A Short Total Synthesis of the Alkaloids Piperolactam C, Goniopedaline, and Stigmalactam

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The total synthesis of the polyalkoxylated alkaloids piperolactam C, goniopedaline and stigmalactam by combinatorial metalation/cyclization strategies has been achieved. The synthetic route involved the preliminary construction of the polyalkoxylated isoindolinone template by Parham's technique. Benzylic lactam deprotonation allowed connection of a hydroxybenzyl appendage, and the synthesis of the target natural products was completed by subsequent E1cB elimination, radical cyclization and final deprotection.

Introduction

Aristolactams are a minor group of fused phenanthrene lactam alkaloids structurally and biogenetically related to aporphines.[1−4] The richest source of this class of alkaloids is undoubtedly plants of the family *Aristolochiaceae*.[5,6] Extracts of these plants have been used since antiquity and still find some applications in traditional medicine in Turkey,[7] India,[8] Argentina[9] and southern China.[10] These phenanthrene lactams are also considered to be the principal detoxification metabolites of aristolochic acids,[11] which have been implicated in an endemic renal fibrosis known as Chinese herbs nephropathy.[12] They have also been detected in urine and faeces from mammals, including humans, but their exact mode of action has not yet been elucidated.[13]

As a part of a program aiming to synthesize a range of aristolactamic products with oxygenated functions at the 2- and 3-positions of the phenanthrene nucleus for subsequent pharmacological evaluation, we were initially interested in the synthesis of the representative naturally occurring alkaloids piperolactam C (**1**), goniopedaline (**2**) and stigmalactam (**3**). Piperolactam C (**1**) has been isolated from the stem bark of *Piper argyrophylum*,[14] *Piper wightii*,[15] *Piper acutisleginum*[16] and from other Indian *Piper* species, namely *P. boehimerifolium* and *P. longum*.[17] Recent investigations of extracts from *Fissistigma balansae* and *F. oldanii* have also resulted in the isolation of this trimethoxylactam.[18] It is worth noting that a short and skilful synthesis of this alkaloid has recently been reported by V. Snieckus et al.[19] Goniopedaline (**2**) has been isolated from the leaves and twigs of *Goniothalamus sesquipedalis*[20] and very recently *Uvaria hamiltonii*,[21] whilst stigmalactam (**3**) is a new aristolactamic compound recently extracted from *Fissistigma* species found in a climbing shrub indigenous to the broad-leafed tree zone of China and Taiwan.[18] As far as we are aware, no total syntheses of natural products **2** or **3** have appeared in print.

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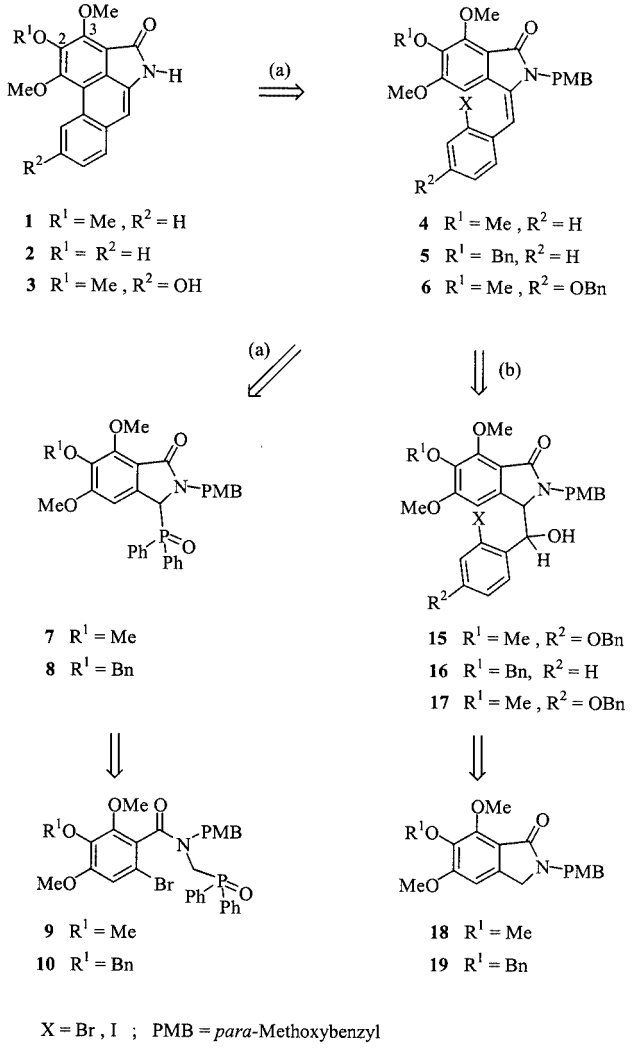
Results and Discussion

The main general synthetic approaches to these phenanthrene lactam compounds involve: (i) oxidation of dehydroaporphines,[22] (ii) metalation/carbonylation of bromophenanthrylamines,[23] (iii) metalation/carbonation of aminophenanthrenes, and (iv) catalytic hydrogenation of the corresponding aristolochic acids.[24] However, these methods are inadequate for the synthesis of models with diverse and dense functionality on their compact framework, particularly with hydrophenolic functions in specific positions on the basic phenanthrene nucleus.

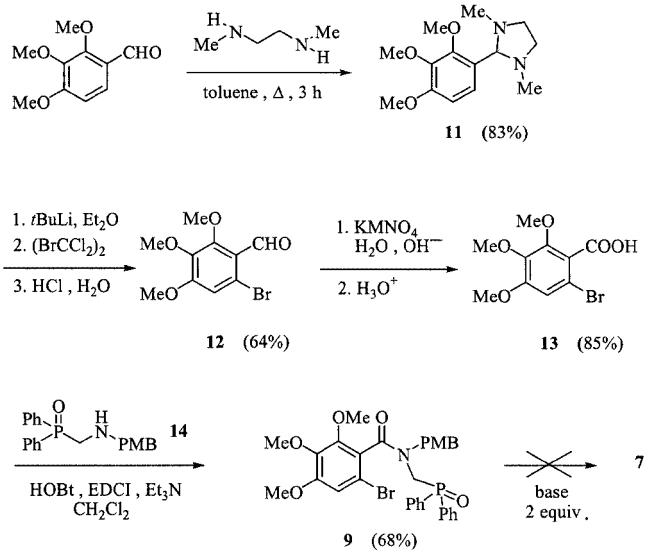
For the synthesis of the target natural products **1**−**3** we initially envisaged the adoption of a strategy hinging on the preliminary synthesis of the (arylmethylene)isoindolinones **4**−**6** (retrosynthetic Scheme 1). Cyclization of these stilbenic intermediates followed by sequential or concomitant deprotection of the primarily annulated compounds should then complete the synthesis of the desired alkaloids. A contentious issue in the construction of the diversely functionalized isoindolinones **4**−**6**, each with a pendant (haloaryl)methylene unit, was the initial judgement of the proper strategy for the stereoselective synthesis of the required models with the mandatory (*E*) stereochemistry. To reach this goal we first opted for the synthetic route depicted in the retrosynthetic Scheme 1 (path a), which has been successfully applied to the synthesis of other members of the aristolactamic series.[25−27] This synthetic approach



Scheme 1

relies upon the construction of the (arylmethylene)isoindolinones **4**–**6** by the Horner process, which is precisely governed by the bulkiness of the substituent connected to the lactam nitrogen atom.[25–28] It was assumed that the first facet of this synthesis, the elaboration of the parent isoindolinones **7** and **8**, each with the phosphoryl appendage and the bulky *p*-methoxybenzyl protective group, should be accomplishable through aryne-mediated cyclization of the halo-*N*-[(diphenylphosphoryl)methyl]benzamide derivatives **9** and **10**.[28,29]

To test the feasibility of such a process on polyalkoxylated models we first set out to prepare the trimethoxy parent model **9** (Scheme 2). The synthesis started with 2,3,4-trimethoxybenzaldehyde, which was converted into the imidazolidine derivative **11** in order to retain the formyl functionality and to direct lithiation to the *ortho* ring position.[30–32] Metalation with *tert*-butyllithium and subsequent quenching with 1,2-dibromotetrachloroethane resulted, as anticipated, in bromination exclusively adjacent to the imidazolidine group. Regeneration of the formyl functionality followed by classical oxidation of the resulting bromobenzaldehyde **12** provided a 45% yield (over three steps) of the bromobenzoic acid **13**. Coupling of this carboxylic acid with the secondary phosphorylated amine **14** – obtained beforehand by treatment of the appropriate hexahydrotriazine with diphenylphosphane oxide[15,25,33] – delivered the required parent bromobenzamide **9**. Somewhat disappointingly, compound **9** was completely unamenable to the aryne-mediated cyclization conditions likely to give access to the required phosphorylated isoindolinone **7** even after considerable experimentation with various solvents, bases and temperatures, with or without crown ethers, instead giving an inextricable mixture of compounds. One can reasonably assume that this failure may be attributable partly to intramolecular nucleophilic aromatic substitution competing with the generation of the aryne functionality, a phenomenon for which there is precedent.[34]



Scheme 2

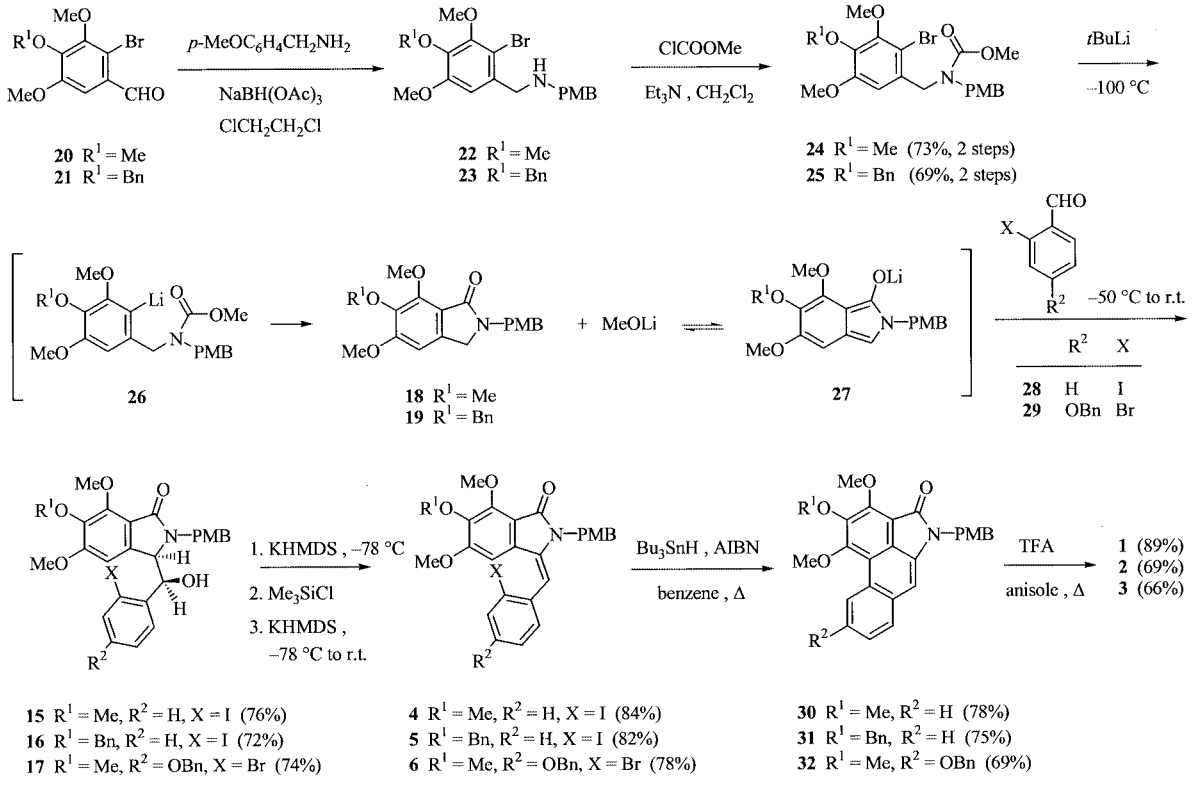
Consequently, we decided to change our plans and to adopt the alternative synthetic tactics depicted in the retrosynthetic Scheme 1 (path b) to achieve the stereoselective preparation of (*E*)-(arylmethylene)isoindolinones **4**–**6**. This work was based on the following premises: (i) the installation of the hydroxyalkyl appendage should be easily achievable by metalation of the parent isoindolinones **18** and **19** and subsequent quenching with the appropriate halobenzaldehyde derivative,[35] and (ii) dehydration of *erythro* and/or *threo* adducts **15**–**17** through an E1cB mechanism would give rise selectively to the desired arylideneisoindolinones **4**–**6** with the (*E*) configuration.[36]

Critical to the success of this strategy then was the construction of the parent isoindolinones **18** and **19** with methyl- or benzyl-protected hydroxy groups. Syntheses of these lactam compounds have been widely investigated, but the application of traditional methods is quite limited and unsatisfactory because of restrictions in the choice of substitu-

ents: namely in their nature, their number and their position on the aromatic nucleus.[29] We thus chose to adopt a new conceptual approach in which the lactam ring would be assembled by lithium/halogen exchange in the bromoaryl derivative **24** and **25**, followed by Parham-type cyclization of the resulting lithiated intermediate **26** (R^1 = Me, Bn), with the carbamate group acting as the internal electrophile (Scheme 3). The synthesis started with the elaboration of the dibenzylamine derivatives **22** and **23**, which were readily obtained by reductive amination of the appropriate bromobenzaldehydes **20** and **21** with *p*-methoxybenzylamine. Treatment of amines **22** and **23** with methyl chloroformate delivered the carbamates **24** and **25** in excellent yields (73 and 69% for **24** and **25**, respectively, over two steps). To ensure the formation of the lithiated intermediate **26**, a THF solution of the aryl bromides **24** and **25** was treated with *tert*-butyllithium. The intramolecular ring-closure was instantaneous, as demonstrated by the isolation solely of the annulated compounds **18** and **19** upon immediate aqueous workup. This annulation reaction releases lithium methoxide, and we assumed that this species might be of sufficient kinetic basicity to induce the formation of the highly stabilized transient carbanion **27**. To test this hypothesis, compounds **24** and **25** were treated with *tert*-butyllithium and subsequently with the appropriate halobenzaldehydes **28** and **29**. To our delight, this approach delivered single compounds, unambiguously identified as alcohols **15**−**17** with *erythro* configurations.[37] As an example, the ^{1}H NMR spectrum of **15** showed a coupling constant of 3.2 Hz between the C-3 and C-α protons, which is in agreement with the *erythro* configuration.[38,39] E1cB elimination was performed by prior *O*-silylation of the hydroxyalkyl adducts **15**−**17** followed by benzylic lactam deprotonation. Gratifyingly, this technique exclusively delivered the (*E*)-configured arylideneisoindolinones **4**−**6**,[36] suitable candidates for the ultimate cyclization step. Oxidative radical cyclization of these stilbenic intermediates proceeded uneventfully to furnish the primarily annulated compounds **30**−**32** in fairly good yields (Scheme 3). Removal of the benzyl protection of the phenolic hydroxy groups of **31** and **32** and of the nitrogen lactams of **30**−**32** was achieved simultaneously by treatment with trifluoroacetic acid, and this single operation delivered the target natural products piperolactam C (**1**), goniopedaline (**2**) and stigmalactam (**3**) in 44, 31 and 26% yields, respectively (over four steps).

Conclusion

In conclusion, we have completed a new conceptual approach to the synthesis of the contiguously polyalkoxylated aristolactam alkaloids. This new route, illustrated by the synthesis of three representative examples, hinges upon the initial construction of the polyalkoxylated isoindolinone template by the Parham procedure. Subsequent hydroxyalkylation of the lactam unit, dehydration of the adducts through an E1cB mechanism and final cyclization complete the total synthesis of the target natural products. The advantages of this synthesis, which lie mainly in the small



Scheme 3

number of steps, their procedural simplicity and high efficiency and the mildness of reaction conditions, provide a strong incentive for the elaboration of similar structurally modified naturally occurring alkaloids.

Experimental Section

General: Tetrahydrofuran (THF) and diethyl ether (Et_2O) were predried with anhydrous Na_2SO_4 and distilled from sodium benzophenone ketyl under Ar before use. Dichloromethane (CH_2Cl_2), 1,2-dichloroethane, triethylamine (NEt_3), toluene and benzene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under Ar. The glassware was fitted 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 taken with a Reichert-Thermopan apparatus and are not corrected. NMR: Bruker AM 300 (300 MHz, 75 MHz and 121 MHz, for ^1H, ^{13}C and ^{31}P, respectively); for ^1H and ^{13}C NMR, $CDCl_3$ as solvent, TMS as internal standard; for ^{31}P NMR, $CDCl_3$ as solvent, H_3PO_4 as external standard. Microanalyses were performed by the CNRS microanalysis centre. Bromobenzaldehyde derivatives **20**,[40] **21**,[41] **28**[42] and **29**[43] were prepared by literature methods. The phosphorylated amine **14**[25] was also synthesized by a reported procedure. The petroleum ether used had a boiling range of 40−60 °C. Abbreviations that have been used in the descriptions that follow: HOBt = 1-hydroxybenzotriazole, EDCl = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.

Preparation of the Phosphorylated Benzamide Derivative 9

6-Bromo-2,3,4-trimethoxybenzaldehyde (12): A solution of 2,3,4-trimethoxybenzaldehyde (9.81 g, 50 mmol) and *N*,*N*′-dimethylethylenediamine (5.43 g, 63 mmol) in toluene (100 mL) was heated at reflux for 3 h in a Dean−Stark apparatus. Toluene was removed in vacuo and the crude product was distilled to afford the 1,3-dimethyl-2-(2,3,4-trimethoxyphenyl)imidazolidine (**11**) (oil, 11.05 g, 83%), b.p. 105−108 °C (0.2 Torr). ^1H NMR: δ = 2.16 (s, 3 H, NCH_3), 2.17 (s, 3 H, NCH_3), 2.53−257 (m, 2 H, NCH_2), 3.32−3.36 (m, 2 H, NCH_2), 3.76 (s, 1 H, NCHN), 3.83 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 7.30 (d, *J* = 8.8 Hz, 1 H, aromatic H), 6.71 (d, *J* = 8.8 Hz, 1 H, aromatic H) ppm. ^{13}C NMR: δ = 39.7, 53.3, 55.9, 60.7, 61.2, 83.9, 108.0, 123.8, 125.0, 141.3, 153.1, 153.7 ppm. $C_{14}H_{22}N_2O_3$ (266.3): calcd. C 63.14, H 8.33, N 10.52; found C 62.86, H 8.53, N 10.21. *t*BuLi (9.8 mL, 1.7 M in pentane, 16.7 mmol) was added dropwise by syringe over 30 min to a stirred solution of freshly distilled imidazolidine **11** (2 g, 7.5 mmol) in Et_2O (50 mL). The mixture was stirred under Ar at room temperature for 6 h. A solution of dibromotetrachloroethane (5.40 g, 16.6 mmol) in Et_2O was then slowly added, and the mixture was stirred at room temperature overnight. Hydrolysis of the aminal was effected with aqueous HCl (ca. 150 mL, 2 M, 30 min, room temp.). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 50 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (100 mL). The organic layers were again combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography with Et_2O/hexanes (3:7) as eluent to afford the title compound **12**, which was recrystallized from hexane: (1.32 g, 64%), m.p. 51−52 °C (ref.[44] oil, b.p. 195 °C, 0.8 Torr). ^{13}C NMR: δ = 56.4, 61.1, 62.4, 113.4, 119.7, 121.5, 142.0, 156.9, 157.8, 189.4 (CH=O) ppm.

6-Bromo-2,3,4-trimethoxybenzoic Acid (13): A suspension of **12** (1 g, 3.6 mmol) in water (30 mL) was stirred at 75 °C, and a solution of $KMnO_4$ (0.86 g, 5.5 mmol) in water (20 mL) was added dropwise over a period of 20 min. After the mixture had been stirred at 75 °C for a further 2 h and then allowed to cool to room temperature, aqueous KOH (20%) was added until pH = 12, and the reaction mixture was filtered through Celite. The filtrate was then acidified (HCl, 10%) until pH = 2, and the mixture was then extracted with Et_2O (3 × 50 mL). The dried (Na_2SO_4) extract was concentrated and the residue was recrystallized from hexane/CH_2Cl_2 to give the acid **13** (0.89 g, 85%), m.p. 112−114 °C (ref.[44] 113−114.5 °C). ^{13}C NMR: δ = 56.4, 60.5, 61.9, 111.3, 112.0, 125.3, 141.1, 150.3, 154.3, 166.3 (COOH) ppm.

6-Bromo-*N*-[(diphenylphosphoryl)methyl]-2,3,4-trimethoxy-*N*-(4-methoxybenzyl)benzamide (9): A solution of acid **13** (882 mg, 3.0 mmol), HOBt (0.45 g, 3.35 mmol), EDCI (645 mg, 3.35 mmol) and Et_3N (460 mg, 4.6 mmol) in freshly distilled CH_2Cl_2 (50 mL) was stirred at 0 °C under Ar for 1 h. A solution of the phosphorylated amine **14** (1.06 g, 3.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise, and the mixture was allowed to warm to room temperature overnight. Aqueous HCl (5%, 10 mL) was added and the separated organic layer was subsequently washed with aqueous KOH (5%, 10 mL), water (20 mL) and brine (20 mL). Concentration of the dried extract left a solid residue, which was purified by flash column chromatography with acetone/petroleum ether (2:3) as eluent to afford the phosphorylated benzamide derivative **9**, which was finally recrystallized from hexane/toluene (1.27 g, 68%), m.p. 155−156 °C. ^1H NMR: δ = 3.66 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.19 (dd, *J* = 6.4, 15.5 Hz, 1 H, NCH_2P), 4.63 (d, *J* = 14.9 Hz, 1 H, NCH_2), 4.70 (dd, *J* = 4.3, 15.5 Hz, 1 H, NCH_2P), 4.80 (d, *J* = 14.9 Hz, 1 H, NCH_2), 6.75 (s, 1 H, aromatic H), 6.84 (d, *J* = 8.6 Hz, 2 H, aromatic H), 7.35 (d, *J* = 8.6 Hz, 2 H, aromatic H), 7.40−7.49 (m, 6 H, aromatic H), 7.84−7.97 (m, 4 H, aromatic H) ppm. ^{13}C NMR: δ = 41.4 (d, $J_{C,P}$ = 77 Hz, NCH_2P), 52.4, 55.2, 56.3, 60.9, 61.8, 111.9, 113.2, 114.0, 124.7, 127.1, 128.6 (d, $J_{C,P}$ = 12 Hz, 4 C), 130.5, 131.1 (d, $J_{C,P}$ = 10 Hz), 131.6 (d, $J_{C,P}$ = 10 Hz), 131.9 (d, $J_{C,P}$ = 95 Hz), 132.0 (d, $J_{C,P}$ = 3 Hz), 132.2 (d, $J_{C,P}$ = 3 Hz), 141.9, 151.0, 154.6, 159.2, 166.3 (NC=O) ppm. ^{31}P NMR: δ = 30.9 ppm. $C_{31}H_{31}BrNO_6P$ (624.5): calcd. C 59.63, H 5.00, N 2.24; found C 59.84, H 5.21, N 2.01.

Preparation of the Carbamates 24, 25

General Procedure for the Synthesis of the Dibenzylamine Derivatives 22 and 23: *p*-Methoxybenzylamine (3.4 g, 25 mmol) and bromobenzaldehyde derivative **20** or **21** (25 mmol) were mixed in dry 1,2-dichloroethane (100 mL) and treated with $NaBH(OAc)_3$ (7.5 g, 35 mmol). The mixture was stirred at room temperature under Ar for 12 h. The reaction mixture was quenched by addition of aqueous NaOH (1 M, 10 mL) and the product was extracted with Et_2O (3 × 50 mL). The organic extract was dried (Na_2SO_4) and the solvents were evaporated to leave an oily residue. The ^1H NMR spectrum clearly indicated the exclusive presence of the dibenzylamine **22** or **23**, which was then used directly in the next step without further purification.

***N*-(2-Bromo-3,4,5-trimethoxybenzyl)-*N*-(4-methoxybenzyl)amine (22):** 9.5 g, 96%, oil. ^1H NMR: δ = 3.73 (s, 2 H, NCH_2), 3.78 (s, 3 H, OCH_3), 3.81 (s, 2 H, NCH_2), 3.84 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 5.27 (s, 1 H, NH), 6.80 (s, 1 H, aromatic H), 6.86 (d, *J* = 8.5 Hz, 2 H, aromatic H), 7.26 (d, *J* = 8.5 Hz, 2 H, aromatic H) ppm. ^{13}C NMR: δ = 52.6, 53.3, 55.3, 56.1, 61.0, 61.1, 109.1, 109.9, 113.8, 129.4, 132.2, 134.9, 142.1, 150.9, 152.6, 158.7 ppm.

***N*-(4-Benzyloxy-2-bromo-3,5-dimethoxy)-*N*-(4-methoxybenzyl)amine (23):** 11.1 g, 94%, oil. ^{1}H NMR: δ = 3.77 (s, 2 H, NCH_2), 3.80 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.85 (s, 2 H, NCH_2), 3.91 (s, 3 H, OCH_3), 5.04 (s, 2 H, OCH_2), 5.30 (s, 1 H, NH), 6.84 (s, 1 H, aromatic H), 6.89 (d, *J* = 8.6 Hz, 2 H, aromatic H), 7.30 (d, *J* = 8.6 Hz, 2 H, aromatic H), 7.32−7.41 (m, 3 H, aromatic H), 7.50−7.54 (m, 2 H, aromatic H) ppm. ^{13}C NMR: δ = 52.7, 53.3, 55.3, 56.2, 61.1, 75.5, 109.2, 110.0, 113.8, 128.1, 128.4 (four peaks overlapping), 129.4, 132.0, 135.2, 137.5, 141.0, 151.3, 152.9, 158.3 ppm.

General Procedure for the Synthesis of the Carbamates 24 and 25: A solution of methyl chloroformate (1.7 g, 18 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise at 0 °C to a solution of dibenzylamine **22** or **23** (12 mmol) and NEt_3 (2.42 g, 24 mmol) in CH_2Cl_2 (100 mL). The mixture was allowed to warm to room temperature and was stirred for an additional 3 h. Water (25 mL) was added, and the organic layer was dried with $MgSO_4$. Evaporation of the solvent left a residue, which was purified by flash column chromatography with acetone/petroleum ether (3:7) as eluent. Compound **24** was finally recrystallized from hexane/toluene.

Methyl *N*-(2-Bromo-3,4,5-trimethoxybenzyl)-*N*-(4-methoxybenzyl)-carbamate (24): 4.0 g, 73%, m.p. 66−67 °C. ^{1}H NMR: δ = 3.77 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.36−4.53 (m, 4 H, NCH_2Ar), 6.43 (s, 1 H, aromatic H), 6.83 (d, *J* = 8.6 Hz, 2 H, aromatic H), 7.11−7.20 (m, 2 H, aromatic H) ppm. ^{13}C NMR: δ = 49.4, 49.9, 53.0, 55.3, 56.1, 61.0, 61.1, 106.6, 108.1, 113.9, 128.9, 129.3, 129.7, 132.2, 150.8, 152.9, 157.4, 159.0 ppm. $C_{20}H_{24}BrNO_6$ (454.3): calcd. C 52.88, H 5.32, N 3.08; found C 53.01, H 5.39, N 3.13.

Methyl *N*-(4-Benzyloxy-2-bromo-3,5-dimethoxy)-*N*-(4-methoxybenzyl)carbamate (25): 4.4 g, 69%, oil. ^{1}H NMR: δ = 3.76 (s, 3 H, OCH_3), 3.78 (s, 6 H, 2 × OCH_3), 3.88 (s, 3 H, OCH_3), 4.38−4.56 (m, 4 H, NCH_2Ar), 5.02 (s, 2 H, NCH_2), 6.46 (s, 1 H, aromatic H), 6.85 (d, *J* = 8.6 Hz, 2 H, aromatic H), 7.10−7.22 (m, 2 H, aromatic H), 7.30−7.41 (m, 3 H, aromatic H), 7.49−7.56 (m, 2 H, aromatic H) ppm. ^{13}C NMR: δ = 49.4, 50.0, 53.0, 55.3, 56.2, 61.0, 75.4, 106.9, 108.3, 113.9, 128.1, 128.3, 128.9, 129.4, 129.7, 132.3, 137.4, 141.3, 151.2, 152.3, 157.4, 159.0 ppm. $C_{26}H_{28}BrNO_6$ (530.4): calcd. C 58.88, H 5.32, N 2.64; found C 60.07, H 5.11, N 2.58.

General Procedure for the Synthesis of the Hydroxyalkylated Isoindolinones 15−17: A solution of carbamate **24** or **25** (2.2 mmol) in dry THF (50 mL) was cooled to −100 °C under Ar, and *t*BuLi (1.4 mL, 1.7 M in pentane, 2.4 mmol) was added dropwise by syringe. The reaction mixture was allowed to warm to −50 °C over a period of 30 min, and a solution of halobenzaldehyde **28** or **29** (2.4 mmol) in THF (5 mL) was then added dropwise. The mixture was allowed to warm to 0 °C, followed by addition of saturated aqueous NH_4Cl and extraction with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated in a rotary evaporator to afford **15−17** as single diastereomers, which were finally purified by recrystallization from EtOH.

3-[(4-Benzyloxy-2-iodophenyl)(hydroxy)methyl]-5,6,7-trimethoxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (15): 960 mg, 76%, m.p. 209−210 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 3.50 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 4.15 (d, *J* = 15.5 Hz, 1 H, NCH_2), 4.58 (d, *J* = 3.2 Hz, 1 H, CH), 5.16 (d, *J* = 15.5 Hz, 1 H, NCH_2Ar), 5.22−5.24 (m, 1 H, CHO), 5.65 (s, 1 H, aromatic H), 5.90 (d, *J* = 4.8 Hz, 1 H, OH), 6.87 (d, *J* = 8.6 Hz, 2 H, aromatic H), 7.11 (dt, *J* = 1.5, 7.5 Hz, 1 H, aromatic H), 7.20 (d, *J* = 8.6 Hz, 2 H, aromatic H), 7.33 (dd, *J* = 1.4, 7.6 Hz, 1 H, aromatic H), 7.46 (t, *J* = 7.4 Hz, 1 H, aromatic H), 7.87 (d, *J* = 7.4 Hz, 1 H, aromatic H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 42.8, 55.0, 55.5, 60.8, 60.9, 62.2, 73.6, 97.2 (C−I), 103.6, 113.9, 117.5, 127.7, 129.0, 129.7, 130.0, 130.2, 138.9, 139.2, 141.0, 142.3, 150.4, 155.0, 158.4, 166.5 (C=O) ppm. $C_{26}H_{26}INO_6$ (575.4): calcd. C 54.27, H 4.55, N 2.43; found C 54.49, H 4.29, N 2.17.

6-Benzyloxy-3-[(hydroxy)(2-iodophenyl)methyl]-5,7-dimethoxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (16): 1.03 g, 72%, m.p. 193−194 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 3.52 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 4.19 (d, *J* = 15.4 Hz, 1 H, NCH_2), 4.63 (d, *J* = 2.7 Hz, 1 H, CH), 4.91 (s, 2 H, OCH_2), 5.19 (d, *J* = 15.4 Hz, 1 H, NCH_2Ar), 5.27 (br. s, 1 H, CHO), 5.70 (s, 1 H, aromatic H), 5.93 (d, *J* = 4.6 Hz, 1 H, OH), 6.89 (d, *J* = 8.5 Hz, 2 H, aromatic H), 7.12 (t, *J* = 6.9 Hz, 1 H, aromatic H), 7.23 (d, *J* = 8.5 Hz, 2 H, aromatic H), 7.31−7.63 (m, 7 H, aromatic H), 7.88 (d, *J* = 7.8 Hz, 1 H, aromatic H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 42.9, 55.1, 55.6, 60.9, 62.3, 73.0, 97.3 (C−I), 103.7, 114.0, 117.6, 127.7, 127.9, 128.0, 128.2, 129.1, 129.8, 130.0, 130.2, 137.6, 139.1, 140.0, 142.4, 150.6, 155.2, 158.5, 166.5 (C=O) ppm. $C_{32}H_{30}INO_6$ (651.5): calcd. C 59.00, H 4.64, N 2.15; found C 58.78, H 4.44, N 2.30.

3-[(4-Benzyloxy-2-bromophenyl)(hydroxy)methyl]-5,6,7-trimethoxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (17): (1.03 g, 74%), m.p. 154−155 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 3.45 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 4.18 (d, *J* = 15.4 Hz, 1 H, NCH_2), 4.48 (br. s, 1 H, CH), 5.14 (s, 2 H, OCH_2), 5.20 (d, *J* = 15.4 Hz, 1 H, NCH_2), 5.33 (br. s, 1 H, CHO), 5.67 (s, 1 H, aromatic H), 5.80 (d, *J* = 4.4 Hz, 1 H, OH), 6.88 (d, *J* = 8.3 Hz, 2 H, aromatic H), 7.11 (t, *J* = 8.5 Hz, 1 H, aromatic H), 7.18 (d, *J* = 8.3 Hz, 2 H, aromatic H), 7.28−7.44 (m, 7 H, aromatic H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 42.8, 55.1, 55.5, 60.8 (two peaks overlapping), 62.2, 68.4, 69.5, 103.3, 113.8, 113.9, 117.5, 118.6, 121.0, 127.6, 127.9, 128.5, 129.1, 129.6, 130.8, 131.5, 136.6, 138.9, 140.9, 150.4, 155.1, 158.4, 158.5, 166.4 (C=O) ppm. $C_{33}H_{32}BrNO_7$ (634.5): calcd. C 62.47, H 5.08, N 2.21; found C 62.71, H 4.92, N 2.46.

Preparation of Isoindolinones 18 and 19: Aqueous NH_4Cl addition to the crude reaction mixture resulting from treatment of **24** or **25** with *t*BuLi as described above allowed the isolation of the isoindolinones **18** and **19**, which were obtained in very good yield by this method.

5,6,7-Trimethoxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (18): (640 mg, 85%), m.p. 94−95 °C (from hexane/toluene). ^{1}H NMR: δ = 3.75 (s, 3 H, OCH_3), 3.84 (s, 6 H, 2 × OCH_3), 4.09 (s, 2 H, NCH_2), 4.12 (s, 3 H, OCH_3), 4.62 (s, 2 H, NCH_2), 6.60 (s, 1 H, aromatic H), 6.81 (d, *J* = 8.7 Hz, 2 H, aromatic H), 7.19 (d, *J* = 8.7 Hz, 2 H, aromatic H). ^{13}C NMR: δ = 45.5, 48.8, 55.3, 56.2, 61.4, 62.6, 101.3, 114.0, 117.4, 129.4, 129.5, 138.7, 141.0, 151.5, 157.0, 159.0, 166.8 (C=O). $C_{19}H_{21}NO_5$ (343.4): calcd. C 66.46, H 6.16, N 4.08; found C 66.36, H 6.07, N 3.95.

6-Benzyloxy-5,7-dimethoxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (19): 755 mg, 82%, oil. ^{1}H NMR: δ = 3.76 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.10 (s, 5 H, OCH_3 + NCH_2), 4.64 (s, 2 H, NCH_2), 5.01 (s, 2 H, OCH_2), 6.60 (s, 1 H, aromatic H), 6.84 (d, *J* = 8.0 Hz, 2 H, aromatic H), 7.22 (d, *J* = 8.0 Hz, 2 H, aromatic H), 7.25−7.37 (m, 3 H, aromatic H), 7.48−7.50 (m, 2 H, aromatic H) ppm. ^{13}C NMR: δ = 45.6, 48.9, 55.3, 56.2, 62.6, 75.7, 101.4, 114.1, 117.5, 128.0, 128.3, 128.5, 129.4, 129.5, 137.5, 138.9, 140.6, 151.8, 157.3, 159.1, 166.8 (C=O) ppm. $C_{25}H_{25}NO_5$ (419.3): calcd. C 71.58, H 6.01, N 3.34; found C 71.71, H 6.22, N 3.53.

General Procedure for the Synthesis of the (Arylmethylene)isoindolinones 4−6: Potassium bis(trimethylsilyl)amide (KHMDS, 3.3 mL, 0.5 M in toluene, 1.65 mmol) was added dropwise at −78 °C to a stirred solution of **15**−**17** (1.5 mmol) in THF (50 mL). Freshly distilled Me_3SiCl (180 mg, 1.65 mmol) was added, and the reaction mixture was allowed to warm to room temperature over a period of 1 h. The mixture was recooled to −78 °C, treated with KHMDS (3.3 mL, 0.5 M in toluene, 1.65 mmol), again allowed to warm to room temperature and finally quenched with saturated aqueous NH_4Cl before extraction with Et_2O (3 × 20 mL) and CH_2Cl_2 (3 × 25 mL). The organic extracts were combined, washed with water (10 mL) and brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the (arylmethylene)isoindolinones **4**−**6**, which were purified by flash column chromatography with EtOAc/petroleum ether (2:3) as eluent and finally recrystallized from hexane/toluene to obtain the pure products (*E*)-**4**−**6**.

(*E*)-3-(2-Iodobenzylidene)-5,6,7-trimethoxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindolin-1-one (4): 700 mg, 84%, m.p. 133−134 °C. ^{1}H NMR: δ = 3.44 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.13 (s, 3 H, OCH_3), 5.00 (s, 2 H, NCH_2), 6.19 (s, 1 H, aromatic H), 6.24 (s, 1 H, CH=), 6.85 (d, *J* = 8.6 Hz, 2 H, aromatic H), 7.03 (t, *J* = 8.0 Hz, 1 H, aromatic H), 7.29 (d, *J* = 8.6 Hz, 2 H, aromatic H), 7.35 (t, *J* = 7.9 Hz, 1 H, aromatic H), 7.44 (d, *J* = 7.8 Hz, 1 H, aromatic H), 7.93 (d, *J* = 8.0 Hz, 1 H, aromatic H) ppm. ^{13}C NMR: δ = 42.6, 55.3, 55.7, 61.4, 62.5, 101.1 (C−I), 102.1, 113.4, 114.1, 115.1, 127.9, 128.7, 129.1, 129.4, 129.5, 130.9, 132.0, 136.0, 139.8, 142.9, 151.1, 156.7, 158.8, 164.9 (C=O) ppm. $C_{26}H_{24}INO_5$ (557.4): calcd. C 56.03, H 4.34, N 2.51; found C 56.31, H 4.08, N 2.32.

(*E*)-6-Benzyloxy-3-(2-iodobenzylidene)-5,7-dimethoxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindolin-1-one (5): 780 mg, 82%, m.p. 118−119 °C. ^{1}H NMR: δ = 3.43 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.09 (s, 3 H, OCH_3), 5.01 (s, 4 H, OCH_2 + NCH_2), 6.21 (s, 1 H, aromatic H), 6.28 (s, 1 H, CH=), 6.86 (d, *J* = 8.7 Hz, 2 H, aromatic H), 7.03 (t, *J* = 7.4 Hz, 1 H, aromatic H), 7.25−7.38 (m, 6 H, aromatic H), 7.45−7.49 (m, 3 H, aromatic H), 7.93 (d, *J* = 8.0 Hz, 1 H, aromatic H) ppm. ^{13}C NMR: δ = 42.6, 55.3, 55.8, 62.6, 75.7, 101.1 (C−I), 102.2, 113.4, 114.1, 115.2, 127.9, 128.1, 128.3, 128.4, 128.8, 129.2, 129.4, 130.9, 132.2, 136.1, 137.3, 139.3, 139.9, 142.0, 151.5, 157.0, 158.9, 165.0 (C=O) ppm. $C_{32}H_{28}INO_5$ (633.5): calcd. C 60.67, H 4.46, N 2.21; found C 60.93, H 4.49, N 2.46.

(*E*)-3-(4-Benzyloxyl-2-bromobenzylidene)-5,6,7-trimethoxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindolin-1-one (6): 720 mg, 78%, m.p. 107−108 °C. ^{1}H NMR: δ = 3.44 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.12 (s, 3 H, OCH_3), 4.98 (s, 2 H, OCH_2), 5.08 (s, 2 H, NCH_2), 6.21 (s, 1 H, aromatic H), 6.43 (s, 1 H, CH=), 6.84 (d, *J* = 8.6 Hz, 2 H, aromatic H), 6.90 (dd, *J* = 2.5, 8.5 Hz, 1 H, aromatic H), 7.26−7.39 (m, 9 H, aromatic H) ppm. ^{13}C NMR: δ = 42.5, 55.3, 55.8, 61.4, 62.5, 70.2, 102.0, 109.2, 114.0, 115.2, 119.1, 125.4, 127.3, 128.2, 128.3, 128.6, 128.7, 129.2, 132.1, 132.2, 135.9, 136.1, 142.9, 151.1, 156.6, 158.8, 164.8 (C=O) ppm. $C_{33}H_{30}BrNO_6$ (616.5): calcd. C 64.29, H 4.90, N 2.27; found C 64.05, H 5.11, N 2.04.

General Procedure for the Synthesis of the Annulated Compounds 30−32: A solution of nBu$_3$SnH (378 mg, 1.3 mmol) and AIBN (164 mg, 1 mmol) in dry degassed benzene (50 mL) was added by syringe over a period of 30 min to a solution of (*E*)-**4**−**6** (1 mmol) in dry degassed benzene (500 mL) at reflux under Ar. Once addition was complete, heating at reflux was continued for a further 3 h. The benzene was evaporated under reduced pressure, and the residue was dissolved in CH_3CN (100 mL). The solution was washed with hexane (3 × 50 mL) and concentrated in vacuo to a solid residue, which was recrystallized from EtOH to afford **30**−**32**.

1,2,3-Trimethoxy-5-(4-methoxybenzyl)-4,5-dihydrodibenzo[*cdf*]indol-4-one (30): 195 mg, 78%, m.p. 108−109 °C. ^{1}H NMR: δ = 3.75 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.17 (s, 3 H, OCH_3), 4.56 (s, 3 H, OCH_3), 5.11 (s, 2 H, NCH_2Ar), 6.83 (d, *J* = 6.7 Hz, 2 H, aromatic H), 7.03 (s, 1 H, aromatic H), 7.31 (d, *J* = 6.7 Hz, 2 H, aromatic H), 7.47−7.56 (m, 2 H, aromatic H), 7.74−7.78 (m, 1 H, aromatic H), 9.15−9.19 (m, 1 H, aromatic H) ppm. ^{13}C NMR: δ = 43.4, 55.3, 60.8, 61.6, 63.1, 105.5, 108.6, 114.1, 116.2, 124.7, 125.7, 126.4, 126.5, 126.8, 128.7, 128.8, 129.0, 133.2, 135.5, 146.3, 154.0, 156.9, 159.0, 165.5 (C=O) ppm. $C_{26}H_{23}NO_5$ (249.5): calcd. C 72.71, H 5.40, N 3.26; found C 72.59, H 5.55, N 3.30.

2-Benzyloxy-1,3-trimethoxy-5-(4-methoxybenzyl)-4,5-dihydrodibenzo[*cdf*]indol-4-(5*H*)-one (31): 380 mg, 75%, m.p. 96−97 °C. ^{1}H NMR: δ = 3.84 (s, 3 H, OCH_3), 4.18 (s, 3 H, OCH_3), 4.50 (s, 3 H, OCH_3), 5.10 (s, 2 H, NCH_2Ar), 5.14 (s, 2 H, OCH_2), 6.85 (d, *J* = 8.7 Hz, 2 H, aromatic H), 7.03 (s, 1 H, aromatic H), 7.34 (d, *J* = 8.7 Hz, 2 H, aromatic H), 7.37−7.46 (m, 3 H, aromatic H), 7.50−7.60 (m, 4 H, aromatic H), 7.76−7.79 (m, 1 H, aromatic H), 9.17−9.23 (m, 1 H, aromatic H) ppm. ^{13}C NMR: δ = 43.4, 55.3, 61.0, 63.0, 76.1, 105.5, 108.7, 114.1, 116.3, 124.9, 125.7, 126.4, 126.8, 128.3, 128.5, 128.6, 128.8, 129.1, 133.3, 135.6, 137.2, 145.3, 154.2, 157.2, 159.0, 165.5 (C=O) ppm. $C_{32}H_{27}NO_5$ (505.6): calcd. C 76.02, H 5.38, N 2.77; found C 76.04, H 5.47, N 2.87.

9-Benzyloxy-1,2,3-trimethoxy-5-(4-methoxybenzyl)-4,5-dihydrodibenzo[*cdf*]indol-4-(5*H*)-one (32): (370 mg, 69%), m.p. 98−99 °C. ^{1}H NMR: δ = 3.75 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 4.57 (s, 3 H, OCH_3), 5.09 (s, 2 H, NCH_2), 5.27 (s, 2 H, OCH_2), 6.83 (d, *J* = 8.5 Hz, 2 H, aromatic H), 6.97 (s, 1 H, aromatic H), 7.24 (dd, *J* = 2.5, 8.8 Hz, 1 H, aromatic H), 7.30−7.43 (m, 5 H, aromatic H), 7.50−7.52 (m, 2 H, aromatic H), 7.68 (d, *J* = 8.8 Hz, 1 H, aromatic H), 8.76 (d, *J* = 2.5 Hz, 1 H, aromatic H) ppm. ^{13}C NMR: δ = 43.4, 55.2, 60.8, 61.6, 63.1, 70.1, 105.5, 108.7, 109.6, 114.1, 115.8, 116.8, 124.9, 127.3, 127.7, 127.9, 128.0, 128.5, 128.6, 128.7, 129.1, 129.8, 133.8, 137.1, 146.0, 154.1, 156.8, 156.9, 159.0, 165.3 (C=O) ppm. $C_{33}H_{29}NO_6$ (535.6): calcd. C 74.00, H 5.46, N 2.62; found C 74.12, H 5.61, N 2.51.

General Procedure for the Synthesis of the Target Products 1−3: A solution of **30**−**32** (0.5 mmol) and anisole (1.07 g, 10 mmol) in trifluoroacetic acid (30 mL) was heated at reflux under Ar for 12 h (for **30**) or for 60 h (for **31** and **32**). The solvent and excess anisole were removed under vacuum. The residue was dissolved in CH_2Cl_2 (20 mL), and NEt_3 (1 mL) was added with stirring. Water (2 mL) was then added, and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated to yield a solid residue, which was recrystallized from EtOH. The analytical data of synthetic **1**−**3** matched those reported for the natural products.

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