, d, J = 7.4 Hz); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 36.41, 41.27 (d), 54.25 (d), 111.58, 112.15, 121.01, 121.12, 122.65, 123.13, 123.17, 124.14, 127.56, 134.30, 154.45, 155.42, 155.55; ^{31}P NMR (DMSO-d_6, TFA, 300 MHz) δ 12.16; $[\alpha]^{25}_D$ = +55.31 (c = 0.9, NaOH 0.1 N); MS (ES^{1-}) m/z 372 (M − 1). Anal. ($C_{16}H_{16}N_5O_4P\cdot 3/4H_2O$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-[phosphonomethylamino]-propionic Acid Methyl Ester (28).** To a stirred suspension of **16** (57.5 g, 188 mmol) in EtOAc (300 mL) and H_2O (300 mL) was added powdered $NaHCO_3$ (19 g, 0.226 mmol). To this mixture cooled to 12 °C and vigorously stirred was added an aqueous solution of 37% aqueous formaldehyde (18.4 mL, 244 mmol). The slurry was stirred at ambient temperature for 15 h. A mixture of H_2O (600 mL), EtOAc (400 mL), and CH_2Cl_2 (50 mL) was added. The solid was filtered and collected. The remaining portion of product was obtained by drying the organic layer of the filtrate over $MgSO_4$, then concentrating it under reduced pressure. The solid fractions were combined to give the intermediate hexahydrotriazine 2-[3,5-bis(2-dibenzofuran-3-yl-1-methoxycarbonylethyl)-[1,3,5]triazinan-1-yl]-3-dibenzofuran-3-ylpropionic acid as a white solid: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.91−3.05 (2H, m), 3.58 (3H, s), 3.73 (1H, m), 3.84 (2H, s), 6.92 (1H, d), 7.21−7.31 (2H, m), 7.40 (1H, m), 7.50 (1H, d), 7.53 (1H, d), 7.76 (1H, d).

To a stirred solution of the above hexahydrotriazine (52.8 g, 180 mmol) in toluene (650 mL) under nitrogen atmosphere was added diphenyl phosphite (76% pure, 69.6 g, 220 mmol), followed by toluene (100 mL). The solution was stirred at 70 °C (preheated bath) for 2 h, then cooled to ambient temperature, and concentrated under reduced pressure to a volume of 300 mL. Hexanes (150 mL) were added, and the precipitate was filtered, then washed with Et_2O:hexanes. The solid was collected and dried under high vacuum at 40 °C to give **28** (78.93 g, 81%): mp 123−124 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.03−3.24 (3H, m), 3.43 (1H, m), 3.69 (3H, s), 3.80 (1H, m), 7.03−7.16 (7H, m), 7.16−7.30 (4H, m), 7.33 (1H, m), 7.45 (1H, m), 7.57 (1H, d, J = 8.1 Hz), 7.85 (1H, d, J = 8.1 Hz), 7.92 (1H, dd, J = 0.74 and 7.72 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.82, 43.37 (d), 63.50 (d), 111.67, 112.36, 120.54, 120.60, 120.65, 122.76, 123.08, 124.06, 125.23, 127.04, 129.76, 136.50, 150.09, 150.22, 156.34, 156.42, 173.89; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 18.60; $[\alpha]^{25}_D$ = +10.17 (c = 1, $CHCl_3$); MS (ES^{1+}) m/z 515 (M + 1). Anal. ($C_{29}H_{26}NO_6P$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-[phosphonomethylamino]-propionic Acid (29).** A stirred suspension of **28** (78.8 g, 153 mmol) in AcOH (670 mL) and 9 N HCl (2.5 L) was heated to 100 °C (internal temperature) for 2 h. The reaction mixture was cooled by addition of ice-cold H_2O (2 L). The solid was filtered, then washed successively with H_2O (1L) and Et_2O (1L). The solid was slowly added to a solution of $NaHCO_3$ (51.4 g, 612 mmol) in H_2O (1.5 L). The turbid solution was extracted with EtOAc (4 × 400 mL). The aqueous layer was clarified by filtration through microfiber glass. To this stirred solution were cautiously added 2 N HCl (400 mL) and Et_2O to control foaming. The gelatinous white precipitate was filtered, collected, and then heated at 70 °C in H_2O (1 L). The white powder was filtered, washed with H_2O (5 × 500 mL), and dried at 50 °C under high vacuum for 18 h to yield **29** (50.2 g, 94%): mp >250 °C; ^1H NMR (DMSO-d_6, TFA, 300 MHz) δ 3.19−3.34 (3H, m), 3.48−3.55 (1H, m), 4.39−4.44 (1H, m), 7.29 (1H, d, J = 8.0 Hz), 7.36−7.41 (1H, m), 7.50 (1H, t, J = 7.2 Hz), 7.61 (1H, s), 7.68 (1H, d, J = 8.2 Hz), 8.06−8.12 (2H, m); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 34.93, 41.72 (d, J = 142 Hz), 60.88 (d, J = 7 Hz), 111.62, 112.53, 121.04, 122.64, 123.16, 123.33, 124.50, 127.53, 134.81, 155.51, 155.6, 169.21; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 12.13. Anal. ($C_{16}H_{13}NO_6P\cdot NaOH$) C, H, N.

The enantiomeric purity of **29** was determined as follows:[38] racemic 3-dibenzofuran-3-yl-2-[phosphonomethylamino]propionic acid (prepared from **13**) (7 mg) and *(R)*-(+)-1-(1-naphthyl)-ethylamine (100 μL) were mixed for 2 min then diluted with methanol-d_4 (0.5 mL). NMR analysis showed a 43-Hz baseline separation of the two equally intense peaks corresponding to the enantiotopic methine protons appearing at 3.725 ppm (*S* enantiomer) and 3.638 ppm (R enantiomer). When this methodology was applied to the sample of **29** obtained by enzymatic resolution, peak integration indicated an enantiomeric of 99%.

***(S)*-3-Dibenzofuran-3-yl-2-[phosphonomethylamino]-propionic acid 2-(4-biphenylyl)ethylamide (30)**: ^1H NMR (DMSO-d_6, TFA, 300 MHz) δ 2.50−2.62 (2H, m), 2.75−3.26 (5H, m), 3.36−3.42 (2H, m), 6.97 (2H, d), 7.18 (1H, d), 7.26−7.53 (10H, m), 7.56 (1H, d), 8.07 (2H, dd); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 34.29, 35.84, 42.70, 62.00 (d), 111.73, 112.60, 121.14, 122.90, 123.28, 123.57, 124.73, 126.45, 126.52, 127.25, 127.64, 128.91, 129.13, 134.74, 138.18, 138.34, 140.00, 155.77, 166.14; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 12.07; MS (ES^{1-}) m/z 527 (M − 1). Anal. ($C_{30}H_{27}N_2O_5PNa_2\cdot 5/4H_2O$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-[phosphonomethylamino]-propionic acid 2-phenethylamide (31)**: mp > 200 °C dec; ^1H NMR (DMSO-d_6, TFA, 500 MHz) δ 2.39−2.48 (1H, m), 2.50−2.57 (1H, m), 2.96−3.06 (2H, m), 3.15−3.22 (2H, m), 3.28−3.37 (2H, m), 4.17 (1H, dd, J = 5.4 and 8.9 Hz), 6.93−6.94 (2H, m), 7.02−7.09 (3H, m), 7.14−7.16 (1H, m), 7.32−7.35 (1H, m), 7.41−7.47 (1H, m), 7.45 (1H,s), 7.61 (1H, d, J = 8.2 Hz), 7.99 (1H, d, J = 7.9 Hz), 8.05 (1H, d, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6, TFA, 126 MHz) δ 35.22, 36.42, 40.57, 42.19 (d, J_{C-P} = 143.9 Hz), 62.59 (d, J_{C-P} = 7.9 Hz), 112.07, 113.11, 121.42, 123.38, 123.59, 124.04, 125.13, 126.60, 127.94, 128.69, 128.96, 135.12, 139.46, 156.27, 156.34, 166.57; ^{31}P NMR (DMSO-d_6, TFA, 202 MHz) δ 11.81; MS (ES^{1-}) m/z 451 (M − 1). Anal. ($C_{24}H_{23}N_2O_5PNa_2\cdot 3/2NaOH$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-[phosphonomethylamino]-propionic acid *(S)*-phenylalaninamide (32)**: mp > 200 °C dec; ^1H NMR (DMSO-d_6, TFA, 500 MHz) δ 2.64−2.81 (3H, m), 3.06−3.10 (1H, m), 3.22−3.26 (1H, m), 3.32−3.36 (1H, m), 4.20−4.23 (1H, m), 4.50−4.53 (1H, m), 7.08−7.20 (6H, m), 7.31−7.34 (1H, m), 7.42−7.46 (1H, m), 7.50 (1H, s), 7.59 (1H, d, J = 8.2 Hz), 7.95 (1H, d, J = 7.9 Hz), 8.02−8.04 (1H, m); ^{13}C NMR (DMSO-d_6, TFA, 126 MHz) δ 36.61, 37.50, 42.42 (d, J_{C-P} = 144 Hz), 54.08, 62.81, 113.25, 121.38, 121.46, 123.39, 123.54, 124.17, 125.23, 127.23, 127.88, 128.78, 129.71, 134.96, 137.66, 156.40, 166.54, 172.35; ^{31}P NMR (DMSO-d_6, TFA, 202 MHz) δ 11.77. Anal. ($C_{25}H_{22}N_2O_7PNa_3\cdot NaOH$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-[phosphonomethylamino]-propionic acid *(S)*-leucinamide (33)**: mp 233−235 °C dec; ^1H NMR (DMSO-d_6, TFA, 300 MHz) δ 0.77 (3H, d, J = 5.5 Hz), 0.87 (3H, d, J = 5.6 Hz), 1.45−1.57 (3H, m), 3.05 (2H, d, J = 13.6 Hz), 3.25−3.28 (2H, m), 4.18−4.21 (1H, m), 4.34−4.38 (1H, m), 7.3 (1H, d, J = 8.0 Hz), 7.34−7.39 (1H, m), 7.46−7.51 (1H, m), 7.6 (1H, s), 7.66 (1H, d, J = 8.2 Hz), 8.03 (1H, d, J = 7.9 Hz), 8.09 (1H, d, J = 7.2 Hz); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 20.83, 22.59, 23.98, 35.70, 41.57 (d, J_{C-P} = 144 Hz), 41.57, 50.40, 61.26 (d, J_{C-P} = 6.5 Hz), 111.49, 112.65, 120.81, 120.90, 122.58, 122.96, 123.36, 124.64, 127.32, 134.18, 155.56, 166.14, 172.86; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 12.23. Anal. ($C_{21}H_{27}N_2O_7P\cdot 1/4H_2O$) C, H; N: calcd, 6.16; found, 5.59.

***(S)*-3-Dibenzofuran-3-yl-2-[phosphonomethylamino]-propionic acid β-alaninamide (34)**: mp >275 °C dec; ^1H NMR (DMSO-d_6, TFA, 300 MHz) δ 2.16−2.19 (1H, m), 2.26−2.30 (1H, m), 3.09 (2H, d, J = 13.6 Hz), 3.20 (3H, s), 3.36−3.37 (1H, m), 4.21 (1H, s), 7.19 (1H, d, J = 6.7 Hz), 7.30−7.35 (1H, m), 7.40−7.50 (1H, m), 7.51 (1H, s), 7.61 (1H, d, J = 7.9 Hz), 8.00 (1H, d, J = 7.4 Hz), 8.04 (1H, d, J = 6.6 Hz); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 33.64, 35.18, 36.35, 42.14 (d, J_{C-P} = 143.8 Hz), 62.33 (d, J_{C-P} = 7.2 Hz), 112.06, 113.08, 121.36, 121.43, 123.30, 123.52, 124.00, 125.06, 127.87, 135.04,

156.21, 156.29, 166.75, 173.06; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 11.85. Anal. (75% $C_{19}H_{18}N_2O_7PNa_3$ + 25% $C_{19}H_{19}N_2O_7PNa_2$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-[phosphonomethylamino]-propionic acid glycinamide (35)**: mp 253−255 °C dec; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 3.02−3.20 (2H, m), 3.26−3.42 (2H, m), 3.70−3.84 (2H, m), 4.31 (1H, dd, J = 5.2 and 8.2 Hz), 7.26 (1H, d, J = 8.0 Hz), 7.38 (1H, t, J = 7.5 Hz), 7.47−7.52 (1H, m), 7.57 (1H, s), 7.68 (1H, d, J = 8.2 Hz), 8.05 (1H, d, J = 7.9 Hz), 8.11 (1H, d, J = 7.6 Hz); ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 12.04; MS (ES^{1-}) m/z 405 (M − 1). Anal. ($C_{18}H_{19}N_2O_7P\cdot HCl$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-[phosphonomethylamino]-propionic acid *(S)*-(3-dibenzofuran-3-yl)alaninamide (36)**: IR (KBr) 1604, 1205, 1128, 985 cm^{-1}; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 2.92 (2H, dd), 3.06 (1H, dd), 3.24−3.38 (3H, m), 4.29 (1H, t), 4.57 (1H, dd), 7.14 (1H, d), 7.00 (1H, d), 7.31−7.43 (2H, m), 7.45−7.50 (4H, m), 7.60 (2H, dd), 7.87 (1H, d), 7.95−7.97 (2H, m), 8.03 (1H, d); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 36.09, 37.20, 41.46, 42.61, 54.08, 62.11 (d), 111.79, 112.33, 122.82, 114.08, 120.08, 121.12, 121.19, 122.44, 122.97, 123.17, 123.26, 123.72, 123.76, 124.55, 124.84, 127.43, 127.61, 134.61, 137.40, 155.89, 166.39, 171.86; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 11.81; MS (ES^{1-}) m/z 585 (M − 1). Anal. ($C_{31}H_{24}N_2O_8PNa_3$ + 14% inorganic byproduct) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-(3-naphthalen-1-yl-1-dimethylphosphonopropylamino)propionic Acid Methyl Ester (37a,b)**. To a stirred suspension of **16** (0.3 g, 1.00 mmol) in CH_2Cl_2 (3.5 mL) under nitrogen was added triethylamine (0.14 mL, 1.00 mmol), followed by 1-naphthyl-3-propionaldehyde (0.2 g, 1.1 mmol) and Na_2SO_4 (0.6 g, 4 mmol). The heterogeneous mixture was stirred for 1 h and filtered directly into another flask, while washing the cake with CH_2Cl_2 (2 mL). The filtrate was maintained under nitrogen while being cooled with an ice bath. To the cold solution was added trimethyl phosphite (0.19 mL, 1.6 mmol), followed by $BF_3\cdot Et_2O$ (0.14 mL, 1.1 mmol). The reaction mixture was stirred at ambient temperature for 14 h. The solution was diluted with CH_2Cl_2 (5 mL) and washed with water (10 mL). The organic layer was dried over $MgSO_4$ and concentrated. The diastereomers were separated by flash chromatography on SiO_2 (150 g), eluting with EtOAc:hexanes (7:3). The less polar diastereomer (**37a**) was obtained as a white solid (0.225 g, 47%). The more polar diastereomer (**37b**) was obtained as a pale yellow oil (0.169 g, 31%).

37a: mp 112−113 °C; IR (CH_2Cl_2) 1734, 1239, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.97 (1H, m), 2.25 (1H, m), 3.00−3.42 (5H, m), 3.61 (3H, d), 3.65 (3H, d), 3.66 (3H, s), 4.17 (1H, m), 7.22 (1H, dd), 7.28−7.37 (3H, m), 7.39−7.58 (5H, m), 7.69 (1H, d), 7.80−7.94 (3H, m), 8.02 (1H, d); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.31 (d), 31.52, 40.10, 51.93, 52.68, 52.74, 53.15, 53.26, 55.22, 61.53, 111.68, 112.43, 120.44, 120.54, 122.73, 122.96, 123.69, 124.03, 124.16, 125.50, 125.93, 125.98, 126.83, 127.00, 128.75, 131.73, 133.86, 136.50, 137.45, 156.33, 156.40, 174.38; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 28.9; $[\alpha]^{25}_D$ = −3.00 (c = 1, $CHCl_3$). Anal. ($C_{31}H_{32}NO_6P$) C, H, N.

37b: ^{1}H NMR ($CDCl_3$ + 2 drops DMSO-d_6, 300 MHz) δ 1.69 (1H, m), 1.92 (1H, m), 2.65−2.80 (2H, m), 2.86 (1H, m), 2.97−3.11 (2H, m), 3.48−3.70 (10H, m), 6.91 (1H, d), 7.02−7.34 (8H, m), 7.39 (1H, d), 7.48 (1H, d), 7.61−7.82 (4H, m).

***(S)*-3-Dibenzofuran-3-yl-2-(3-naphthalen-1-yl-1-dimethylphosphonopropylamino)propionic Acid (38a).** To a stirred solution of **37a** (0.24 g, 0.44 mmol) in a mixture of THF (3 mL) and methanol (0.5 mL) was added 1 N NaOH (0.88 mL, 0.88 mmol). After 3 h, 1 N HCl (0.75 mL) was added. The organic solvents were evaporated in vacuo and the residue was diluted CH_2Cl_2 (10 mL) and water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give **38a** as a glassy solid (0.20 g) which was used directly in the next step. Partial hydrolysis of the dimethyl phosphonate is sometimes observed as a side reaction.

***(S)*-3-Dibenzofuran-3-yl-2-(3-naphthalen-1-yl-1-phosphonopropylamino)propionic Acid Trisodium Salt (40a).** To a stirred solution of **38a** (0.18 g, 0.339 mmol) in CH_2Cl_2 (0.5 mL) was added TMSBr (0.35 mL, 2.7 mmol). The solution was stirred under nitrogen atmosphere for 5 h then concentrated under reduced pressure at ambient temperature. Water (3 mL) was added to the yellow foam and the solution was placed in the refrigerator (5 °C) for 14 h. The white solid was filtered, washed with water (3 mL), and dried under high vacuum at 65 °C for 1 h. The white solid (0.16 g) was dissolved in 1 N NaOH (1 mL, 1 mmol) and placed on a column filled with MCI CHP-20 gel (75−150 μL). The product was eluted with water (20 mL), then with a gradient of methanol (5% to 40%) in water. The pure fractions, according to HPLC analysis (column: YMC ODS; eluent: 65% MeCN:35% 0.1% H_3PO_4 in $NaClO_4$ 0.1 M; isocratic; flowrate = 1.5 mL/min), were combined and lyophilized to provide a white solid (0.09 g, 47%): mp 275−280 °C dec; IR (KBr) 1635, 1597, 1204, 1126, 1078 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 1.82 (1H, m), 2.17 (1H, m), 2.64−3.26 (5H, m), 3.9 (1H, s), 6.74 (1H, m), 6.88−7.72 (12H, m), 7.8 (1H, m); ^{13}C NMR (D_2O: DMSO-d_6, 75 MHz) δ 29.42, 29.95, 36.61, 57.08 (d, J = 127.5 Hz), 62.88, 112.30, 112.63, 121.61, 121.79, 123.58,123.90, 124.23, 124.36, 124.88, 126.45, 126.61, 126.86, 127.06, 127.52, 128.21, 129.47, 131.91, 134.22, 135.96, 137.83, 156.46, 156.50, 164.84, 174.05; MS (ES^{1-}) m/z 502 (free acid, M − 1); $[\alpha]^{25}_D$ = +51.47 (c = 0.76, H_2O). Anal. ($C_{28}H_{23}NO_6PNa_3$) C, H, N.

The other analogues **40b**−**v** were prepared similarly.

40b: mp 270−273 °C dec; IR (KBr) 1635, 1597, 1204, 1077 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 1.32 (1H, m), 1.76 (1H, m), 2.62−2.96 (4H, m), 3.15 (1H, m), 3.67 (1H, m), 6.78 (1H, d), 6.9−7.35 (10H, m), 7.42−7.58 (2H, m), 7.66 (1H, m); ^{13}C NMR (D_2O, 75 MHz) δ 29.33, 29.63, 38.06, 58.41 (d), 65.17, 112.08, 112.50, 121.53, 121.63, 123.44, 123.54, 123.88, 124.11, 124.56, 125.84, 126.16, 126.36, 126.78, 127.26, 127.89, 129.34, 131.67, 133.95, 136.08, 138.04, 156.23, 156.31, 175.14; ^{31}P NMR (D_2O, 121 MHz) δ 12.38; MS (ES^{1-}) m/z 502 (free acid, M − 1). Anal. ($C_{28}H_{23}NO_6PNa_3$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-[3-(2,3-dimethoxyphenyl)-1-phosphonopropylamino]propionic acid (40c):** mp 211−213 °C; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 2.03−2.18 (2H, m), 2.78−2.84 (2H, m), 3.25−3.36 (2H, m), 3.52−3.57 (1H, m), 3.70 (3H, s), 3.77 (3H, s), 4.76−4.8 (1H, m), 6.78 (1H, d, J = 7.2 Hz), 6.88 (1H, d, J = 7.7 Hz), 6.95−7.00 (1H, m), 7.3 (1H, d, J = 7.9 Hz), 7.39 (1H, t, J = 7.4 Hz), 7.48−7.53 (1H, m), 7.61 (1H, s), 7.68 (1H, d, J = 8.2 Hz), 8.08−8.13 (2H, m); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 26.27, 29.6, 35.98, 54.3 (d, J = 149 Hz), 55.49, 60.13, 60.22, 111.05, 111.64, 112.52, 121.05, 121.28, 122.63, 123.17, 123.33, 123.86, 124.42, 127.54, 134.10, 135.01, 146.63, 152.44, 155.51, 155.61, 169.52; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 15.35; MS (ES^{1-}) m/z 512 (M − 1). Anal. ($C_{26}H_{28}NO_8P$) C, H, N.

40d (contains 20% of **40c**): mp >250 °C; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 1.9−2.15 (2H, m), 2.55−2.7 (1H, m), 2.75−2.85 (1H, m), 3.23−3.41 (2H, m), 3.55−3.62 (1H, m), 3.67 (3H, s), 3.75 (3H, s), 4.44−4.48 (1H, m), 6.72−6.75 (1H, m), 6.85−6.89 (1H, m), 6.93−7.00 (1H, m), 7.29 (1H, d, J = 7.9 Hz), 7.39 (1H, t, J = 7.5 Hz), 7.48−7.53 (1H, m), 7.60 (1H, s), 7.68 (1H, d, J = 8.2 Hz), 8.07−8.12 (2H, m); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 26.23, 28.32, 35.2, 53.54 (d, J = 146 Hz), 55.39, 59.53, 60.08, 110.97, 111.57, 112.30, 120.99, 121.2, 122.61, 123.09, 123.26, 123.83, 124.33, 127.48, 134.00, 134.88, 146.50, 152.35, 155.47, 155.57, 169.36; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 15.24; MS (ES^{1-}) 512 (M − 1). Anal. ($C_{26}H_{25}NO_8PNa_3$) C, H, N.

3-Dibenzofuran-3-yl-2-(*S*)-[3-(3,4-dimethoxyphenyl)-1-phosphonopropylamino]propionic acid (40e): mp >250 °C; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 1.99−2.19 (2H, m), 2.75 (1H, t, J = 7.7 Hz), 3.25−3.32 (2H, m), 3.5−3.56 (1H, m), 3.7 (3H, s), 3.73 (3H, s), 4.78 (1H, dd, J = 5.0, 8.0 Hz), 6.70−6.72 (1H, m), 6.78−6.79 (1H, m), 6.84 (1H, d, J = 8.2 Hz), 7.29 (1H, d, J = 8.0 Hz), 7.39 (1H, t, J = 7.4 Hz), 7.48−7.53 (1H, m), 7.61 (1H, s), 7.68 (1H, d, J = 8.2 Hz), 8.08−8.13 (2H, m); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 30.67, 31.39, 36.06, 54.02 (d, J = 145 Hz), 55.45, 55.55, 60.30, 111.73, 112.01, 112.32, 112.59, 120.27, 121.15, 122.75, 123.27, 123.43, 124.50, 127.64, 133.12, 135.08, 147.32, 148.77, 155.62, 155.72, 169.54; ^{31}P

NMR (DMSO-d_6, TFA, 121 MHz) δ 15.3. Anal. (75% $C_{26}H_{26}NO_8PNa_2$ + 25% $C_{26}H_{25}NO_8PNa_3$) C, H, N.

40f: ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 2.05−2.15 (2H, m), 2.57−2.75 (2H, m), 3.23−3.30 (2H, m), 3.54 (1H, dd, J = 4.8, 14.0 Hz), 3.67 (3H, s), 3.70 (3H, s), 4.48 (1H, dd, J = 5.2, 9.2 Hz), 6.65−6.68 (1H, m), 6.76−6.81 (2H, m), 7.28 (1H, d, J = 8.83 Hz), 7.35−7.40 (1H, m), 7.47−7.52 (1H, m), 7.61 (1H, s), 7.67 (1H, d, J = 8.1 Hz), 8.06 (1H, d, J = 8.1 Hz), 8.10 (1H, d, J = 7.0 Hz); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 29.25, 31.41, 35.2, 53.34 (d, J = 144 Hz), 55.2, 55.29, 59.55, 111.54, 111.74, 111.98, 112.32, 120.03, 120.97, 122.6, 123.08, 123.25, 124.36, 127.47, 132.94, 134.85, 147.14, 148.62, 155.47, 155.56, 169.35; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 15.11. Anal. (50% $C_{26}H_{25}NO_8PNa_3$ + 50% $C_{26}H_{26}NO_8PNa_2$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-[3-(3,4,5-trimethoxyphenyl)-1-phosphonopropylamino]propionic acid trisodium salt (40g):** mp >250 °C; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 2.02−2.56 (2H, m), 2.77 (2H, t, J = 7.6 Hz), 3.25−3.34 (2H, m), 3.53 (1H, dd, J = 5.0, 14.5 Hz), 3.60 (3H, s), 3.74 (6H, s), 4.80 (1H, dd, J = 5.1, 8.0 Hz), 6.49 (2H, s), 7.28−7.31 (1H, m), 7.34−7.39 (1H, m), 7.45−7.51 (1H, m), 7.61−7.66 (2H, m), 8.05−8.10 (2H, m); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 30.21, 31.81, 35.86, 53.68 (d, J = 145 Hz), 55.53, 59.70, 60.09, 105.46, 111.48, 112.43, 120.86, 122.61, 123.00, 123.27, 124.32, 127.38, 134.82, 135.77, 136.16, 152.78, 155.49, 155.58, 169.33; ^{31}P NMR (DMSO-d_6, 121 MHz) δ 15.24. Anal. (50% $C_{27}H_{27}NO_9PNa_3$ + 50% $C_{27}H_{28}NO_9PNa_2$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-[3-(3,4,6-trimethoxyphenyl)-1-phosphonopropylamino]propionic acid trisodium salt (40i):** mp >250 °C; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 1.8−2.0 (1H, m), 2.05−2.20 (1H, m), 2.66−2.76 (2H, m), 3.01−3.07 (1H, m), 3.21−3.28 (1H, m), 3.54−3.73 (10H, m), 4.67−4.71 (1H, m), 6.61 (1H, s), 6.78 (1H, s), 7.29 (1H, d, J = 8.0 Hz), 7.36 (1H, t, J = 7.4 Hz), 7.45−7.50 (1H, m), 7.60−7.65 (2H, m), 7.99 (1H, d, J = 7.9 Hz), 8.06(1H, d, J = 7.6 Hz); ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 15.67; ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 26.04, 29.88, 36.44, 38.57, 55.17 (d, J = 143.2 Hz), 55.78, 55.99, 56.26, 61.03, 98.35, 111.57, 112.46, 114.64, 120.30, 120.79, 120.94, 122.32, 123.07, 123.41, 124.50, 127.37, 135.81, 142.30, 147.76, 151.20, 155.50, 155.54, 157.82, 170.75;. Anal. (90% $C_{27}H_{28}NO_9PNa_2$ + 10% $C_{27}H_{27}NO_9PNa_3$) C, H, N.

40j: mp >250 °C; ^{1}H NMR (DMSO-d_6, TFA, 500 MHz) δ 1.92−2.13 (2H, m), 2.56−2.62 (1H, m), 2.69−2.75 (1H, m), 3.2−3.30 (2H, m), 3.55 (1H, dd, J = 4.7, 13.8 Hz), 3.65 (3H, s), 3.68 (3H, s), 3.73 (3H, s), 4.38 (1H, dd, J = 4.8, 9.3 Hz), 6.61 (1H, s), 6.73 (1H, s), 7.29 (1H, dd, J = 1.1, 8.0 Hz), 7.37−7.40 (1H, m), 7.49−7.52 (1H, m), 7.59 (1H, s), 7.68 (1H, d, J = 8.2 Hz), 8.07 (1H, d, J = 7.9 Hz), 8.10−8.12 (1H, m); ^{31}P NMR (DMSO-d_6, TFA, 202 MHz) δ 14.82; ^{13}C NMR (DMSO-d_6, TFA, 125 MHz) δ 26.20, 27.65, 35.56, 53.68 (d, J = 143.7 Hz), 55.86, 56.05, 56.38, 59.60, 98.56, 111.68, 112.38, 114.79, 119.64, 121.11, 122.65, 123.21, 123.38, 124.44, 127.58, 135.28, 142.48, 148.11, 151.27, 155.51, 155.66, 169.58. Anal. (50% $C_{27}H_{27}NO_9PNa_3$ + 50% $C_{27}H_{28}NO_9PNa_2$) H, N; C: calcd, 54.20; found, 54.67.

***(S)*-3-Dibenzofuran-3-yl-2-[3-(2,3,4-trimethoxyphenyl)-1-phosphonopropylamino]propionic acid trisodium salt (40k):** mp >250 °C; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 1.98−2.49 (2H, m), 2.74 (2H, t, J = 7.8 Hz), 3.25−3.38 (2H, m), 3.53 (1H, dd, J = 4.9, 13.3 Hz), 3.71 (3H, s), 3.73 (3H, s), 3.76 (3H, s), 4.77 (1H, dd, J = 5.0, 8.0 Hz), 6.68 (1H, d, J = 8.6 Hz), 6.85 (1H, d, J = 8.5 Hz), 7.29 (1H, d, J = 8.0 Hz), 7.35−7.40 (1H, m), 7.46−7.51 (1H, m), 7.61 (1H, s), 7.66 (1H, d, J = 8.2 Hz), 8.06−8.11 (2H, m); ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 15.48; ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 26.08, 29.56, 35.92, 54.10 (d, J = 145 Hz), 55.57, 60.08, 60.15, 60.64, 107.59, 111.55, 112.49, 120.94, 122.65, 123.08, 123.32, 123.54, 124.38, 126.11, 127.44, 134.90, 141.82, 151.35, 152.03, 155.52, 155.62, 169.39;. Anal. (50% $C_{27}H_{28}NO_9PNa_2$ + 50% $C_{27}H_{27}NO_9PNa_3$) C, H, N.

40l: mp >250 °C; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 1.85−2.15 (2H, m), 2.5−2.62 (1H, m), 2.65−2.80 (1H, m), 3.23−3.30 (2H, m), 3.52−3.58 (1H, m), 3.68 (3H, s), 3.72 (6H, s), 4.39−4.43 (1H, m), 6.66 (1H, d, J = 8.6 Hz), 6.78 (1H, d, J = 8.5 Hz), 7.30 (1H, d, J = 7.9 Hz), 7.39 (1H, t, J = 7.5 Hz), 7.48−7.53 (1H, m), 7.61 (1H, s), 7.69 (1H, d, J = 8.1 Hz), 8.07−8.13 (2H, m); ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 15.41; ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 26.13, 28.54, 35.44, 53.66 (d, J = 143 Hz), 55.68, 59.68, 60.12, 60.70, 107.71, 111.60, 112.30, 121.02, 122.54, 123.13, 123.28, 123.51, 124.38, 126.18, 127.50, 135.18, 141.74, 151.22, 151.93, 155.47, 155.56, 169.65. Anal. (50% $C_{27}H_{27}NO_9PNa_3$ + 50% $C_{27}H_{28}NO_9PNa_2$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-(3-quinolin-8-yl-1-phosphonopropylamino)propionic acid trisodium salt (40m):** mp 286−287 °C; IR (KBr) 1600, 1204, 1128, 982, 796, 744 cm^{-1}; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 2.20−2.28 (2H, m), 3.32−3.57 (5H, m), 4.80 (1H, t), 7.28−8.15 (11H, m), 9.01 (1H, d), 9.09 (1H, d); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 27.87, 29.64, 36.34, 54.02 (d), 60.53, 111.93, 113.06, 121.32, 122.17, 123.11, 123.46, 123.71, 124.90, 127.84, 128.13, 129.07, 129.50, 133.89, 134.37, 135.06, 138.87, 145.39, 146.84, 155.95, 156.03, 169.89; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 14.02; $[\alpha]^{25}_D$ = +28.60 (c = 1.05, H_2O); MS (ES^{1-}) m/z 503 (M − 1). Anal. (70% $C_{27}H_{22}N_2O_6PNa_3$ + 30% $C_{27}H_{23}N_2O_6PNa_2$) C, H, N.

40n: mp >300 °C; IR (KBr) 1603, 1198, 775, 757 cm^{-1}; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 2.17−2.25 (2H, m), 3.20−3.59 (5H, m), 4.53 (1H, dd), 7.23−8.17 (11H, m), 9.04 (1H, d), 9.17 (1H, d); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 27.78, 28.35, 35.41, 53.21 (d, J = 141.9 Hz), 59.87, 111.86, 112.64, 121.23, 121.27, 122.13, 122.95, 123.38, 123.59, 124.68, 127.77, 128.10, 129.04, 129.40, 133.96, 134.12, 135.16, 136.78, 138.61, 145.50, 146.75, 155.81, 155.92, 169.77; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 14.39; $[\alpha]^{25}_D$ = −10.00 (c = 0.95, H_2O); MS (ES^{1-}) m/z 503 (M − 1). Anal. ($C_{27}H_{22}N_2O_6PNa_3 \cdot H_2O$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-(4-amino-1-phosphonobutylamino)propionic acid trisodium salt (40o):** mp 209−211 °C; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 1.21 (4H, s), 1.76−1.88 (2H, m), 2.75 (2H, s), 3.17−3.32 (2H, m), 3.5−3.58 (1H, m), 4.76−4.8 (1H, m), 7.3 (1H, d, J = 8.0 Hz), 7.36−7.41 (1H, m), 7.48−7.53 (1H, m), 7.62 (1H, s), 7.68 (1H, d, J = 8.1 Hz), 7.7−7.8 (1H, m), 8.07−8.12 (2H, m); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 22.84, 26.42, 27.98, 35.85, 38.14, 54.22 (d, J = 145 Hz), 60.17, 111.55, 112.50, 120.94, 122.59, 123.10, 123.28, 124.39, 127.47, 134.83, 155.46, 155.56, 169.38; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 15.07. MS (ES^{1-}) m/z 419 (M − 1). Anal. (50% $C_{20}H_{24}N_2O_6PNa$ + 50% $C_{20}H_{23}N_2O_6PNa_2$) C, H, N.

40p: mp >250 °C; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 1.35−1.6 (4H, m), 1.75−1.9 (2H, m), 2.15−2.8 (2H, m), 3.22−3.3 (2H, m), 3.58 (1H, dd, J = 4.8, 13.6 Hz), 4.47−4.52 (1H, m), 7.3 (1H, d, J = 8.0 Hz), 7.38 (1H, t, J = 7.5 Hz), 7.47−7.53 (1H, m), 7.61 (1H, s), 7.67 (1H, d, J = 8.2 Hz), 8.06−8.11 (2H,m); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 23.15, 26.72, 26.78, 26.92, 35.40, 38.44, 38.53, 53.76 (d, J = 144 Hz), 59.77, 111.81, 112.59, 121.23, 122.91, 123.35, 123.53, 124.64, 127.74, 135.08, 155.76, 155.86,169.64; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 15.06; MS (ES^{1-}) m/z 419 (M − 1). Anal. (25% $C_{20}H_{23}N_2O_6PNa_2$ + 75% $C_{20}H_{24}N_2O_6PNa$) C, N; H: calcd, 5.34; found, 4.74.

***(S)*-3-Dibenzofuran-3-yl-2-(4-amino-1-phosphonopropylamino)propionic acid trisodium salt (40q):** mp >300 °C; IR (KBr) 1633, 1603, 1206, 1127, 1080, 743 cm^{-1}; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 1.72−2.06 (4H, m), 2.51−2.64 (2H, m), 3.25−3.33 (2H, m), 3.53 (1H, dd), 4.77 (1H, dd), 7.27−7.37 (2H, m), 7.46 (1H, t), 7.61−7.63 (1H, m), 8.01−8.07 (2H, m); ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 14.157; ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 24.78, 26.28, 36.42, 54.59, 60.84, 112.07, 113.21, 121.43, 123.33, 123.60, 123.93, 125.03, 127.97, 135.22, 156.16, 156.26, 169.99; $[\alpha]^{25}_D$ = +15.644 (c = 1.1, H_2O). Anal. ($C_{19}H_{20}N_2O_6PNa_3$) C, H, N.

40r: mp >300 °C; IR (KBr) 1602, 1583, 1457, 1205, 1129, 1104, 975 cm^{-1}; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 1.64−2.0 (4H, m), 2.7−2.87 (2H, s), 3.17−3.42 (2H, m), 3.61 (1H, dd), 4.46 (1H, dd), 7.28−7.48 (2H, m), 7.47 (1H, t), 7.50−7.65 (2H, m), 8.06 (2H, t); ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 14.41; ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 24.61, 24.79, 35.49, 53.46, 59.90. 59.95, 111.92, 112.71, 121.28, 123.04,

123.44, 123.71, 124.81, 127.81, 135.31, 155.94, 156.03, 169.83; $[\alpha]^{25}_D = +7.3939$ ($c = 1$, H_2O). Anal. ($C_{19}H_{20}N_2O_6PNa_3$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-(4-methyl-1-phosphonopentylamino)propionic acid trisodium salt (40s):** mp >250 °C; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 0.84 (3H, d, $J = 3.9$ Hz), 0.86 (3H, d, $J = 3.9$ Hz), 1.37−1.53 (3H, m), 1.72−1.9 (2H, m), 3.15−3.32 (2H, m), 3.51−3.57 (1H, m), 4.80 (1H, dd, $J = 5.0$, 8.0 Hz), 7.3 (1H, d, $J = 7.9$ Hz), 7.36−7.41 (1H, m), 7.47−7.53 (1H, m), 7.62−7.69 (2H, m), 8.09 (2H, t, $J = 8.0$ Hz); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 22.09, 22.11, 26.62, 27.33, 34.65 (d, $J = 5.1$ Hz), 35.93, 54.9 (d, $J = 144.1$ Hz), 60.36, 111.60, 112.49, 120.98, 122.60, 123.13, 123.35, 124.40, 127.49, 135.10, 155.52, 155.61, 157.62, 158.11, 158.61, 159.11, 169.48; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 15.3. Anal. (40% $C_{21}H_{24}NO_6PNa_2$ + 60% $C_{21}H_{23}NO_6PNa_3$) C, H, N.

***(S)*-3-Dibenzofuran-3-yl-2-(1-phosphonoethylamino)-propionic acid (40u):** mp 235−236 °C; IR (KBr) 1736, 1613, 1204, 1128, 942, 747, 721 cm^{-1}; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 1.42 (3H, dd), 3.26 (1H, dd), 3.40−3.54 (2H, m), 4.70 (1H, dd), 7.27 (1H, d), 7.37 (1H, t), 7.49 (1H, t), 7.59 (s, 1H), 7.66 (1H, s), 8.08 (2H, t); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 13.98, 36.01, 48.93, 50.87, 59.92, 112.80, 117.76, 121.15, 121.18, 122.83, 123.31, 124.65, 127.69, 134.78, 155.65, 155.75, 169.55; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 15.49; $[\alpha]^{25}_D = +43.538$ ($c = 1.19$, 1 N NaOH); MS (ES^{1-}) m/z 362 (M − 1). Anal. ($C_{17}H_{18}NO_6P$) C, H, N.

40v (contains 43% of **40u**): mp 228−230 °C; IR (KBr) 1746, 1603, 1208, 1160, 1068, 753, 726 cm^{-1}; ^{1}H NMR (DMSO-d_6, TFA, 300 MHz) δ 1.43 (3H, dd), 3.22 (1H, dd), 3.42−3.60 (2H, m), 4.63 (1H, dd), 7.27 (1H, d), 7.37(1H, t), 7.49 (1H, t), 7.59 (s, 1H), 7.66 (1H, s), 8.08 (2H, t); ^{13}C NMR (DMSO-d_6, TFA, 75 MHz) δ 12.79, 35.27, 48.75, 49.91, 59.56, 112.56, 117.76, 121.15, 121.23, 122.88, 123.39, 124.65, 127.75, 135.21, 155.65, 155.75, 169.55; ^{31}P NMR (DMSO-d_6, TFA, 121 MHz) δ 14.91; MS (ES^{1-}) m/z 362 (M − 1). Anal. ($C_{17}H_{18}NO_6P$) C, H, N.

***(S)*-[1-[2-Dibenzofuran-3-yl-1-(1-(2-cyanoethyl)-1*H*-tetrazol-5-yl)ethylamino]-3-naphthalen-1-ylpropyl]phosphonic Acid Dimethyl Ester (41a,b).** To a stirred suspension of formate salt **24** (0.195 g, 0.51 mmol) in CH_2Cl_2 under nitrogen atmosphere was added triethylamine (0.072 mL, 0.51 mmol). To this homogeneous solution was added 1-naphthyl-3-propionaldehyde (0.11 g, 0.57 mmol) in CH_2Cl_2 (2 mL), followed by Na_2SO_4 (0.3 g, 2.1 mmol). The reaction mixture was stirred for 75 min, then transferred after filtration and washing with CH_2Cl_2 (1 mL) directly into another flask. The solution was maintained under nitrogen while being cooled with an ice bath. To this cold solution was added, under stirring, trimethyl phosphite (0.11 mL, 0.9 mmol), followed by $BF_3{\cdot}Et_2O$ (0.07 mL, 0.57 mmol). The solution was allowed to warm to ambient temperature for 2 h then stirred for 18 h. The reaction mixture was diluted with CH_2Cl_2 and washed with ice-cold water. The organic extracts were dried over $MgSO_4$ then concentrated. The residue was purified by flash chromatography using a gradient of EtOAc in hexanes (70% to 90%) to provide a 1:1 mixture of diastereomers **41a** and **41b** (0.21 g, 67%): ^{31}P NMR ($CDCl_3$, 121 MHz) δ 26.59 and 26.32. This mixture was used directly in the next step.

***(S)*-[1-[2-Dibenzofuran-3-yl-1-(1*H*-tetrazol-5-yl)ethylamino]-3-naphthalen-1-ylpropyl]phosphonic Acid Dimethyl Ester (42a,b).** A 1:1 mixture of diastereomers **42a** and **42b** (0.21 g, 0.345 mmol) in CH_2Cl_2 (3 mL) was treated with DBU (0.21 mL, 1.38 mmol) and stirred for 2.5 h. The mixture was diluted with EtOAc (20 mL) and washed with pH 4 buffer (20 mL). The aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was chromatographed on Lichroprep DIOL (E. Merck) eluting with a gradient of EtOAc in hexanes (70% to 80%). The more polar diastereomer (**42a**) was obtained as a white powder (0.072 g, 38%). The less polar diastereomer (**42b**) was also a white solid (0.077 g, 40%).

42a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.13−2.52 (2H, m), 3.08 (1H, m), 3.21 (1H, m), 3.34−3.52 (3H, m), 3.73 (3H, d), 3.84 (3H, d), 5.61 (1H, dd), 6.90 (1H, d), 7.07 (1H, d), 7.22 (1H, m), 7.28−7.41 (2H, m), 7.42−7.58 (4H, m), 7.70−7.93 (5H, m); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 20.51.

42b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.92 (1H, m), 2.17 (1H, m), 2.76−2.97 (2H, m), 3.18 (1H, m), 3.50 (1H, m), 3.62−3.97 (1H,m), 3.72 (3H, d), 3.86 (3H, d), 5.02 (1H, m), 6.83 (1H, m), 7.08 (1H, m), 7.17−7.41 (5H, m), 7.40−7.53 (3H, m), 7.58 (1H, d), 7.64 (1H, d), 7.74 (1H, d), 7.78−7.90 (2H, m); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 26.56.

***(S)*-[1-[2-Dibenzofuran-3-yl-1-(1*H*-tetrazol-5-yl)ethylamino]-3-naphthalen-1-ylpropyl]phosphonic Acid Sodium Salt (43a,b).** Dimethyl phosphonate **42a** (70 mg, 0.126 mmol) was dissolved in a 30% solution of HBr in AcOH (1.5 mL) for 3.5 h. Water (7 mL) was added causing the product to precipitate. The mixture was stirred for 5 min then filtered. The precipitate was washed with water (5 mL) then dried at 50 °C under high vacuum, affording the desired phosphonic acid (61 mg). The solid was dissolved in 1 N NaOH (0.35 mL) and the solution was placed on a column filled with MCI CHP-20 gel (75−150 μm). The product was eluted with water (25 mL) then with a gradient of methanol (10% to 50%) in water. The pure fractions, according to HPLC analysis (column: YMC ODS; eluent: 65% MeCN:35% H_3PO_4 0.1% in $NaClO_4$ 0.1 M; isocratic; flowrate = 1.5 mL/min), were combined and lyophilized to provide a white solid (0.042 g, 51%): mp > 300 °C dec; IR (KBr) 1635, 1204, 1075 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 1.70−1.80 (1H, m), 2.00−2.20 (1H, m), 2.50−2.70 (1H, m), 2.78−3.05 (2H, m), 3.10−3.26 (2H, m), 4.50−4.60 (1H, m), 6.70−6.80 (1H, m), 6.92 (1H, s), 7.00−7.10 (1H, m), 7.12−7.42 (7H, m), 7.45−7.58 (2H, m), 7.65−7.70 (1H, m), 7.80−7.90 (1H, m); ^{13}C NMR (D_2O, 75 MHz) δ 30.08, 30.18, 41.35, 55.77 (d, $J = 137.3$ Hz), 111.97, 112.42, 121.21, 122.93, 123.49, 124.06, 124.47, 124.66, 126.44, 126.50, 126.54, 126.92, 127.20, 127.74, 129.30, 131.90, 134.15, 137.31, 139.13, 156.28; ^{31}P NMR (D_2O, 121 MHz) δ 16.64; MS (ES^{1-}) m/z 526 (free acid, M − 1). Anal. ($C_{28}H_{23}N_5O_4PNa_3{\cdot}3/4H_2O$) C, N; H: calcd, 4.07; found, 4.51.

43b: starting from **42b**, the above procedure afforded **43b** as a white solid; mp > 250 °C dec; IR (KBr) 1580, 1105 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 1.61 (1H, m), 2.10 (1H, m), 2.70−2.90 (3H, m), 3.18−3.42 (2H, m), 4.65−4.80 (1H, m, masked), 6.7 (1H, d), 6.92 (1H, s), 7.00−7.17 (2H, m), 7.17−7.34 (3H, m), 7.36−7.57 (3H, m), 7.56−7.68 (2H, m), 7.78 (1H, d), 7.84 (1H, d); ^{13}C NMR (D_2O, 75 MHz) δ 33.86, 33.95, 35.26, 43.76, 60.75 (d), 115.95, 116.42, 116.48, 125.12, 125.18, 126.82, 127.50, 128.00, 128.46, 128.56, 130.47, 130.54, 130.76, 130.98, 131.28, 131.76, 133.34, 135.80, 138.18, 140.59, 142.27, 160.22, 164.60; ^{31}P NMR (D_2O, 121 MHz) δ 15.94; MS (ES^{1-}) m/z 526 (free acid, M − 1). Anal. ($C_{28}H_{23}N_5O_4PNa_3{\cdot}3/4H_2O$) C, H, N.

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Supporting Information Available: Experimental procedures and characterization of 2-bromomethyl-9-methyl-9*H*-carbazole, 2-bromomethyl-fluoren-9-one, and 3-iododibenzofuran, the starting materials for the preparation of **7b**, **7c**, and **12**, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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