Total Syntheses of Taliscanine, Velutinam, and Enterocarpam II

Axel Couture,* Eric Deniau, Pierre Grandclaudon, and Christophe Hoarau

Laboratoire de Chimie Organique Physique, URA CNRS 351, Université des Sciences et Technologies de Lille, F-59655 Villeneuve d'Ascq Cedex, France

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Introduction

The aristolactams (**1**−**4**, see Scheme 1) are a minor group of naturally occurring aporphinoid alkaloids biogenetically derived from isoquinolines.[1] They are characterized by a tetracyclic skeleton with a phenanthrene core and are found exclusively among the plants of the family *Aristolochiaceae*.[2] The current interest elicited by these fused phenanthrene lactams arises from their varied pharmaceutical and biological activities emphasized by their use in folk medicine[3] and as immunostimulant and anticancer agents.[2] In addition, the structural complexities of aristolactams as exemplified by taliscanine, velutinam, and enterocarpam II (**1**−**3**) make them challenging synthetic targets and therefore represent an interesting proving ground for organic chemists. The main general approaches to the synthesis of these compounds involve (i) the catalytic hydrogenation of the appropriately substituted aristolochic acid derivatives,[4] (ii) the oxidation of dehydroaporphines,[5] and (iii) the metalation−carbonylation reaction of bromophenanthrylamines obtained by Pschorr reaction of aminostilbene carboxylic acids, themselves obtained from a Perkin condensation of phenylacetic acid and nitrobenzaldehyde derivatives.[6] These methods are rather laborious, low yielding, and generally inadequate for the synthesis of models carrying specific substituents, namely one or several hydroxyphenolic groups in particular positions on the basic phenanthrene nucleus. In recent years, Castedo and his group have considerably enriched the repertoire of the synthetic methods available for the elaboration of these aristolactams by suggesting four different alternative routes. The key step in three of these approaches was the construction of the phenanthrene ring system which was assembled in the ultimate step (i) by photoinduced electrocyclic ring closure of a stilbenic precursor[7] or by (ii) inter-[8] and (iii) intramolecular[9] benzyne cycloaddition of (di)enamides. A fourth approach involved contraction of the lactone ring of dehydrodibenzochromanones and subsequent lactamization of the five-membered lactone.[10] However, these elegant and skillful routes suffer from the main drawback associated with the synthesis of unsymmetrical derivatives and for their lack of regioselectivity. Consequently, they have been mainly confined to the synthesis of models incorporating dimethoxy groups, such as in cepharanone B (**4**).[7,11] We therefore considered that for the convenient synthesis of a range of aristolactamic natural products, a more versatile procedure would be necessary, and we thus set out to prepare the representative aristolactams taliscanine (**1**), velutinam (**2**), and enterocarpam II (**3**). Taliscanine occurs in the rhizomes of *Aristolochia taliscanina*,[12] and enterocarpam II has been extracted from the stem bark of *Orophea enterocarpa* (*Annoniacecae*).[13] Velutinam has been isolated from extracts of leaves and twigs of *Goniothalamus velutinus* which have been used as mosquito repellents and for treating headaches and cases of food poisoning.[14] As far as we know the total synthesis of these compounds has not been reported to date.

Results and Discussion

Our approach to the synthesis of compounds **1**−**3**, which is depicted in the retrosynthetic analysis shown in Scheme 1, involved four phases. Of central importance was the construction of the isoindolinone template contiguously and differentially substituted by phenolic methoxy- and benzyl-protected hydroxy groups on the aromatic moiety. Once prepared, this lactam intermediate served, via the organometallic derivatives **13**, **14**, as a framework for the introduction of the halogenoarylmethylene unit at the 3-position of the heterocyclic nucleus. Horner reaction and subsequent free radical cyclization of the stilbenic intermediates **10**−**12** to generate the phenanthrene ring system followed by sequential *O*- and *N*-deprotection of the primarily annulated products **5**−**7** then completed the synthesis of the target natural products.

* To whom correspondence should be addressed. Fax +33 − (0)3 20 43 65 61. e-mail Axel.Couture@univ-lille1.fr.

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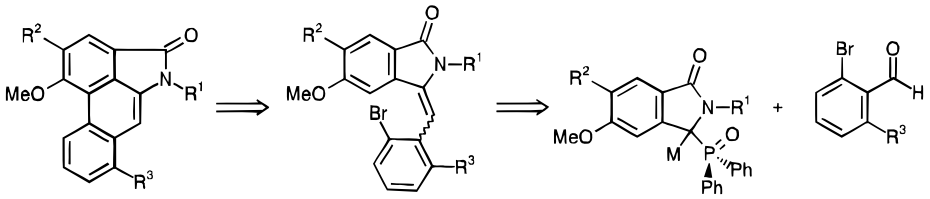
Scheme 1

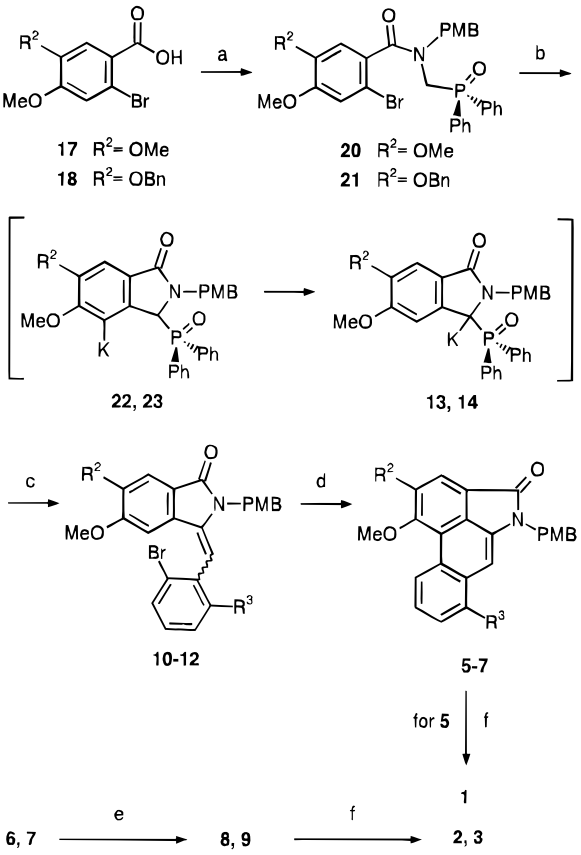


1	R^1 = H, R^2 = R^3 = OMe	**10**	R^1 = PMB, R^2 = R^3 = OMe
2	R^1 = H, R^2 = OH, R^3 = OMe	**11**	R^1 =PMB, R^2 = OBn, R^3 = OMe
3	R^1 = H, R^2 = OMe, R^3 = OH	**12**	R^1 = PMB, R^2 = OMe, R^3 = OBn
4	R^1 = R^3 = H, R^2 = OMe	**13**	R^1 = PMB, R^2 = OMe
5	R^1 = PMB, R^2 = R^3 = OMe	**14**	R^1 = PMB, R^2 = OBn
6	R^1 = PMB, R^2 = OBn, R^3 = OMe	**15**	R^3 = OMe
7	R^1 = PMB, R^2 = OMe, R^3 = OBn	**16**	R^3 = OBn
8	R^1 = PMB, R^2 = OH, R^3 = OMe		M = metal
9	R^1 = PMB, R^2 = OMe, R^3 = OH		PMB = 4-$MeOC_6H_4CH_2$

The first facet of this synthesis, the construction of the isoindolinone unit was accomplished by taking advantage of a newly developed aryne-mediated cyclization methodology applied to halogeno-*N*-(phosphinylmethyl)benzamide derivatives.[15] Syntheses of phthalimidine (2,3-dihydro-1*H*-isoindol-1-one) derivatives have been widely investigated, but the applications of traditional methods are quite limited and unsatisfactory because of severe reaction conditions,[16] difficulties in purification,[17] and above all, limitations in substituents.[18] To obviate these problems a direct annulation approach based on a four-component condensation involving phenyllithium, an imine, diversely substituted *o*-iodobenzoates, and BF_3–Et_2O has been recently proposed, but the isoindolinones were invariably aryl- or alkylated at the 3-position of the heterocyclic nucleus.[19] Phthalimidines may also be obtained by reduction of the corresponding phthalimides, but this strategy is always fraught with difficulties associated with the regioselective reduction of unsymmetrically disubstituted models.[20] We therefore decided to apply the aryne-mediated cyclization of halogeno *N*-[(diphenylphosphinoyl)methyl]benzamide derivatives, which represents a conceptually new approach to the synthesis of these heterobicyclic compounds, to the assembly of the required isoindolinone units embedded in the aristolactam skeletons.

The required parent phosphorylated carboxamides **20**, **21** were synthesized by coupling *N*-[(diphenylphosphinoyl)methyl]-*N*-(4-methoxybenzyl)amine **19** with the acid chlorides derived from the carboxylic acids **17**, **18** obtained by bromination and subsequent oxidation of veratraldehyde and *O*-benzylisovanillin, respectively (Scheme 2). The phosphorylated amine **19** was readily obtained beforehand by treatment of the appropriate

Scheme 2[a]



[a] Reaction conditions and reagents: (a) $SOCl_2$, DMF cat., rt, 12 h then 4-$MeOC_6H_4CH_2NHCH_2P(O)Ph_2$ **19**, CH_2Cl_2, Et_3N, rt, 2 h; (b) KHMDS (2 equiv), THF, −78 °C to −30 °C, 3 h; (c) **15**, **16** (1 equiv), THF, −30 °C to rt, 0.5 h, then H_3O^+; (d) Bu_3SnH (1.5 equiv), AIBN cat., benzene, reflux, 3 h; (e) $HCOONH_4$, Pd on C, aqueous CH_3OH, reflux, 0.5 h; (f) TFA (10 equiv), anisole (10 equiv), $ClCH_2CH_2Cl$, reflux, 24 h.

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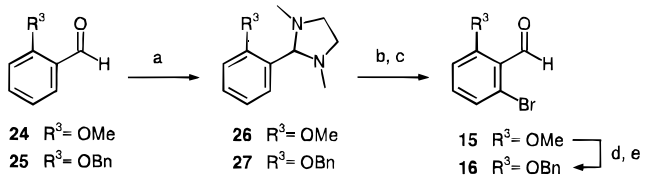
Table 1. Compounds Prepared

phosphorylated benzamide (yield, %)	benzaldehyde (yield, %)	arylmethylene isoindolinone (*E*/*Z* ratio; yield, %)	primarily annulated product (yield, %)	*N*-protected hydroxy aristolactam (yield, %)	target natural product (yield, %)
20 (92)	**15** (78)	**10** (80/20; 80)	**5** (85)	-	**1** (91)
21 (91)	**15** (78)	**11** (70/30; 81)	**6** (75)	**8** (96)	**2** (89)
20 (92)	**16** (64)	**12** (100/−; 84)	**7** (65)	**9** (95)	**3** (88)

hexahydrotriazine with diphenylphosphine oxide.[21] Exposure of the phosphorylated bromobenzamide derivatives **20**, **21** to potassium hexamethyldisilazide (KHMDS, 2 equiv) at −78 °C in THF induced the formation of the aryne unit and the concomitant regioselective formation of the phosphoryl stabilized carbanion. Addition of this suitably placed carbon nucleophile across the aryne moiety causes an intramolecular arylation reaction and gives rise to the metalated isoindolinones **22**, **23**. Due to the presence of the diphenylphosphinoyl group which survived the metalation−addition step, a potassium counterion shift was observed thus providing the benzylic-based carbanions **13**, **14** as shown by D_2O quenching at this step and observation of exclusive incorporation of deuterium at the 3-position of the lactam ring. Hence it could be envisioned to perform the first two phases of the total synthesis with which we were concerned as a single, one-pot reaction. The suitably substituted *o*-bromobenzaldehydes **15**, **16** were thus added to the crude reaction mixture, and, gratifyingly, conducting the reaction according to this procedure afforded straightforwardly the arylmethylene isoindolinones **10**−**12** in fairly good yields (Table 1). Initially the synthesis of the required 2-bromo-6-alkoxybenzaldehydes **15**, **16** proved to be unexpectedly more problematic than we had anticipated. Indeed, the Reimer−Tiemann protocol for the formylation of 3-bromophenol was not appealing since it has been reported as a very low-yielding process (2%)[22] and further modifications did not improve the yield to an acceptable level (15%).[23] We therefore switched our attention to the metalation reaction of 2-hydroxybenzaldehyde. Unfortunately, this reaction has been recently a subject of controversy,[24,25] and it has been unambiguously demonstrated that even though the phenoxide group ranks modestly in the hierarchy of the *ortho*-directing metalation groups,[26] lithiation occurs selectively and exclusively at the *ortho*-position of the phenolic hydroxy group.[25] Consequently we found it more judicious to perform the metalation bromination process on the 2-alkoxybenzaldehydes **24**, **25** (Scheme 3). Critical to the success of this strategy was then the ability to identify a masked carboxaldehyde synthon that was capable not only of retaining the formyl functionality but also of directing subsequent lithiation to the *ortho* ring position. After considerable experimentation with various temperatures, ethereal solvents, bases and bromination agents we found that adding 3 equiv of *tert*-butyllithium in pentane to 1 equiv of imidazolidine **26**[27] in Et_2O at room temperature and then quenching with 1,2-dibromotetrachloroethane led to bromination exclusively adjacent to the imidazolidine group. Regeneration of the formyl functionality provided a 78% yield of 2-bromo-6-methoxybenzaldehyde **15**. However, all attempts to apply this protocol to the bromination of the lithio derivative of **27** were unrewarding probably due to the sensitivity of the benzyloxy protective group with regards to alkyllithium reagents and/or to the hydrolytic conditions employed.[28] Consequently compound **16** was finally synthesized by sequential demethylation (BBr_3, CH_2Cl_2) and *O*-benzylation (KOH, EtOH, BnBr) of the methoxy derivative **15** (Scheme 3).

Scheme 3[a]



[a] Reaction conditions and reagents: (a) $MeNH(CH_2)_2NHMe$, EtOH, rt, 20 h; (b) *tert*-butyllithium (3 equiv), Et_2O, rt, 6 h, then $BrCCl_2CCl_2Br$ (3 equiv), Et_2O, rt, 12 h; (c) aqueous HCl 2 M; (d) BBr_3 (5 equiv), CH_2Cl_2, −70 °C, 1 h then rt, 2 h; (e) BnBr, KOH, EtOH, reflux, 5 h.

The arylmethylene-1*H*-isoindolin-1-ones **10**−**12** were obtained in both *E* and *Z* forms with the *E* form predominant by a large margin (Table) as unambiguously assigned from their ^1H NMR spectra with the help of NOE experiments.[29] Since thermal *Z*−*E* isomerization was observed upon recrystallization of the *Z*-forms, stereochemical considerations about the central double bond were therefore not crucial for the radical−mediated cyclization resulting in the formation of the biaryl bond of the phenanthrene ring system. Compounds **10**−**12**, *E* and *Z*, were then directly subjected to the well documented oxidative radical cyclization conditions (Scheme 2).[30] The radical reaction was performed by slow (10 min) dropwise addition of a benzene solution of tributyltin hydride (1.5 equiv) and AIBN to a refluxing benzene solution of **10**−**12** under argon. This protocol delivered the fused aristolactams **5**−**7** with satisfactory yields (Table 1). The benzyl protection of the phenolic hydroxy group of **6**, **7** was readily removed ($HCOONH_4$, Pd on C, MeOH), thus providing a 96 and 95% yield of the hydroxy aristolactams **8**, **9** respectively. Final removal of the *p*-methoxybenzyl protective group in **5**, **8**,

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(28) Under the same metalation conditions and upon acidic aqueous workup, a considerable amount of α-hydroxybenzaldehyde was recovered.

(29) The structure and the *E*/*Z* ratio were established by NOE difference experiments. The *N*-methylene H_2 (δ 5.06 ppm) showed a strong NOE to vinylic H (δ 5.99 ppm, 16%) (values given for **10** *E*).

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and **9** proceeded uneventfully even though there are only a few known examples of *N*-benzylated aromatic enamides which have been successfully deprotected.[31] Thus treatment of the methoxy and hydroxy lactams **5**, **8**, and **9** with trifluoroacetic acid−anisole (1:1) in boiling 1,2-dichloroethane[32] led to the target natural products taliscanine (**1**) in 65% yield (over three steps), and velutinam (**2**) and enterocarpam II (**3**) in 51 and 44% yield, respectively (over four steps). The analytical and spectral data of synthetic **1**−**3** agree with those reported for the natural alkaloids.[12−14,33]

To sum up the goal of our program has been to develop a new, general and versatile approach to the synthesis of aristolactams. This new route, which has been illustrated by the total synthesis of three exemplary representatives, offers special advantages including high regioselectivity, high efficiency, procedural simplicity, and mildness of reaction conditions. We are currently exploring the utility of this tactically new approach in the synthesis of other natural products.

Experimental Section

General. All reactions were carried out under argon. Melting points are uncorrected. Solvents were dried by distillation from a drying agent and stored over 3-Å molecular sieves under Ar: toluene was distilled over sodium; dichloromethane, hexanes, and triethylamine were distilled from CaH_2. Ethanol and methanol were distilled from magnesium turnings. Tetrahydrofuran (THF) and ether (Et_2O) were predried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded at 300, 75, and 121 MHz, respectively, on a Bruker AM 300 apparatus with TMS as internal standard or with H_3PO_4 as external standard. Infrared spectra were recorded in a KBr pellet on a Perkin-Elmer 881. Elemental analyses were performed by the CNRS microanalysis center. For flash chromatography, Merck silica gel 60 (230−400 mesh ASTM) was used.

Materials. The phosphorylated amine **19** was prepared by treatment of *N*-[(4-methoxyphenyl)methyl]hexahydrotriazine[34] with diphenylphosphine oxide.[21,34]

The bromobenzoic acid derivatives **17**,[35] **18**[36] were synthesized according to already reported procedures.

2-Bromo-6-methoxybenzaldehyde (15). A solution of *o*-anisaldehyde (10 g, 74 mmol) and *N*,*N*′-dimethylethylenediamine (7.9 g, 90 mmol) in EtOH (350 mL) was stirred at room temperature for 20 h. $MgSO_4$ (ca. 14 g) was added, and the resulting mixture was stirred for a further 15 min. The reaction mixture was filtered and washed with Et_2O, and the Et_2O/EtOH was removed in vacuo. The crude product was distilled to afford the 2-(2-methoxyphenyl)-1,3-dimethylimidazolidine (**26**) which was finally purified by recrystallization from hexane (11.7 g, 77%): mp 41−42 °C (lit.[37] bp 96−100 °C/2 mbar); ^1H NMR ($CDCl_3$) δ 2.18 (s, 6H), 2.56 (m, 2H), 3.30 (m, 2H), 3.80 (s, 3H), 4.02 (s, 1H), 6.85 (dd, J = 8.3, 0.9 Hz, 1H), 6.95 (dt, J = 7.5, 0.9 Hz, 1H), 7.22 (m, 1H), 7.65 (dd, J = 7.5, 1.8 Hz, 1H);^{13}C NMR ($CDCl_3$) δ 158.9, 129.2, 128.8, 127.6, 121.1, 110.3, 82.7, 55.4, 53.5, 39.7.

To a stirred solution of freshly recrystallized imidazolidine **26** (1 g, 4.9 mmol) in Et_2O (40 mL) was added *tert*-BuLi (8.8 mL, 1.7 M in pentane, 15 mmol) dropwise by syringe over 30 min. The mixture was stirred under Ar at room temperature for 6 h. A solution of dibromotetrachloroethane (5 g, 15 mmol) in Et_2O (10 mL) was then slowly added, and the mixture was stirred at room temperature overnight. Hydrolysis of the aminal was effected using aqueous 2 M HCl (ca. 150 mL, 30 min, rt). The organic layer was separated and the aqueous layer extracted with $CHCl_3$ (2 × 50 mL). The combined organic extracts were washed with aqueous NH_4Cl (100 mL), and the aqueous layer was extracted with $CHCl_3$ (2 × 50 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 3:7 Et_2O/hexanes as eluent to afford the title compound **15** that was recrystallized from hexane−toluene (815 mg, 78%): mp 57−58 °C (lit.[22b] 57.5−58 °C); ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 6.95 (dd, J = 8.1, 0.9 Hz, 1H), 7.23 (dd, J = 8.1, 1.0 Hz, 1H), 7.32 (t, J = 8.1 Hz, 1H), 10.40 (s, 1H);^{13}C NMR ($CDCl_3$) δ 190.4, 161.9, 134.8, 126.5, 111.0, 56.2, IR (KBr) 2780, 1695, 780 cm^{-1}.

2-(Benzyloxy)-6-bromobenzaldehyde (16). To a cooled (−70 °C) solution of the bromomethoxybenzaldehyde (**15**) (500 mg, 2.3 mmol) in CH_2Cl_2 (20 mL) was added dropwise with stirring under Ar a solution of boron tribromide (12 mL, 1 M in CH_2Cl_2, 12 mmol). After the addition was complete the mixture was stirred at −70 °C for an additional 1 h and then at room temperature for 2 h. The mixture was then recooled to −70 °C and quenched by the dropwise addition of 25 mL of anhydrous MeOH with vigorous stirring. The reaction mixture was concentrated in vacuo, and the residue was treated with an additional 25 mL of MeOH and again concentrated in vacuo. This procedure was repeated twice more. Finally the residue was dried in vacuo over P_2O_5 overnight and was used directly for the next step without further purification. Thus the residue was dissolved in a solution of benzyl bromide (430 mg, 2.5 mmol) in EtOH (40 mL) containing KOH pellets (140 mg, 2.5 mmol). The mixture was refluxed for 5 h and filtered, and EtOH was removed under vacuum. Et_2O (50 mL) was added and the solution washed three times with aqueous KOH (10%, 10 mL). The organic layer was then washed with water and brine and dried ($MgSO_4$). The dried extract was concentrated in vacuo to afford a crude solid which was finally purified by recrystallization from hexane−toluene (565 mg, 84%): mp 66−67 °C; ^1H NMR ($CDCl_3$) δ 5.28 (s, 2H), 6.90 (dd, J = 8.2, 1.5 Hz, 1H), 7.24 (m, 1H), 7.32 (m, 6H), 10.47 (s, 1H);^{13}C NMR ($CDCl_3$) δ 190.0, 161.2, 135.7, 134.7, 128.7, 128.3, 127.1, 126.9, 124.2, 112.5, 70.9; IR (KBr) 2780, 1693, 780 cm^{-1}. Anal. Calcd for $C_{14}H_{11}BrO_2$: C, 57.76; H, 3.81, Br 27.44. Found: C, 57.91; H, 3.70, Br 27.52.

Typical Procedure for the Synthesis of Phosphorylated Bromobenzamides 20, 21. A mixture of the benzoic acid derivative **17**, **18** (20 mmol) and dimethylformamide (0.5 mL) in freshly distilled thionyl chloride (50 mL) was stirred under Ar for 12 h. The excess thionyl chloride was removed under vacuum. Toluene (25 mL) was added to the residue which was again concentrated in vacuo. This procedure was repeated twice more. The residue was then dissolved in CH_2Cl_2 (150 mL), and a solution of Et_3N (10 g, 100 mmol) in CH_2Cl_2 (50 mL) containing the phosphorylated amine **19** (7 g, 20 mmol) was added dropwise at 0 °C. The mixture was stirred at room temperature for 2 h. Water (50 mL) was added. The organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a solid residue which was recrystallized from hexane−toluene.

***N*-[(Diphenylphosphinyl)methyl]-*N*-[(4-methoxyphenyl)methyl]-2-bromo-4,5-dimethoxybenzamide (20):** mp 149−150 °C; ^1H NMR ($CDCl_3$) δ 3.62 (s, 3H), 3.70 (s, 3H), 3.75 (s, 3H), 4.40−4.58 (m, 3H), 4.75 (d, J = 15.0 Hz, 1H), 6.17 (s, 1H), 6.80 (d, J = 8.5 Hz, 2H), 6.88 (s, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.15−7.40 (m, 6H), 7.85−8.05 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 168.9, 159.3, 150.1, 148.4, 132.2 (m), 131.4 (d, J_{CP} = 8 Hz), 131.2 (d, J_{CP} = 8.5 Hz), 129.8, 129.6 (d, J_{CP} = 103 Hz), 128.8 (d, J_{CP} = 9 Hz), 128.6 (d, J = 11.5 Hz), 127.2, 115.5, 114.0, 110.7, 110.0, 56.3, 55.7, 52.7, 42.1 (d, J_{CP} = 76 Hz); ^{31}P NMR ($CDCl_3$) δ 30.9; IR (KBr) 1649, 1258 cm^{-1}. Anal. Calcd for $C_{30}H_{29}BrO_5P$: C, 60.62; H, 4.92; N, 2.36. Found: C, 60.71; H, 5.05; N, 2.14.

***N*-[(Diphenylphosphinyl)methyl]-*N*-[(4-methoxyphenyl)methyl]-5-(benzyloxy)-2-bromo-4-methoxybenzamide (21):** mp 184−185 °C; ^1H NMR ($CDCl_3$) δ 3.78 (s, 3H), 3.84 (s, 3H), 4.29−4.57 (m, 2H), 4.47 (d, J = 15.0 Hz, 1H), 4.51 (d, J = 15.0 Hz, 1H), 4.82 (d, J = 12.1 Hz, 1H), 4.97 (d, J = 12.1 Hz, 1H), 6.25 (s, 1H), 6.80 (d, J = 8.6 Hz, 2H), 7.05 (s, 1H), 7.15 (d,

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J = 8.6 Hz, 2H), 7.31−7.59 (m, 11H), 7.85−8.00 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 168.8, 159.3, 150.8, 147.2, 136.0, 132.3 (m), 131.3 (m), 129.8, 128.7 (m), 128.2, 127.4, 127.2, 116.0, 114.1, 113.8, 110.7, 71.1, 56.2, 55.2, 47.7, 42.0 (d, J = 76.5 Hz); ^{31}P NMR ($CDCl_3$) δ 30.8; IR (KBr) 1258, 1649 cm^{-1}. Anal. Calcd for $C_{36}H_{33}BrNO_5P$: C, 64.48; H, 4.96; N, 2.09. Found: C, 64.61; H, 5.19; N, 1.9.7.

Typical Procedure for the Synthesis of Arylmethylene Isoindolinones 10−12. A solution of KHMDS (14 mL, 0.5 M in toluene, 7 mmol) was added dropwise over a period of 5 min to a stirred solution of compounds **20**, **21** (3.4 mmol) in THF (50 mL) at −78 °C under Ar. The solution was stirred for 30 min at this temperature and then allowed to warm to −30 °C within 3 h. A solution of the appropriate aldehyde **15**, **16** (3.4 mmol) in THF (5 mL) was then added by syringe, and the reaction mixture was allowed to warm to room temperature over a period of 30 min. Aqueous NH_4Cl was added, and the mixture was extracted with Et_2O (100 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to a light yellow oil which was purified by flash column chromatography with AcOEt−hexanes (75:25) as eluent.

3-[(2-Bromo-6-methoxyphenyl)methylene]-2,3-dihydro-5,6-dimethoxy-2-[(4-methoxyphenyl)methyl]-1*H*-isoindol-1-one (10): *E* and *Z* isomers (ratio 80:20 from ^{1}H NMR spectrum). *E* isomer ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3H), 3.67 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 4.94 (d, J = 15.9 Hz, 1H), 5.19 (d, J = 15.9 Hz, 1H), 5.99 (s, 1H), 6.29 (s, 1H), 6.84 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.9 Hz, 1H), 7.16 (d, J = 8.9 Hz, 1H), 7.19−7.26 (m, 4H); *Z* isomer ^{1}H NMR (partial) δ 3.51 (s, 3H), 3.69 (s, 3H), 6.32 (s, 1H); *E* isomer ^{13}C NMR ($CDCl_3$) δ 166.9, 158.7, 158.6, 152.2, 150.5, 137.1, 129.8, 129.3, 128.4, 126.1, 125.2, 124.9, 123.0, 113.9, 109.6, 105.1, 104.6, 104.5, 56.2, 56.0, 55.6, 55.3, 42.6. Anal. Calcd for $C_{26}H_{24}BrNO_5$: C, 61.19; H, 4.74; N, 2.74. Found: C, 61.01; H, 4.55; Br, 2.91.

6-(Benzyloxy)-3-[(2-bromo-6-methoxyphenyl)methylene]-2,3-dihydro-5-methoxy-2-[(4-methoxyphenyl)methyl]-1*H*-isoindol-1-one (11): *E* and *Z* isomers (ratio 70:30 from ^{1}H NMR spectrum). *E* isomer ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H), 3.69 (s, 3H), 3.78 (s, 3H), 4.91 (d, J = 12.8 Hz, 1H), 5.11−5.25 (m, 3H), 5.99 (s, 1H), 6.29 (s, 1H), 6.84 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.1 Hz, 1H), 7.18−7.53 (m, 10H); *Z* isomer ^{1}H NMR (partial) δ 3.52 (s, 3H), 3.72 (s, 3H), 3.78 (s, 3H), 6.01 (s, 1H), 6.35 (s, 1H); *E* isomer ^{13}C NMR ($CDCl_3$) δ 166.9, 158.6, 152.8, 149.6, 137.1, 136.2,129.8, 129.3, 128.6, 128.4, 128.1, 127.3, 126.0, 124.7, 122.9, 113.9, 109.6, 106.6, 105.4, 104.5, 70.9, 56.0, 55.7, 55.3, 42.6. Anal. Calcd for $C_{32}H_{28}BrNO_5$: C, 65.54; H, 4.81; N, 2.39. Found: C, 65.38; H, 5.00; N, 2.44.

3-[(2-(Benzyloxy)-6-bromophenyl)methylene]-2,3-dihydro-5,6-dimethoxy-2-[(4-methoxyphenyl)methyl]-1*H*-isoindol-1-one (12): *E* isomer, mp 153−154 °C; ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 3H), 3.71 (s, 3H), 3.93 (s, 3H), 4.88 (d, J = 12.1 Hz, 1H), 4.95 (d, J = 12.1 Hz, 1H), 5.00 (s, 2H), 6.02 (s, 1H), 6.23 (s, 1H), 6.72 (d, J = 7.5 Hz, 2H), 6.92 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 7.5 Hz, 2H), 7.05−7.28 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 167.0, 158.6, 152.2, 150.5, 137.2, 136.1, 129.7, 129.1, 128.4, 128.2, 127.9, 127.0, 126.2, 125.8, 125.2, 122.9, 113.9, 111.4, 105.0, 104.6, 104.2, 70.6, 56.2, 55.5, 42.6, 35.2; IR (KBr) 1695, 1639 cm^{-1}. Anal. Calcd for $C_{32}H_{28}BrNO_5$: C, 65.54; H, 4.81; N, 2.39. Found: C, 65.51; H, 4.65; N, 2.18.

Typical Procedure for the Synthesis of Aristolactams 5−7. To a solution of **10−12** (0.3 mmol) in dry degassed benzene (150 mL), refluxing under Ar, was added a solution of *n*-Bu_3-SnH (130 mg, 0.45 mmol) and AIBN (25 mg, 0.15 mmol) in dry degassed benzene (25 mL) dropwise over 10 min. Once addition had finished, refluxing was kept up for a further 3 h. The benzene was evaporated under reduced pressure, and the residue was dissolved in CH_3CN (100 mL). This solution was washed with hexane (3 × 50 mL) and concentrated in vacuo to a solid residue which was recrystallized from EtOH to obtain a bright yellow solid.

1,2,7-Trimethoxy-5-[(4-methoxyphenyl)methyl]-dibenz[*cd*,*f*]indol-4(5*H*)-one (5): mp 223−224 °C; ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3H), 3.98 (s, 3H), 4.05 (s, 3H), 4.07 (s, 3H), 5.10 (s, 2H), 6.82 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.46 (t, J = 8.1 Hz, 1H), 7.50 (s, 1H), 7.82 (s, 1H), 8.82 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 167.8, 158.9, 155.7, 154.3, 151.5, 135.6, 129.3, 128.8, 127.9, 125.8, 125.2, 123.0, 121.1, 120.7, 119.9, 114.0, 110.0, 107.7, 98.9, 60.3, 56.9, 55.8, 55.2, 43.3; IR (KBr) 1730, 1695 cm^{-1}. Anal. Calcd for $C_{26}H_{23}NO_5$: C, 72.71; H, 5.40; N, 3.26. Found: C, 72.93; H, 5.54; Br, 3.07.

2-(Benzyloxy)-1,7-dimethoxy-5-[(4-methoxyphenyl)-methyl]-dibenz[*cd*,*f*]indol-4(5*H*)-one (6): mp 170−171 °C; ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H), 3.98 (s, 3H), 4.11 (s, 3H), 5.10 (s, 2H), 5.29 (s, 2H), 6.82 (d, J = 7.2 Hz, 2H), 7.03 (d, J = 7.9 Hz, 1H), 7.29−7.68 (m, 9H), 7.87 (s, 1H), 8.84 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 166.7, 158.9, 155.8, 153.3, 152.0, 136.5, 135.6, 129.3, 128.8, 128.7, 128.2, 127.5, 127.55, 126.2, 125.2, 121.1, 120.8, 120.1, 119.9, 114.1, 112.1, 107.7, 99.0, 72.1, 60.5, 55.8, 55.2, 43.3; IR (KBr) 1710, 1652 cm^{-1}. Anal. Calcd for $C_{32}H_{27}NO_5$: C, 76.02; H, 5.38; N, 2.77. Found: C, 75.92; H, 5.60; N, 3.04.

7-(Benzyloxy)-1,2-dimethoxy-5-[(4-methoxyphenyl)-methyl]-dibenz[*cd*,*f*]indol-4(5*H*)-one (7): mp 160−161 °C; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H), 4.04 (s, 3H), 4.07 (s, 3H), 5.06 (s, 2H), 5.27 (s, 2H), 6.81 (d, J = 7.4 Hz, 2H), 7.06 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.4 Hz, 2H), 7.41−7.63 (m, 7H), 7.81 (s, 1H), 8.82 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 167.7, 159.0, 154.8, 154.3, 151.4, 137.2, 135.6, 129.3, 129.1, 128.6, 128.0, 127.7, 127.3, 125.7, 125.6, 123.0, 121.0, 120.6, 120.3, 114.0, 110.0, 109.3, 99.3, 72.5, 60.3, 26.9, 55.2, 43.4; IR (KBr) 1707, 1647 cm^{-1}. Anal. Calcd for $C_{32}H_{27}NO_5$: C, 76.02; H, 5.38; N, 2.77. Found: C, 76.21; H, 5.15; N, 2.72.

Typical Procedure for the *O*-Benzyl Deprotection of the Aristolactams 6, 7. A mixture of aristolactam **6**, **7** (0.1 mmol), palladium on charcoal (10%, 10 mg), and ammonium formate (63 mg, 1 mmol) in MeOH−CH_2Cl_2 (9:1, 75 mL) was refluxed for 30 min. The reaction mixture was passed through a Celite pad, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (50 mL), washed with water (2 × 10 mL) and brine, and dried ($MgSO_4$). Concentration in vacuo afforded a yellow solid which was recrystallized from EtOH.

2-Hydroxy-1,7-dimethoxy-5-[(4-methoxyphenyl)methyl]-dibenz[*cd*,*f*]indol-4(5*H*)-one (8): mp 245−246 °C; ^{1}H NMR (DMSO-d_6) δ 3.67 (s, 3H), 3.94 (s, 3H), 3.99 (s, 3H), 5.06 (s, 2H), 6.86 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.43 (s, 1H), 7.49 (t, J = 8.1 Hz, 1H), 7.69 (s, 1H), 8.73 (d, J = 8.1 Hz, 1H), 10.41 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.4, 155.3, 152.3, 149.2, 135.4, 129.3, 128.3, 127.0, 125.9, 124.9, 120.9, 120.6, 120.3, 119.2, 114.0, 108.0, 97.4, 59.5, 55.8, 55.0, 42.2; IR (KBr) 3343, 1680, 1240 cm^{-1}. Anal. Calcd for $C_{25}H_{21}NO_5$: C, 72.28; H, 5.10; N, 3.37. Found: C, 72.21; H, 5.19; N, 3.15.

7-Hydroxy-1,2-dimethoxy-5-[(4-methoxyphenyl)methyl]-dibenz[*cd*,*f*]indol-4(5*H*)-one (9): mp 236−237 °C; ^{1}H NMR (DMSO-d_6) δ 3.68 (s, 3H), 3.99 (s, 3H), 4.05 (s, 3H), 5.10 (s, 2H), 6.88 (d, J = 7.6 Hz, 2H), 7.06 (d, J = 6.8 Hz, 1H), 7.26 (d, J = 7.6 Hz, 2H), 7.36 (t, J = 6.8 Hz, 1H), 7.45 (s, 1H), 7.93 (s, 1H), 8.60 (d, J = 6.8 Hz, 2H), 10.15 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 166.5, 158.4, 155.0,153.8, 152.8, 134.7, 129.7, 128.3, 127.8, 126.2, 123.7, 120.9, 120.2, 119.5, 118.0, 114.5, 112.5, 111.0, 99.0, 60.0, 55.1, 54.9, 42.5; IR (KBr) 3418, 1680, 1280 cm^{-1}. Anal. Calcd for $C_{25}H_{21}NO_5$: C, 72.28; H, 5.10; N, 3.37. Found: C, 72.15; H, 5.02; N, 3.21.

Typical Procedure for the Synthesis of Taliscanine (1), Velutinam (2), and Enterocarpam II (3). A solution of trifluoroacetic acid (114 mg, 1 mmol), anisole (110 mg, 1 mmol), and aristolactam **5**, **8**, **9** (0.1 mmol) in dichloroethane (2 mL) was refluxed under Ar for 24 h. The solvents were removed under vacuum. The residue was dissolved in CH_2Cl_2 (20 mL), and Et_3N (0.5 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 and spectral data of synthetic **1−3** matched those reported for the natural products.

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