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A New Approach to Isoindolobenzazepines. A Simple Synthesis of Lennoxamine

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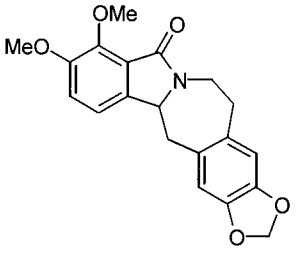
Abstract—A convenient and versatile short-step synthesis of isoindolobenzazepines, illustrated by a total synthesis of the alkaloid lennoxamine **1**, is described.

Introduction

Isoindolobenzazepine alkaloids, exemplified by lennoxamine **1** (Fig. 1), are a new class of alkaloids belonging to the aporhoedane series which have been extracted from Chilean *Berberidaceae*.[1] They are biogenetically related to protoberberines and usually ranked as isoquinoline alkaloids but their main structural feature is the presence of the distinctive isoindolo[1,2-*b*][3]benzazepine unit embedded in their skeleton.

Despite the fact that their structures incorporate the 3*H*-3-benzazepine moiety which possesses important biological activities[2] and equally an isoindolinone ring system which is interesting due to the real and potential biological properties of many of its derivatives,[3–7] these alkaloids appear to be devoid of any useful pharmacology. However, their architecturally sophisticated structures which include five- and seven-membered rings fused with environmentally different aromatic moieties contiguously and differently substituted besides by oxygenated substituents render these molecules attractive and synthetically challenging targets. The ring system which is accessible in vivo and in vitro by oxidation of berbine alkaloids[1,8,9] has been the objective of several synthetic approaches which involve (i) the cyclization of 2-arylbenzazepine derivatives *ortho*-substituted with carboxylate groups[10,11] (ii) the ring-expansion of isoindoloisoquinoline derivatives obtained by cyclization of acyliminium precursors[12] (iii) the Pummerer rearrangement of 3-phenylsulfanylisoindolinones followed by intramolecular electrophilic aromatic substitution and desulfuration[13] and (iv) the photochemically induced cyclization of aromatic enamides.[14] They are also accessible through biomimetic pathways,[15] by means of a regioselective 7-*endo*-*trig* radical cyclization of methylenephthalimidines[16] and by cyclization under harsh conditions of a chlorovinyl ether derived from 3-arylmethylphthalimidines.[17] All these synthetic approaches invariably involve either the formation of the isoindolinone template or of the azepine ring system found in the alkaloid framework for the final step. The sole exception concerns a synthetic route recently developed by C. Saa et al. who incidentally observed the simultaneous formation of the five and seven-membered rings by fluoride-induced transannular macrocyclization of silylated 10-membered-ring-stilbene lactams.[18]



Lennoxamine **1**

Figure 1.

Results and Discussion

We now report an alternative, more efficient and tactically new approach to isoindolobenzazepines, illustrated by the total synthesis of the alkaloid lennoxamine **1**, which has been isolated as a racemate from the Chilean barberries *Berberis darwinii* Hook.[19] Our strategy, which is depicted in retrosynthetic Scheme 1, is based on the use of 3-arylmethylenelactams **4**–**6** as key intermediates (see Table 1).

Keywords: alkaloids; benzazepines; carbanions; cyclisation.
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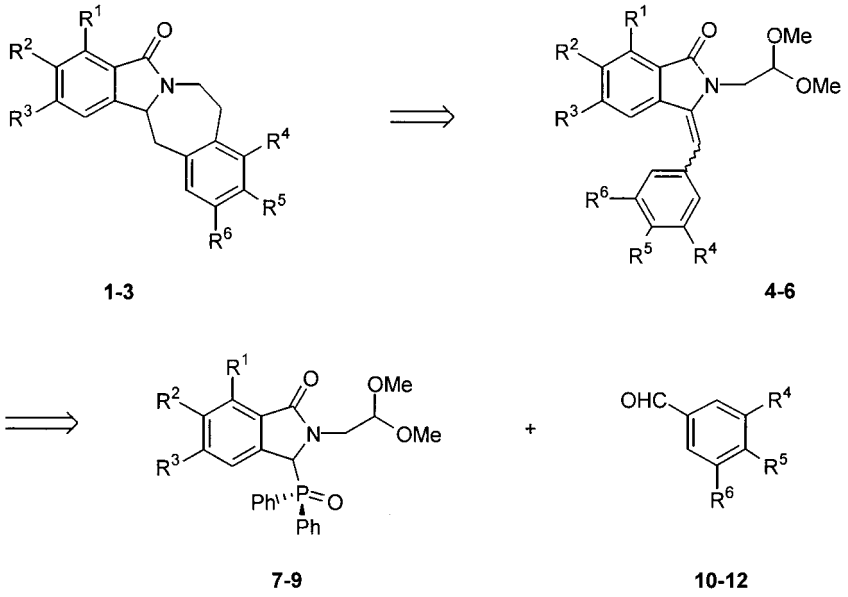


Scheme 1.

These lactams were obtained by Horner reaction between a suitably substituted benzaldehyde **10**–**12** and the phosphorylated isoindolinones possessing an acetaldehyde dimethylacetal appendage **7**–**9**. Two reduction steps supporting a cyclization process performed on the arylmethyleneisoindolinones **4**–**6** then should complete the synthesis of the target isoindolobenzazepines **1**–**3**.

The first facet of this synthesis, the assembly of the phosphorylated isoindolinone unit equipped with the acetal functionality, was accomplished by taking advantage of a newly developed aryne-mediated cyclization methodology applied to halogeno-*N*-(phosphinylmethyl)benzamide derivatives.[20–22] The required parent phosphorylated carboxamides **17**–**19** were easily and efficiently synthesized by coupling the *N*-[(diphenylphosphinyl)methyl]-*N*-(2-yl-acetaldehyde dimethylacetal) **16** with the acid chlorides **13**–**15** (Scheme 2).

This synthetic route necessitated the preliminary elaboration of the polyfunctional secondary amine **16**. We found that this amine could be readily prepared via the two step sequence depicted in Scheme 3 involving the treatment with diphenylphosphine oxide of the appropriate hexahydrotriazine **21**, product of the Mannich reaction of aminoacetaldehyde dimethylacetal **20**.

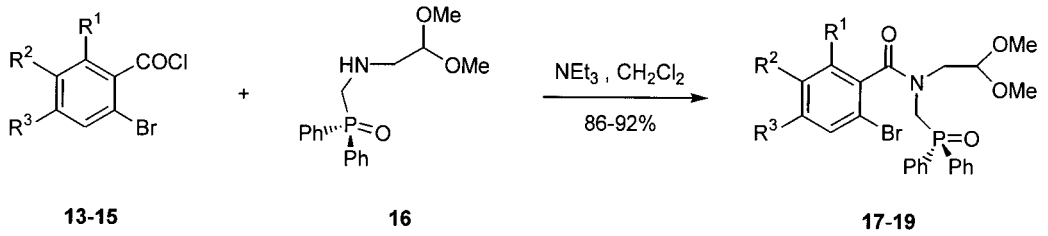
Table 1. Compounds prepared and/or used

Compound	R^1	R^2	R^3	R^4	R^5	R^6
1, 4, 22, 25	OMe	OMe	H	H	–O–CH_2–O	
2, 5, 23, 26	H	H	H	H	OMe	OMe
3, 6, 24, 27	H	–O–CH_2–O		OMe	OMe	OMe
7, 13, 17	OMe	OMe	H	–	–	–
8, 14, 18	H	H	H	–	–	–
9, 15, 19	H	–O–CH_2–O		–	–	–
10	–	–	–	H	–O–CH_2–O	
11	–	–	–	H	OMe	OMe
12	–	–	–	OMe	OMe	OMe

Exposure of the phosphorylated bromobenzamide derivatives **18** and **19** to potassium bis(trimethylsilyl)azide (KHMDS, 2 equiv.) at −78°C in THF induced the regioselective formation of the phosphoryl stabilized α-aminocarbanion and the concomitant formation of the aryne unit. Addition of the carbon nucleophile across the aryne moiety caused an intramolecular arylation reaction and after usual work-up the phosphorylated isoindolinones **8** and **9** were obtained with excellent yields (Scheme 4).

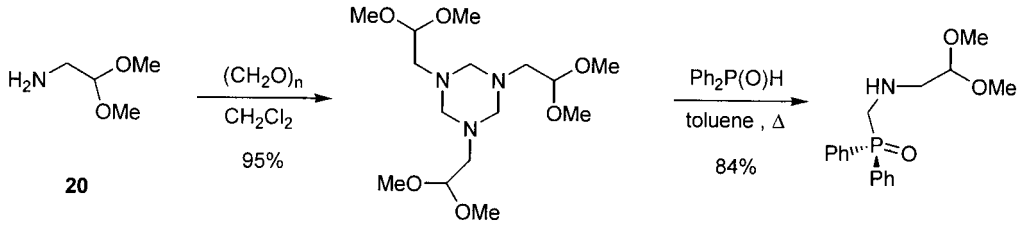
Horner reaction between the metallated isoindolinone **8** and **9** and the suitably substituted aromatic carboxaldehydes **11** and **12** proceeded uneventfully to afford fairly good yields of the 3-arylmethyleneisoindolinones **5** and **6** (Scheme 5) in both *E*- and *Z*-forms but with the *E*-form predominant by a large margin as unambiguously assigned from their ^{1}H NMR spectra with the help of NOE experiments.[†] For the reduction of the exocyclic carbon–carbon double bond of enamides **5** and **6** a rarely employed method making use of Pd on C and ammonium formate[23,24] was tested and, to our delight, this protocol delivered straightforwardly and quantitatively the 3-arylmethylisoindolinones **23** and **24**, candidates for the final cyclization step (Scheme 5). Thus treatment of compounds **23** and **24** with acetic acid in the presence of sulfuric acid gave cyclization of the opened models and formation of the endocyclic aromatic enamides **26** and **27** with very satisfactory yields (Scheme 5). The ultimate reduction of the N–C═C unit of the annulated compounds **26** and **27** was performed by repeating the previously mentioned procedure and this protocol afforded the desired isoindolobenzazepines **2** and **3** in excellent yields (Scheme 5).

[†] The structure and the *E*/*Z* ratio were established by NOE difference experiments. For *E*-isomers, the *N*-methylene H_2 (δ 4.01 ppm) showed a strong NOE to vinylic H (δ 6.68 ppm, 20%) [values given for **5**(*E*)].



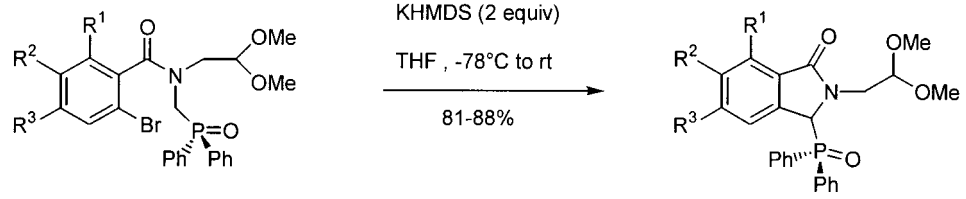
13-15 **16** **17-19**

Scheme 2.



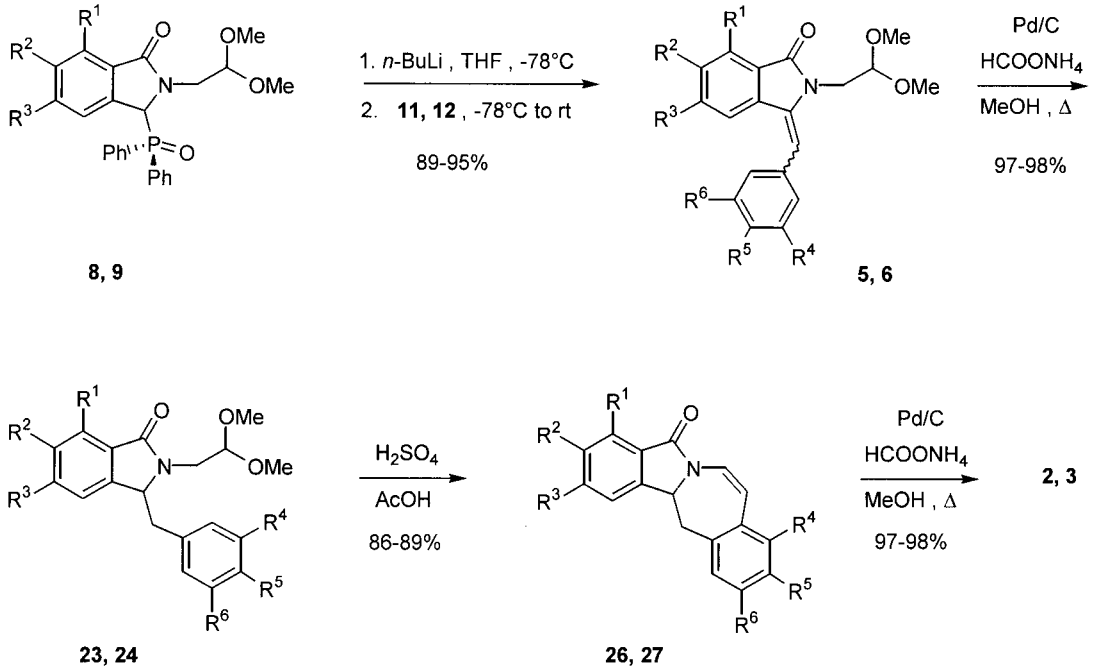
20 **21** **16**

Scheme 3.



18, 19 **8 , 9**

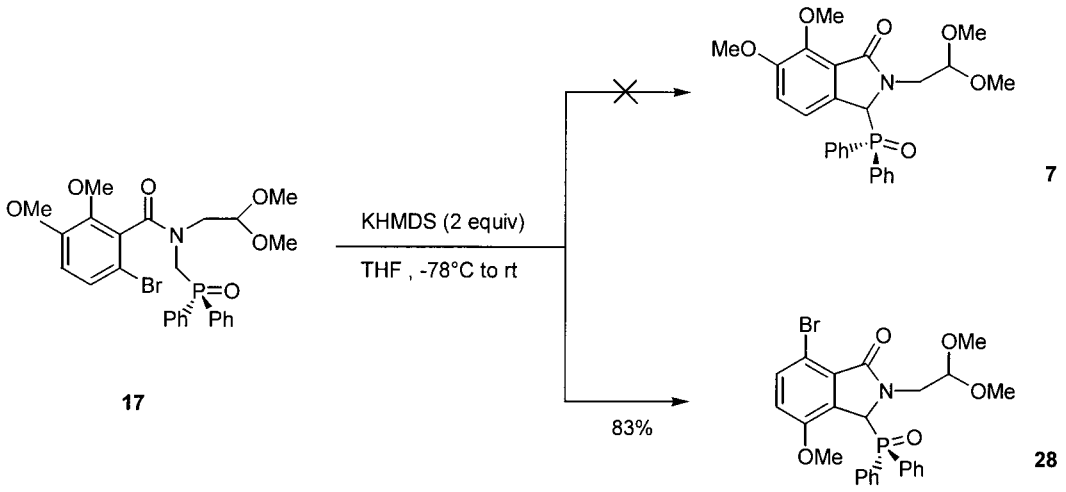
Scheme 4.



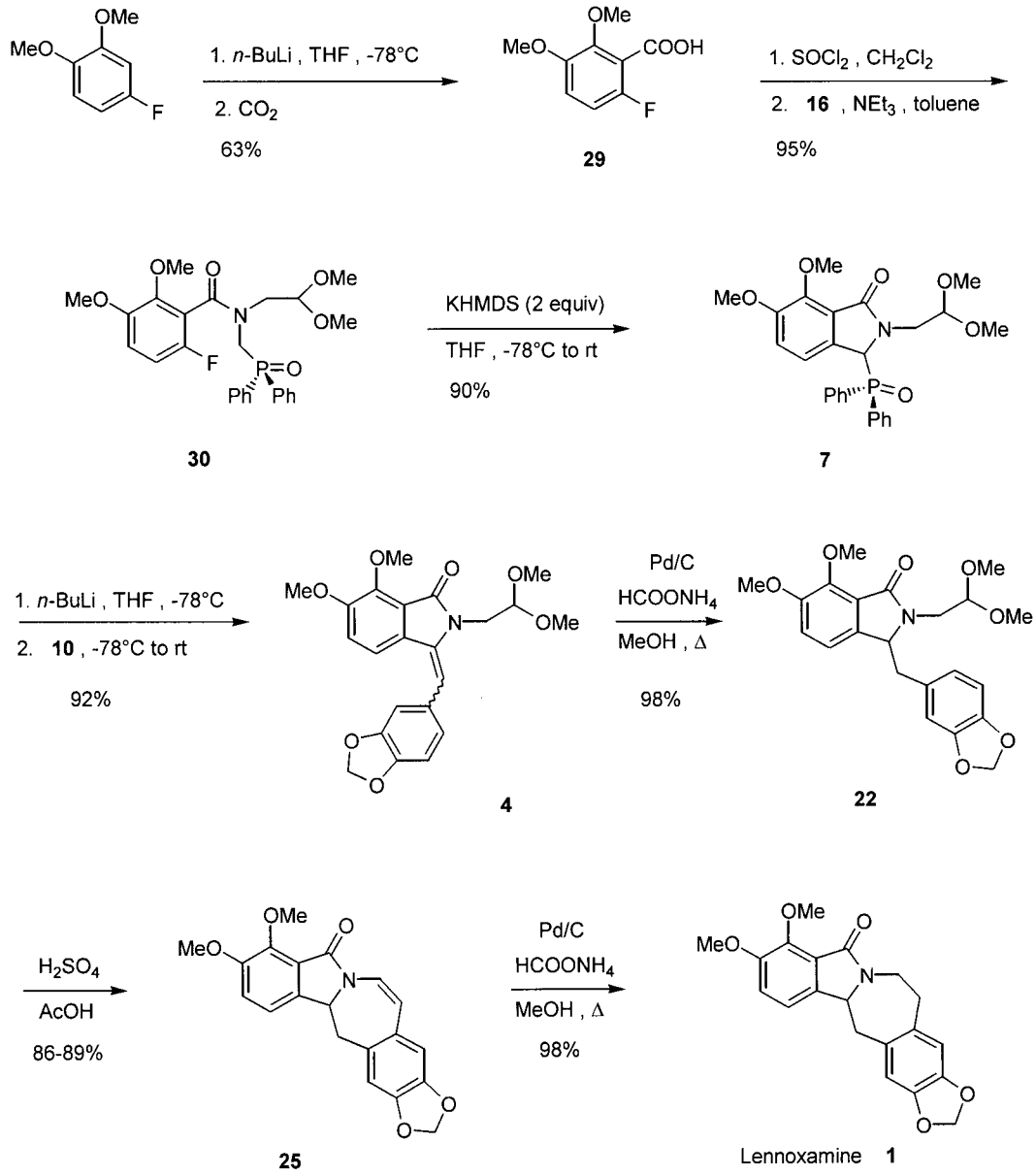
8, 9 **5, 6**

23, 24 **26, 27**

Scheme 5.



Scheme 6.



Scheme 7.

Encouraged by the success of the aryne-mediated cyclization of phosphorylated *o*-bromobenzamides associated with four appealing, convenient and efficient steps of procedural simplicity, we then proceeded to apply this method to the synthesis of isoindolobenzazepine alkaloid lennoxamine **1**. The required parent *ortho*-bromobenzamide derivative **17** was conveniently prepared as depicted in Scheme 2. However, to our surprise, the basic treatment of **17** did not give rise to the expected dimethoxyisoindolinone **7** but instead to the bromomethoxy analogue **28**, product arising from the intramolecular nucleophilic aromatic substitution by the preliminarily generated α-aminocarbanion (Scheme 6).

Assuming that this failure could be attributable to the difficulties associated with the formation of the aryne moiety in compounds such as **17** we then anticipated that the replacement of the bromine by a fluorine atom could circumvent this problem by facilitating the *ortho*-metallation process required for the generation of the aryne functionality.[25] It is indeed well established that the rates of initial proton removal assisted by halogen atoms rank as F>Cl>Br>I.[25] We thus set out to prepare the *ortho*-fluorobenzamide derivative **30**. The synthesis started with the preparation of the *ortho*-fluorobenzoic acid **29** which was easily prepared by regioselective metallation at the 'in between' position of 4-fluoroveratrole[26] and subsequent trapping of the transient lithiated species with carbon dioxide (Scheme 7). This protocol delivered exclusively the *ortho*-fluorobenzoic acid **29** albeit in moderate yield (63%). Conversion into the corresponding acid chloride and subsequent reaction with the phosphorylated amine **16** afforded the desired *ortho*-fluorobenzamide derivative **30** almost quantitatively (Scheme 7).

Gratifyingly our expectations were successfully fulfilled because, when the phosphorylated *ortho*-fluorobenzamide **30** was treated with KHMDS, regioselective cyclization took place to give the desired dimethoxyisoindolinone **7** exclusively and in excellent yield (90%, Scheme 7). Horner reaction between the phosphorylated isoindolinone **7** and piperonal afforded, after reduction of the arylmethylene derivative **4**, the 3-arylmethylisoindolinone **22** (Scheme 7). This compound was in turn subjected to the cyclization conditions described above and the resulting endocyclic enamide **25** was finally transformed into the target natural product lennoxamine **1** in a 66% yield (over the last five steps).

Conclusion

In conclusion the 3-arylmethyleneisoindolinone synthesis, consecutive reduction and sequential cyclization and reduction reactions reported here, proceeds in high yields and affords efficient access to isoindolobenzazepine ring systems. The total synthesis of alkaloid lennoxamine emphasizes the synthetic potential of these exocyclic aromatic enamides and we believe that this work demonstrates a general new methodology for the preparation of other naturally occurring isoindolobenzazepine alkaloids as well as their biogenetically related congeners.

Experimental

General

Methanol and ethanol were distilled from magnesium turnings. Tetrahydrofuran (THF) and ether (Et_2O) were pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. CH_2Cl_2, NEt_3 and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (230–400 mesh ASTM) was used. The melting points were measured on a Reichert–Thermopan apparatus and are not corrected. Unless otherwise stated, proton, carbon and phosphorus NMR spectra were recorded with $CDCl_3$ as solvent at 300, 75 and 121 MHz respectively on a Bruker AM 300 spectrometer. Microanalyses were performed by the CNRS microanalysis centre.

Synthesis of the phosphorylated amine 16

Triazine 21. A suspension of paraformaldehyde (4.3 g) in a solution of aminoacetaldehyde dimethylacetal **20** (15 g, 14.2 mmol) in CH_2Cl_2 (150 mL) was stirred at room temperature for 2 h. After filtration, evaporation of the solvent left a colourless oil (15.9 g, 95%) corresponding to the triazine **21** which was used in the next step without further purification; ^{1}H NMR δ 2.57 (d, J=5.2 Hz, 6H, NCH_2), 3.28 (s, 18H, OCH_3), 3.44 (br. s, 6H, NCH_2N), 4.36 (t, J=5.2 Hz, 3H, $CHOMe_2$); ^{13}C NMR δ *CH* 103.8, *CH* $_2$ 54.3, 75.0, *CH* $_3$ 53.5.

Phosphorylated amine 16. A solution of triazine **21** (12.45 g, 35.5 mmol) and diphenylphosphine oxide[27] (21.5 g, 106.4 mmol) was refluxed in toluene (300 ml) for 1 h under Ar. After evaporation of the solvent under vacuum the crude product was chromatographed on SiO_2 column using acetone/hexane (80:20) as eluent and the phosphorylated amine **16** was finally purified by recrystallization from hexane/toluene: 28.5 g (84%); mp 69–70°C; ^{1}H NMR δ 2.01 (br. s, 1H, NH), 2.75 (d, J=5.4 Hz, 2H, NCH_2), 3.25 (s, 6H, OCH_3), 3.48 (d, J=7.5 Hz, 2H, NCH_2P), 4.35 (t, J=5.4 Hz, 1H, $CHOMe_2$), 7.32–7.48 (m, 6H, H_{arom}), 7.70–7.77 (m, 4H, H_{arom}); ^{13}C NMR δ *C* 131.7 (d, J_{CP}=84 Hz), *CH* 103.6, 128.6 (d, J_{CP}=12 Hz), 131.1 (d, J_{CP}=9 Hz), 131.9 (d, J_{CP}=2 Hz), *CH*$_2$ 49.4, 52.4, *CH* $_3$ 53.9; ^{31}P NMR δ 29.2. Anal. Calcd for $C_{17}H_{22}NO_3P$: C, 69.94; H, 6.94; N, 4.39. Found: C, 70.18; H, 6.73; N, 4.55.

Synthesis of the *ortho*-fluorobenzoic acid 29

Metallation of 4-fluoroveratrole (1.56 g, 10 mmol) was performed according to an already reported procedure[26] by making use of *n*-BuLi (1.6 M in hexanes, 7.8 ml, 12.5 mmol) in THF (40 ml) at −78°C. Dry ice was poured into reaction mixture which was warmed to room temperature for 3 h. Water (40 ml) and Et_2O (30 ml) were added. The aqueous layer was acidified with aq HCl and the crude product was extracted with Et_2O (3×20 ml). Drying over Na_2SO_4 and concentration in vacuo left **29** as a white solid which was recrystallized from EtOH/H_2O: 1.26 g

(63%); mp 148–149°C; ^{1}H NMR δ 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.99 (t, J=9.0 Hz, 1H, H_{arom}), 7.12 (dd, J=9.0, 5.5 Hz, 1H, H_{arom}), 10.53 (br. s, 1H, COOH); ^{13}C NMR δ *C* 124.8 (d, J_{CF}=21 Hz), 150.8 (d, J_{CF}=6.5 Hz), 154.2 (d, J_{CF}=2.5 Hz), 156.9 (d, J_{CF}=240 Hz), 169.5 (CO), *CH* 115.7 (d, J_{CF}=22 Hz), 119.4 (d, J_{CF}=10 Hz), *CH* $_3$ 61.4, 66.3. Anal. Calcd for $C_9H_9FO_4$: C, 54.00; H, 4.53. Found: C, 53.84; H, 4.59.

Phosphorylated amides 17–19, 30

The phosphorylated amides **17**–**19**, **30** were synthesized according to an already reported procedure.[21]

Phosphorylated amide 17. (86%); mp 84–85°C; ^{1}H NMR δ 3.16 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 3.50 (dd, J=15.2, 6.0 Hz, 1H, NCH_2), 3.51 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.77 (dd, J=15.2, 5.2 Hz, 1H, NCH_2), 4.42 (dd, J=6.0, 5.2 Hz, 1H, $CHOMe_2$), 4.68 (dd, J=15.5, 6.1 Hz, 1H, NCH_2P), 4.94 (dd, J=15.5, 5.0 Hz, 1H, NCH_2P), 6.70 (d, J=8.8 Hz, 1H, H_{arom}), 7.09 (d, J=8.8 Hz, 1H, H_{arom}), 7.39–7.50 (m, 6H, H_{arom}), 7.86–7.97 (m, 4H, H_{arom}); ^{13}C NMR δ *C* 109.1, 131.3 (d, J_{CP}=98 Hz), 132.5, 146.0, 152.1, 166.7 (CO), *CH* 103.3, 114.4, 128.2, 128.6, 128.8 (d, J_{CP}=12 Hz), 131.2 (d, J_{CP}=10 Hz), 131.6 (d, J_{CP}=10 Hz), 132.0, 132.1, *CH* $_2$ 44.2 (d, J_{CP}=76 Hz), 49.9, *CH* $_3$ 53.5, 53.9, 56.0, 61.3; ^{31}P NMR δ 30.1. Anal. Calcd for $C_{26}H_{29}BrNO_6P$: C, 55.53; H, 5.20; N, 2.49. Found: C, 55.58; H, 5.05; N, 2.45.

Phosphorylated amide 18. (92%); mp 143–144°C; ^{1}H NMR (mixture of two rotational isomers, 80:20): δ (major rotational isomer) 3.20 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 3.54 (dd, J=15.0, 6.2 Hz, 1H, NCH_2), 3.72 (dd, J=15.0, 4.5 Hz, 1H, NCH_2), 4.45 (dd, J=6.2, 4.5 Hz, 1H, $CHOMe_2$), 4.78 (d, J=5.2 Hz, 2H, NCH_2P), 6.73 (dd, J=7.5, 1.8 Hz, 1H, H_{arom}), 7.08–7.22 (m, 2H, H_{arom}), 7.32–7.56 (m, 7H, H_{arom}), 7.85–7.93 (m, 4H, H_{arom}); ^{13}C NMR (mixture of two rotational isomers) δ (major rotational isomer) *C* 119.2, 131.3 (d, J_{CP}=69 Hz), 136.9, 169.4 (CO), *CH* 103.0, 127.2, 128.5 (d, J_{CP}=9.5 Hz), 128.6, 128.8 (d, J_{CP}=11 Hz), 130.4, 131.2 (d, J_{CP}=10 Hz), 131.4 (d, J_{CP}=10 Hz), 132.2, 132.3, 132.9, *CH* $_2$ 44.4 (d, J_{CP}=76 Hz), 50.3, *CH* $_3$ 54.0, 54.4; ^{31}P NMR δ (major rotational isomer) 30.6. Anal. Calcd for $C_{24}H_{25}BrNO_4P$: C, 57.38; H, 5.02; N, 2.79. Found: C, 57.20; H, 4.83; N, 2.61.

Phosphorylated amide 19. (88%); mp 103–104°C; ^{1}H NMR (mixture of two rotational isomers, 80:20): δ (major rotational isomer) 3.22 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3), 3.56 (dd, J=15.0, 6.4 Hz, 1H, NCH_2), 3.69 (dd, J=15.0, 4.4 Hz, 1H, NCH_2), 4.48 (dd, J=6.4, 4.4 Hz, 1H, $CHOMe_2$), 4.72 (dd, J=6.1, 5.5 Hz, 2H, NCH_2P), 5.89 (d, J=3.2 Hz, 2H, OCH_2O), 6.09 (s, 1H, H_{arom}), 6.83 (s, 1H, H_{arom}), 7.37–7.50 (m, 6H, H_{arom}), 7.82–7.97 (m, 4H, H_{arom}); ^{13}C NMR (mixture of two rotational isomers) δ (major rotational isomer) *C* 110.3, 129.7, 131.0 (d, J_{CP}=98 Hz), 131.3 (d, J_{CP}=98 Hz), 147.2, 148.9, 169.2 (CO), *CH* 102.9, 108.1, 112.9, 128.6 (d, J_{CP}=11.5 Hz), 128.8 (d, J_{CP}=10.5 Hz), 131.2 (d, J_{CP}=10 Hz), 131.4 (d, J_{CP}=10 Hz), 132.2, 132.3, *CH* $_2$ 44.4 (d, J_{CP}=76 Hz), 50.4, 102.1, *CH* $_3$ 54.1, 54.6; ^{31}P NMR (major rotational isomer) δ 30.8. Anal. Calcd for $C_{25}H_{25}BrNO_6P$: C, 54.96; H, 4.61; N, 2.56. Found: C, 55.18; H, 4.53; N, 2.75.

Phosphorylated amide 30. (94%); mp 116–117°C; ^{1}H NMR δ 3.20 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.66 (d, J=5.5 Hz, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 4.40 (t, J=5.5 Hz, 1H, $CHOMe_2$), 4.80 (d, J=5.7 Hz, 2H, NCH_2P), 6.69 (t, J=8.5 Hz, 1H, H_{arom}), 6.78 (dd, J=9.1, 5.2 Hz, 1H, H_{arom}), 7.41–7.56 (m, 6H, H_{arom}), 7.83–7.99 (m, 4H, H_{arom}); ^{13}C NMR δ *C* 119.3 (d, J_{CF}=21 Hz), 131.3 (d, J_{CP}=98 Hz), 131.4 (d, J_{CP}=99 Hz), 145.6 (d, J_{CF}=6.5 Hz), 149.1 (d, J_{CF}=3 Hz), 152.0 (d, J_{CF}=243 Hz), 164.5 (CO), *CH* 103.3, 110.4 (d, J_{CF}=22 Hz), 113.5 (d, J_{CF}=9 Hz), 128.5 (d, J_{CP}=12 Hz), 128.6 (d, J_{CP}=12 Hz), 131.2 (d, J_{CP}=10 Hz), 131.3 (d, J_{CP}=10 Hz), 132.1, *CH* $_2$ 44.6 (d, J_{CP}=76 Hz), 50.1, *CH* $_3$ 53.8, 54.1, 56.3, 61.2; ^{31}P NMR δ 30.0. Anal. Calcd for $C_{26}H_{29}FNO_6P$: C, 62.27; H, 5.83; N, 2.79. Found: C, 62.18; H, 6.03; N, 2.55.

Phosphorylated isoindolinones 7–9, 28

The phosphorylated isoindolinones **7**–**9**, **28** were synthesized according to an already reported procedure.[20]

Phosphorylated isoindolinone 7. (90%); mp 142–143°C; ^{1}H NMR δ 3.27 (s, 3H, OCH_3), 3.33 (s, 3H, OCH_3), 3.34 (dd, J=14.3, 6.9 Hz, 1H, NCH_2), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.98 (dd, J=14.3, 3.7 Hz, 1H, NCH_2), 4.52 (dd, J=6.9, 3.7 Hz, 1H, $CHOMe_2$), 5.67 (d, J=8.7 Hz, 1H, NCHP), 6.68 (dd, J=8.4, 1.4 Hz, 1H, H_{arom}), 6.89 (d, J=8.4 Hz, 1H, H_{arom}), 7.32–7.68 (m, 10H, H_{arom}); ^{13}C NMR δ *C* 124.4 (d, J_{CP}=2.5 Hz), 128.0 (d, J_{CP}=102 Hz), 128.3 (d, J_{CP}=98 Hz), 132.2, 147.1, 152.6, 167.0 (CO), *CH* 60.6 (d, J_{CP}=73 Hz), 102.3, 116.1, 119.4, 128.5 (d, J_{CP}=11.5 Hz), 128.7 (d, J_{CP}=12 Hz), 131.8 (d, J_{CP}=9 Hz), 132.1 (d, J_{CP}=9 Hz), 132.7 (d, J_{CP}=2 Hz), 132.8 (d, J_{CP}=2 Hz), *CH* $_2$ 42.8, *CH* $_3$, 53.4, 54.9, 56.6, 62.5; ^{31}P NMR δ 31.5. Anal. Calcd for $C_{26}H_{28}NO_6P$: C, 64.86; H, 5.86; N, 2.91. Found: C, 64.78; H, 6.00; N, 2.85.

Phosphorylated isoindolinone 8. (88%); mp 175–176°C; ^{1}H NMR δ 3.26 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.46 (dd, J=14.4, 6.6 Hz, 1H, NCH_2), 4.04 (dd, J=14.4, 4.0 Hz, 1H, NCH_2), 4.54 (dd, J=6.6, 4.0 Hz, 1H, $CHOMe_2$), 5.77 (d, J=10.3 Hz, 1H, NCHP), 6.92 (t, J=6.5 Hz, 1H, H_{arom}), 7.28–7.64 (m, 13H, H_{arom}); ^{13}C NMR δ *C* 127.6 (d, J_{CP}=98 Hz), 128.6 (d, J_{CP}=98 Hz), 132.3 (d, J_{CP}=3 Hz), 139.2, 168.9 (CO), *CH* 61.8 (d, J_{CP}=72 Hz), 102.1, 123.8, 124.1, 128.6, 128.65 (d, J_{CP}=12 Hz), 128.7 (d, J_{CP}=12 Hz), 131.3, 131.6 (d, J_{CP}=9 Hz), 132.1 (d, J_{CP}=9 Hz), 132.8 (d, J_{CP}=2.5 Hz), 132.9 (d, J_{CP}=2.5 Hz), *CH* $_2$ 42.7, *CH* $_3$ 53.1, 54.7; ^{31}P NMR δ 31.2. Anal. Calcd for $C_{24}H_{24}NO_4P$: C, 68.40; H, 5.74; N, 3.32. Found: C, 68.62; H, 5.88; N, 3.50.

Phosphorylated isoindolinone 9. (81%); mp 186–187°C; ^{1}H NMR δ 3.25 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.22 (dd, J=14.4, 6.5 Hz, 1H, NCH_2), 3.97 (dd, J=14.4, 4.0 Hz, 1H, NCH_2), 4.49 (dd, J=6.5, 4.0 Hz, 1H, $CHOMe_2$), 5.65 (d, J=10.2 Hz, 1H, NCHP), 5.98 (dd, J=9.1, 1.2 Hz, 2H, OCH_2O), 6.48 (t, J=0.7 Hz, 1H, H_{arom}), 7.01 (s, 1H, H_{arom}), 7.38–7.63 (m, 10H, H_{arom}); ^{13}C NMR δ *C* 129.0, 134.9 (d, J_{CP}=3 Hz), 148.7, 151.1, 168.7 (CO), *CH* 61.4 (d, J_{CP}=72 Hz), 102.2, 103.2, 104.4, 128.7 (d, J_{CP}=12 Hz), 128.75 (d, J_{CP}=11.5 Hz), 131.6 (d,

J_{CP}=9 Hz), 132.0 (d, J_{CP}=9 Hz), 132.8 (d, J_{CP}=2 Hz), 132.9 (d, J_{CP}=2 Hz), *CH* $_2$ 42.9, 102.0, *CH* $_3$ 53.2, 54.8; ^{31}P NMR δ 30.6. Anal. Calcd for $C_{25}H_{24}NO_6P$: C, 64.51; H, 5.20; N, 3.01. Found: C, 64.39; H, 5.02; N, 3.15.

Phosphorylated isoindolinone 28. (83%); mp 75–76°C; ^{1}H NMR δ 3.13 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.50 (dd, *J*=14.5, 6.6 Hz, 1H, NCH_2), 4.00 (dd, *J*=14.5, 3.5 Hz, 1H, NCH_2), 4.46 (dd, *J*=6.6, 3.5 Hz, 1H, $CHOMe_2$), 5.73 (d, *J*=5.6 Hz, 1H, NCHP), 6.61 (d, *J*=8.6 Hz, 1H, H_{arom}), 7.31–7.35 (m, 4H, H_{arom}), 7.38–7.61 (m, 5H, H_{arom}), 7.73–7.80 (m, 2H, H_{arom}); ^{13}C NMR δ *C* 109.0, 128.1 (d, J_{CP}=98 Hz), 130.6 (d, J_{CP}=2 Hz), 130.9, 131.5 (d, J_{CP}=96 Hz), 153.4, 166.6 (CO), *CH* 60.8 (d, J_{CP}=68 Hz), 102.4, 114.0, 128.2 (d, J_{CP}=12 Hz), 128.4 (d, J_{CP}=12 Hz), 131.5 (d, J_{CP}=9.5 Hz), 131.6 (d, J_{CP}=10 Hz), 132.3 (d, J_{CP}=2 Hz), 132.4 (d, J_{CP}=2 Hz), 134.7, *CH* $_2$ 43.2, *CH* $_3$ 53.7, 54.5, 54.8; ^{31}P NMR δ 30.1. Anal. Calcd for $C_{25}H_{25}BrNO_5P$: C, 56.62; H, 4.75; N, 2.64. Found: C, 56.78; H, 4.85; N, 2.59.

3-Arylmethyleneisoindolinones 4–6

The 3-arylmethyleneisoindolinones **4**–**6** were synthesized according to an already reported procedure.[28]

3-Arylmethyleneisoindolinone 4. (92%), (*E*)- and (*Z*)-isomers (ratio 85:15 from ^{1}H NMR spectrum). (*E*)-isomer: mp 154–155°C (lit.[17] 152–154°C); ^{1}H NMR δ 3.38 (s, 6H, OCH_3), 3.79 (s, 3H, OCH_3), 3.90 (d, *J*=5.4 Hz, 2H, NCH_2), 4.01 (s, 3H, OCH_3), 4.63 (t, *J*=5.4 Hz, 1H, $CHOMe_2$), 5.95 (d, *J*=0.8 Hz, 2H, OCH_2O), 6.43 (s, 1H, CH═), 6.74–6.85 (m, 4H, H_{arom}), 7.06 (dd, *J*=9.1, 0.6 Hz, 1H, H_{arom}); ^{13}C NMR δ *C* 122.2, 128.8, 129.1, 135.7, 146.5, 147.0, 147.8, 153.3, 164.8 (CO), *CH* 102.3, 108.5, 108.7, 109.7, 114.9, 118.9, 123.1, *CH* $_2$ 41.8, 101.2, *CH* $_3$ 54.4, 56.4, 62.3.

3-Arylmethyleneisoindolinone 5. (95%). (*E*)- and (*Z*)-isomers (ratio 80:20 from ^{1}H NMR spectrum). *(E)*-isomer: mp 95–96°C; ^{1}H NMR δ 3.43 (s, 6H, OCH_3), 3.84 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.01 (d, *J*=5.4 Hz, 2H, NCH_2), 4.71 (t, *J*=5.4 Hz, 1H, $CHOMe_2$), 6.68 (s, 1H, CH═), 6.91 (d, *J*=8.2 Hz, 1H, H_{arom}), 6.93 (d, *J*=1.7 Hz, 1H, H_{arom}), 6.98–7.01 (m, 1H, H_{arom}), 7.32 (dd, *J*=7.0, 1.2 Hz, 1H, H_{arom}), 7.37–7.42 (m, 2H, H_{arom}), 7.81–7.85 (m, 1H, H_{arom}); ^{13}C NMR δ *C* 127.6, 129.9, 135.2, 136.1, 148.8, 148.9, 166.7 (CO), *CH* 102.2, 111.2, 112.6, 122.1, 123.2, 129.0, 131.5, *CH* $_2$ 41.9, *CH* $_3$ 54.4, 55.9. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.19; H, 6.34; N, 3.66.

3-Arylmethyleneisoindolinone 6. (89%). (*E*)- and (*Z*)-isomers (ratio 95:5 from ^{1}H NMR spectrum). (*E*)-isomer: mp 165–166°C; ^{1}H NMR δ 3.02 (s, 6H, OCH_3), 3.55 (s, 6H, OCH_3), 3.77 (s, 3H, OCH_3), 3.95 (d, *J*=5.4 Hz, 2H, NCH_2), 4.68 (t, *J*=5.4 Hz, 1H, $CHOMe_2$), 5.99 (s, 2H, OCH_2O), 6.56 (s, 1H, CH═), 6.60 (s, 2H, H_{arom}), 6.80 (s, 1H, H_{arom}), 7.18 (s, 1H, H_{arom}); ^{13}C NMR δ *C* 125.0, 130.5, 130.6, 136.3, 137.7, 149.1, 151.1, 153.4, 166.3 (CO), *CH* 102.1, 102.8, 103.6, 106.5, 110.3, *CH* $_2$ 41.9, 102.0, *CH* $_3$ 54.4, 56.2, 61.1. Anal. Calcd for $C_{23}H_{25}NO_8$: C, 62.30; H, 5.28; N, 3.16. Found: C, 62.48; H, 5.34; N, 3.14.

General procedure for the synthesis of the 3-arylmethylisoindolinones 22–24

A solution of compounds **4**–**6** (2 mmol) in methanol (30 ml) was stirred with activated Pd/C (10%, 20 mg) and a solution of $HCOONH_4$ (640 mg, 10 mmol) in distilled water (5 ml) was slowly added. The solution mixture was refluxed for 15 min, filtered through celite® and water was added. Extraction with CH_2Cl_2 (3×20 ml), drying with $MgSO_4$ and concentration in vacuo left a solid which was recrystallized from hexane/toluene.

3-Arylmethylisoindolinone 22. 814 mg (98%); mp 126–127°C (lit.[17] 126–127°C); ^{1}H NMR δ 2.65 (dd, *J*=13.8, 8.0 Hz, 1H, $ArCH_2$), 3.18 (dd, *J*=14.1, 6.6 Hz, 1H, NCH_2), 3.31 (dd, *J*=13.8, 3.8 Hz, 1H, $ArCH_2$), 3.39 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.17 (dd, *J*=14.4, 3.6 Hz, 1H, NCH_2), 4.53 (dd, *J*=6.6, 3.6 Hz, 1H, $CHOMe_2$), 4.79 (dd, *J*=8.0, 3.8 Hz, 1H, ArCHN), 5.90 (d, *J*=1.4 Hz, 2H, OCH_2O), 6.38–6.45 (m, 2H, H_{arom}), 6.62 (d, *J*=8.3 Hz, 1H, H_{arom}), 6.69 (d, *J*=7.8 Hz, 1H, H_{arom}), 6.96 (d, *J*=8.3 Hz, 1H, H_{arom}); ^{13}C NMR δ *C* 124.1, 129.6, 138.9, 146.4, 147.0, 147.5, 152.2, 166.7 (CO), *CH* 60.2, 103.4, 108.1, 109.7, 116.0, 117.9, 122.7, *CH* $_2$ 37.8, 42.2, 100.9, *CH* $_3$ 54.7, 55.3, 56.7, 62.4.

3-Arylmethylisoindolinone 23. 728 mg (98%); mp 107–108°C; ^{1}H NMR δ 2.75 (dd, *J*=13.8, 8.0 Hz, 1H, $ArCH_2$), 3.26 (dd, *J*=14.4, 6.6 Hz, 1H, NCH_2), 3.37–3.47 (m, 7H, 2×OCH_3+$ArCH_2$), 3.67 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.26 (dd, *J*=14.4, 3.6 Hz, 1H, NCH_2), 4.55 (dd, *J*=6.6, 3.6 Hz, 1H, $CHOMe_2$), 4.79 (dd, *J*=8.0, 3.8 Hz, 1H, ArCHN), 6.38 (d, *J*=1.6 Hz, 1H, H_{arom}), 6.59 (dd, *J*=8.1, 1.6 Hz, 1H, H_{arom}), 6.72 (d, *J*=8.1 Hz, 1H, H_{arom}), 6.96–7.04 (m, 1H, H_{arom}), 7.34–7.48 (m, 2H, H_{arom}), 7.71–7.78 (m, 1H, H_{arom}); ^{13}C NMR δ *C* 128.2, 132.0, 145.6, 147.9, 148.5, 168.5 (CO), *CH* 61.2, 103.5, 111.0, 112.5, 121.6, 123.0, 123.6, 128.0, 130.9, CH_2 37.1, 42.0, CH_3 54.7, 55.3, 55.7, 55.8. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 68.08; H, 6.91; N, 3.87.

3-Arylmethylisoindolinone 24. 864 mg (97%); mp 137–138°C; ^{1}H NMR δ 2.61 (dd, *J*=13.8, 8.2 Hz, 1H, $ArCH_2$), 3.18 (dd, *J*=14.5, 6.4 Hz, 1H, NCH_2), 3.31 (dd, *J*=13.8, 4.1 Hz, 1H, $ArCH_2$), 3.37 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.72 (s, 6H, OCH_3), 3.77 (s, 3H, OCH_3), 4.18 (dd, *J*=14.5, 3.5 Hz, 1H, NCH_2), 4.48 (dd, *J*=6.4, 3.5 Hz, 1H, $CHOMe_2$), 4.82 (dd, *J*=8.2, 4.1 Hz, 1H, ArCHN), 5.95 (dd, *J*=3.8, 0.9 Hz, 2H, OCH_2O), 6.22 (s, 2H, H_{arom}), 6.38 (s, 2H, H_{arom}), 7.12 (s, 1H, H_{arom}); ^{13}C NMR δ *C* 125.9, 131.6, 137.0, 141.1, 148.1, 150.9, 153.0, 168.1 (CO), *CH* 60.9, 103.2, 103.4, 103.5, 106.6, 128.3, CH_2 38.0, 42.0, 101.8, CH_3 54.7, 55.3, 56.0, 60.8. Anal. Calcd for $C_{23}H_{27}NO_8$: C, 62.01; H, 6.11; N, 3.14. Found: C, 62.17; H, 6.01; N, 3.27.

General procedure for the synthesis of the cyclocondensed products 25–27

Sulfuric acid (95–98%, 10 ml) was added dropwise to a solution of acetals **22**–**24** (0.5 mmol) in acetic acid (glacial, 6 ml). The mixture was stirred at room temperature for 0.5 h. Neutralisation was performed by slow addition of aqueous ammonia (30%). Extraction with CH_2Cl_2

(2×30 ml), drying with Na_2SO_4 and concentration in vacuo left a yellow solid which was finally purified by recrystallization from Et_2O/methanol.

Dihydroisoindolobenzazepine-8-one 25. 148 mg (84%); mp 227–228°C (lit.[17] 226–228°C); ^{1}H NMR δ 2.98 (dd, J=15.4, 9.5 Hz, 1H, $ArCH_2$), 3.32 (d, J=15.4 Hz, 1H, $ArCH_2$), 3.91 (s, 3H, OCH_3), 4.09 (s, 3H, OCH_3), 4.66 (d, J=9.5 Hz, 1H, ArCHN), 5.65 (d, J=10.4 Hz, 1H, CH═), 5.95 (d, J=1.4 Hz, 2H, OCH_2O), 6.69 (s, 2H, H_{arom}), 7.08 (d, J=10.4 Hz, 1H, CH═), 7.17 (s, 2H, H_{arom}); ^{13}C NMR δ *C* 122.9, 129.2, 130.0, 137.4, 146.4, 146.7, 147.5, 152.8, 163.6 (CO), *CH* 68.0, 109.2, 110.0, 110.5, 117.1, 117.4, 120.0, *CH* $_2$ 42.2, 101.2, *CH* $_3$ 56.8, 59.7.

Dihydroisoindolobenzazepine-5-one 26. 125 mg (86%); mp 182–183°C; ^{1}H NMR δ 3.03 (dd, J=15.4, 9.8 Hz, 1H, $ArCH_2$), 3.42 (dd, J=15.4 Hz, 1H, $ArCH_2$), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.78 (d, J=9.8 Hz, 1H, ArCHN), 5.71 (d, J=10.3 Hz, 1H, CH═), 6.71 (s, 1H, H_{arom}), 6.72 (s, 1H, H_{arom}), 7.11 (d, J=10.3 Hz, 1H, CH═), 7.48 (dt, J=6.9, 1.0 Hz, 1H, H_{arom}), 7.56–7.65 (m, 2H, H_{arom}), 7.85 (d, J=7.5 Hz, 1H, H_{arom}); ^{13}C NMR δ *C* 127.8, 128.5, 130.8, 144.2, 147.6, 147.7, 165.5 (CO), *CH* 60.6, 109.6, 113.2, 114.0, 120.0, 122.2, 124.0, 128.8, 132.7, CH_2 41.5, CH_3 56.0, 56.1. Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.14; H, 5.67; N, 4.41.

Dihydroisoindolobenzazepine-5-one 27. 170 mg (89%); mp 212–213°C; ^{1}H NMR δ 2.98 (dd, J=15.2, 9.7 Hz, 1H, $ArCH_2$), 3.31 (d, J=15.2 Hz, 1H, $ArCH_2$), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.69 (d, J=9.7, 4.1 Hz, 1H, ArCHN), 6.03–6.14 (m, 3H, OCH_2O+CH═), 6.52 (s, 1H, H_{arom}), 6.96 (s, 1H, H_{arom}), 7.10 (d, J=10.6 Hz, 1H, CH═), 7.25 (s, 1H, H_{arom}); ^{13}C NMR δ *C* 122.3, 124.7, 132.1, 140.1, 141.3, 148.8, 151.6, 151.8, 152.4, 165.0 (CO), *CH* 56.0, 101.3, 102.5, 103.5, 109.0, 120.2, CH_2 42.2, 102.2, CH_3 60.5, 60.9, 61.2. Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.14; H, 5.02; N, 3.67. Found: C, 65.89; H, 5.23; N, 3.49.

General procedure for the synthesis of the tetrahydroisoindolobenzazepinone 2, 3 and lennoxamine 1

Compounds **1**–**3** were obtained following the same procedure as described for the reduction of the products **4**–**6** but reflux was maintained for 3 h and compounds **1**–**3** were recrystallized from EtOH.

Tetrahydroisoindolobenzazepine-5-one 2. (97%); mp 178–179°C; ^{1}H NMR δ 2.80–3.05 (m, 4H, CH_2), 3.19 (dd, J=14.7, 1.5 Hz, 1H, CH_2), 3.88 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.42 (d, J=10.0 Hz, 1H, CH), 4.73–4.81 (m, 1H, CH_2), 6.73 (s, 2H, H_{arom}), 6.82 (s, 1H, H_{arom}), 7.44–7.50 (m, 1H, H_{arom}), 7.52–7.61 (m, 2H, H_{arom}), 7.86 (d, J=7.5 Hz, 1H, H_{arom}); ^{13}C NMR δ *C* 129.7, 132.0, 133.7, 144.9, 147.1, 147.6, 167.1 (CO), *CH* 61.3, 113.6, 113.8, 122.0, 123.8, 128.4, 131.5, CH_2 35.9, 41.4, 42.2, CH_3 56.0, 56.1. Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.71; H, 6.30; N, 4.38.

Tetrahydroisoindolobenzazepine-5-one 3. (98%); mp 228–229°C; ^{1}H NMR δ 2.48 (ddd, J=15.0, 11.5, 2.0 Hz, 1H, CH_2), 2.83 (dd, J=13.5, 11.5 Hz, 1H, CH_2), 2.91 (dd, J=14.6, 10.7 Hz, 1H, CH_2), 3.10 (dd, J=14.6, 1.5 Hz, 1H, CH_2), 3.44 (dd, J=15.0, 5.6 Hz, 1H, CH_2), 3.82 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.30 (dd, J=10.7, 1.5 Hz, 1H, CH), 4.74 (ddd, J=13.5, 5.6, 2.0 Hz, 1H, CH_2), 6.05 (s, 2H, OCH_2O), 6.61 (s, 1H, H_{arom}), 6.94 (s, 1H, H_{arom}), 7.23 (s, 1H, H_{arom}); ^{13}C NMR δ *C* 126.0, 127.5, 133.6, 140.2, 148.4, 151.2, 151.5, 166.6 (CO), *CH* 56.1, 102.4, 103.5, 109.5, CH_2 26.2, 41.4, 43.0, 101.9, CH_3 60.7, 60.9, 61.4. Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.14; H, 5.02; N, 3.67. Found: C, 65.89; H, 5.23; N, 3.49.

Lennoxamine 1. (98%); the analytical and spectral data of synthetic **1** matched those reported for the natural product.[1]

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