JOC*Note*

A New Route to Aristocularine Alkaloids: Total Synthesis of Aristoyagonine

Anne Moreau, Axel Couture,* Eric Deniau, and
Pierre Grandclaudon

*Laboratoire de Chimie Organique Physique, UMR 8009
"Chimie Organique et Macromoléculaire", Université des
Sciences et Technologies de Lille, Bâtiment C3(2),
F-59655 Villeneuve d'Ascq Cedex, France*

axel.couture@univ-lille1.fr

Received January 23, 2004

Abstract: A short and efficient synthesis of aristocularines, involving the sequential construction of phosphorylated 4-alkoxyisoindolinones, Horner-type reaction, and ultimate cyclization by diaryl ether coupling, is disclosed. The success of this new conceptual approach is demonstrated by the total synthesis of the aristocularine alkaloid aristoyagonine.

Cularinoids are a group of isoquinoline alkaloids consisting of about 60 members. Their richest natural source is the plant families *Fumariaceae*,[1] particularly the genus *Sarcocapnos enneaphylla*.[2] They are also characterized by a benzoxepine nucleus but they occur naturally in a large variety of oxidation states. Besides the largest group, the cularines (**1**), this family includes other highly oxidized members and among them the aristocularines (**2**), notably the eminent example aristoyagonine (**2a**), which occupies a special place since it is the only example to date of a natural cularine alkaloid incorporating a five-membered lactam (Scheme 1). Due to their low natural occurrence in conjunction with their biological activity against various cell lines[3] several synthetic tactics have been disclosed for the synthesis of these structurally unusual alkaloids.

The main approach to the synthesis of aristocularines, which has been confined to the construction of the sole models **2a**,**b**, relies upon the initial construction of the dibenzoxepine skeleton (Scheme 1). In this perspective two general intermediates, the lactones **3a**,**b**[4] and the dioxocularines **4a**,**b**,[5] have been synthesized. A closer analysis of the literature reveals that improvement of these elegant, skillful, and complementary synthetic approaches has been limited to the development of alternative methods for the synthesis of these key models. Thus the lactones **3a**,**b** have been obtained by a Parham-type cyclization of appropriate brominated carbamates[4,6] derived from the dihydrodibenz[*b*,*f*]oxepin-10-ones **5a**,**b**.[6] The synthetic route going via the dioxocularines **4a**,**b** was more appealing since these compounds could be readily accessible from the 4-hydroxysarcocapnine epimers **6a**,**b**[5] isolated from natural sources[8] or obtained by a Ullman coupling reaction of 1-(2-bromobenzyl)-8-hydroxyisoquinoline derivatives.[9] They could be alternatively assembled by intramolecular cyclization of an aminoacetaldehyde dimethyl acetal derived from **5a**,**b**.[10] Recently, the dioxocularine **4b** was also inadvertently obtained along with the aristocularine **2b** and some xanthene derivatives by cyclization of the aryloxyphenyl acetamide **7b**, and a rather sophisticated mechanism to account for the promotion of this annulation process by oxalyl chloride/stannyl chloride has been proposed.[3,11] All these strategies with the exception of the last one have been exploited for the synthesis of the exemplary representative aristoyagonine (**2a**).

We delineate here a tactically new five-step synthesis of aristocularines that relies upon our longstanding experience in the field of *N*-acylenamine and isoindolinone chemistry[12] and we wish to disclose the success of our new conceptual approach by describing the third total synthesis of the *Fumariaceae* alkaloid aristoyagonine (**2a**).

Results and Discussion. The main issue that had to be addressed for the synthesis of the diversely substituted aristocularines **2a**,**c**,**d** was judging the proper order for the construction of the heterocyclic units embedded in their skeleton. Within this context it appeared that the oxepine ring system could be conceivably assembled by diaryl ether formation from a *cis*-stilbenoid system bearing the mandatory hydroxy and halogenated functionalities. This conceptual approach then entailed the generation of the appropriate bromoarylmethylene hydroxyisoindolinones **8**−**10** which suggested the simple retrosynthetic Scheme 2.

Compounds **8**−**10** would be reasonably obtained by reliance on a Horner-type reaction[13] involving the suitably substituted benzaldehydes **11**−**13** and the 3-phosphorylated isoindolinones **14**−**16**. Of central importance for this strategy then was the ability to identify a synthetic tactic liable to give access to the requisite

---

* Corresponding author. Fax: +33 (0)3 20 33 63 09.

(1) Campello, M. J.; Castedo, L.; Dominguez, D.; Rodriguez de Lera, A.; Saa, J. M.; Suau, R.; Tojo, E.; Vidal, M. C. *Tetrahedron Lett.* **1984**, *25*, 5933−5936.

(2) Tojo, E.; Dominguez, D.; Castedo, L. *Phytochemistry* **1991**, *30*, 1005−1010.

(3) Suau, R.; Rico, R.; Lopez-Romero, J. M.; Najera, F.; Ruiz, A.; Ortiz-Lopez, F. J. *Arkivoc (Zurich, Switz.)* **2002**, *5*, 62−72.

(4) Lamas, C.; Castedo, L.; Dominguez, D. *Tetrahedron Lett.* **1990**, *31*, 6247−6248.

(5) de Lera, A. R.; Suau, R.; Castedo, L. *J. Heterocycl. Chem.* **1987**, *24*, 313−319.

(6) Paleo, R. M.; Lamas, C.; Castedo, L.; Dominguez, D. *J. Org. Chem.* **1992**, *57*, 2029−2033.

(7) Lamas, C.; Garcia, A.; Castedo, L.; Dominguez, D. *Tetrahedron Lett.* **1989**, *30*, 6927−6928.

(8) Castedo, L.; Dominguez, D.; Rodriguez de Lera, A.; Tojo, E. *Tetrahedron Lett.* **1984**, *25*, 4573−4576.

(9) Rodriguez de Lera, A.; Saa, J. M.; Suau, R.; Castedo, L. *J. Heterocycl. Chem.* **1987**, *24*, 613−622.

(10) Garcia, A.; Castedo, L.; Dominguez, D. *Tetrahedron* **1995**, *51*, 8585−8598.

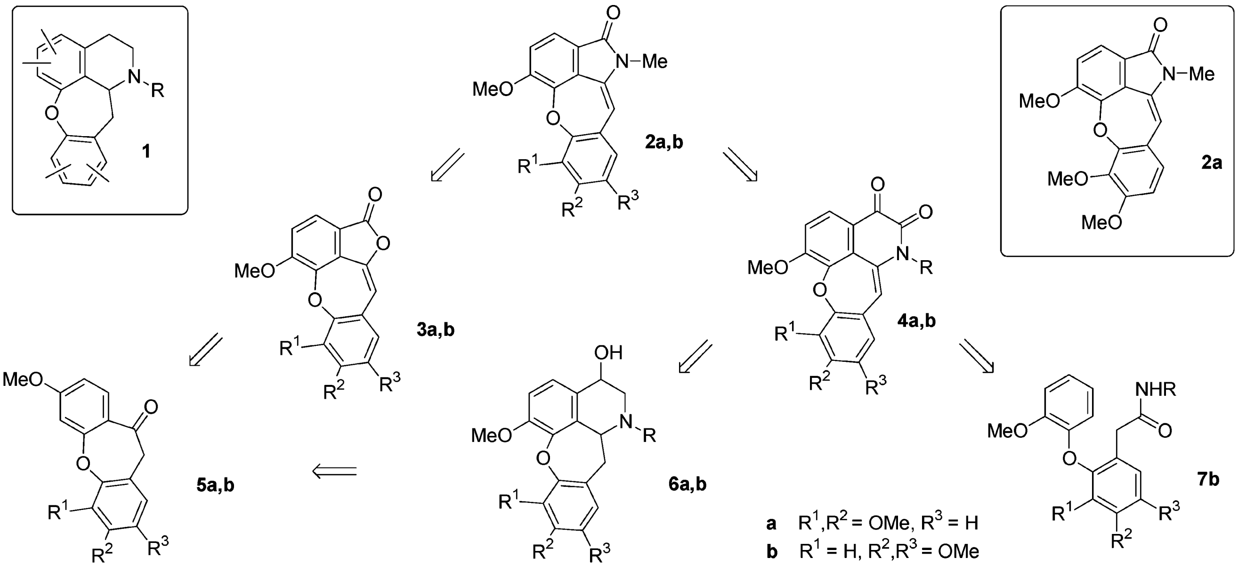
(11) Suau, R.; Lopez-Romero, J. M.; Rico, R. *Tetrahedron Lett.* **1996**, *37*, 9357−9360.

(12) (a) Couture, A.; Grandclaudon, P. *Synthesis* **1986**, 576. (b) Couture, A.; Grandclaudon, P.; Hooijer, S. *J. Org. Chem.* **1991**, *56*, 4977. (c) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron Lett.* **1993**, *34*, 1479. (d) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *J. Org. Chem.* **1998**, *63*, 3128−3132. (e) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Biomol. Chem.* **2003**, *1*, 1701−1706. (f) Hoarau, C.; Couture, A.; Cornet, H.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2001**, *66*, 8064−8069. (g) Hoarau, C.; Couture, A.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2002**, *67*, 5846−5849.

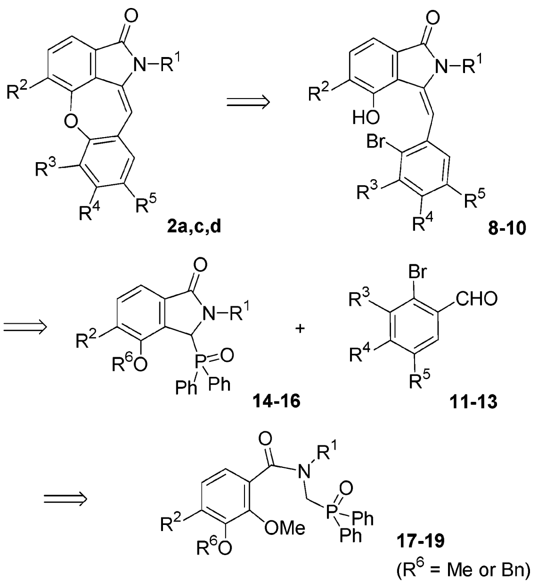
(13) (a) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. (b) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1959**, *92*, 2499. (c) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.

10.1021/jo049869g CCC: $27.50

SCHEME 1. Main Synthetic Routes to Aristocularines



SCHEME 2. Retrosynthetic Scheme



2	R1	R2	R3	R4	R5
a	Me	OMe	OMe	OMe	H
c	Me	H	H	H	H
d	PMB[a]	H	H	O-CH$_2$-O	

[a] PMB = *para*-Methoxybenzyl

contiguously mono- or disubstituted isoindolinones **14**–**16** incorporating a protected phenolic function at the 4-position of the aromatic moiety and further bearing the phosphoryl auxiliary. We have recently developed a new synthetic concept for the assemblage of phosphorylated isoindolinones that hinges upon the base-induced aryne-mediated cyclization of phosphorylated *o*-halogenobenzamides.[10] One major criticism that we have to make about this technique relies upon the participation of a transient aryne moiety, which inevitably precludes the elaboration of any 4-substituted models. However, a synthetic strategy implying such α-aminocarbanionic species was deemed worthy of pursuit since we anticipated that they could be alternatively involved in a nucleophilic aromatic substitution process (S_NAr), notably with a methoxy group acting as the internal nucleofuge. Literature precedent gave support to the feasibility of such an approach. Indeed the sensitivity of alkoxy groups with respect to nucleophilic attack has been skillfully exploited in S_NAr reactions, this process being activated by ester,[14] amide,[15] and above all oxazoline groups[16] (the Meyers reaction) at the ortho site on the aromatic nucleus.

The first facet of the synthesis then was the elaboration of the polyalkoxylated and phosphorylated benzamide derivatives **17**–**19**. This was readily accomplished by coupling the suitably substituted benzoic acid derivatives **20**–**22** via their acyl chlorides to the appropriate phosphorylated amines **23** and **24**. Exposure of the phosphorylated benzamides **17**–**19** to potassium bis(trimethylsilyl)amide (KHMDS, 1.1 equiv) at −78 °C in the presence of 18-crown-6 induced the formation of the phosphoryl-stabilized α-aminocarbanion.[12a,f] Subsequent *o*-methoxy displacement by the transient carbanionic species occurred through the S_NAr process portrayed in Scheme 3 and brought about the intramolecular arylation reaction thus giving rise to the desired phosphorylated isoindolinones **14**–**16** after conventional workup. Interestingly D_2O quenching at this stage led to exclusive incorporation of deuterium at the 3-position of the lactam ring.[17] One can reasonably assume that deprotonation of the phosphorylated benzylic position might be ensured by the methoxylate released upon the annulation step. This phenomenon had some obvious implications on the course of the synthesis since it meant that the metalated isoindolinones **25**, candidates for the planned Horner-

---

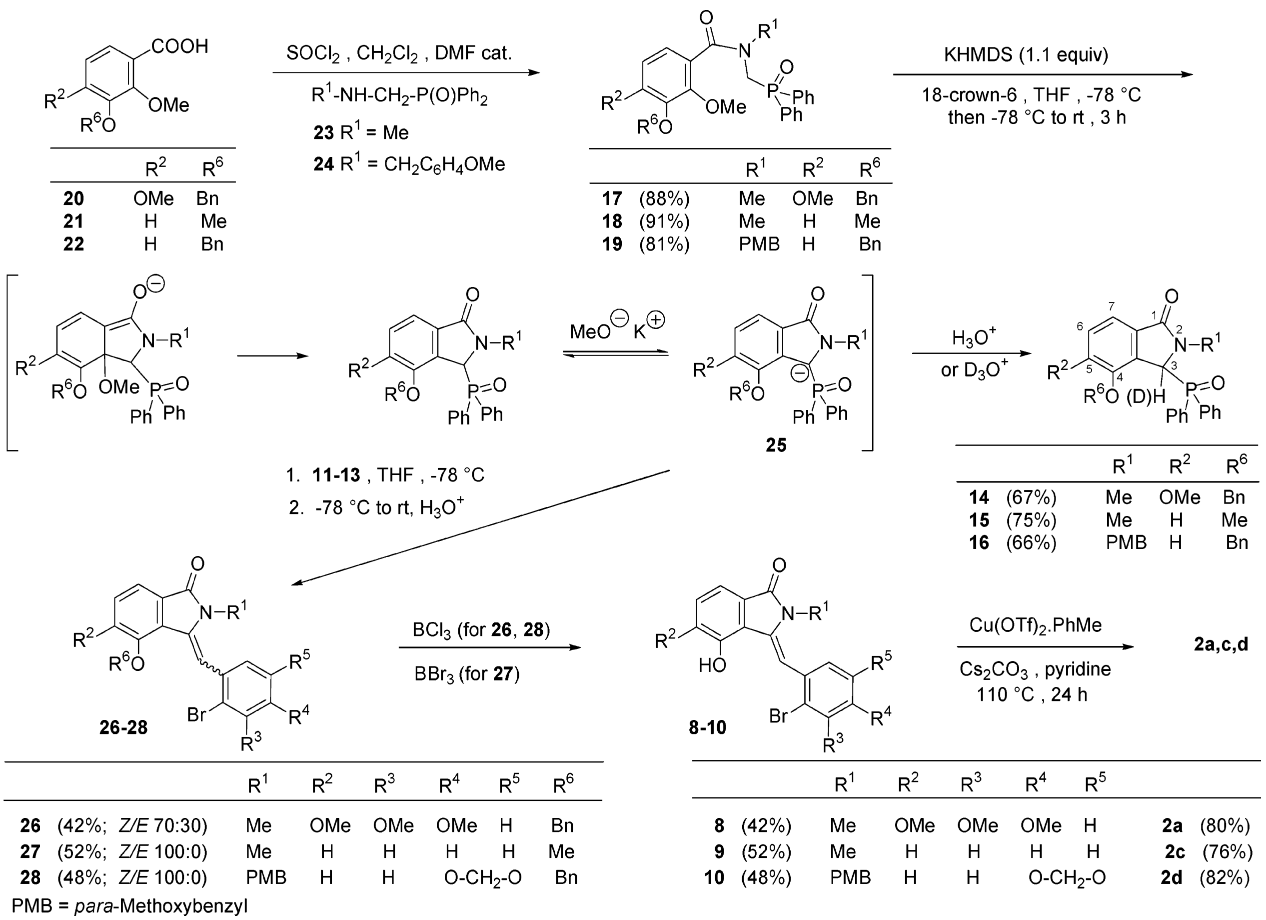
(14) For a recent paper, see: Hattori, T.; Takeda, A.; Suzuki, K.; Koike, N.; Koshiishi, E.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3661–3671.

(15) Clayden, J.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3059–3062.

(16) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297–2360.

(17) Evaluation of deuterium incorporation in compound **14** was assayed by ^{1}H NMR spectroscopy at 300 MHz and integration indicated (78 ± 5)% D at C-3 with a less extensively split signal for the benzylic proton (δ 4.87 ppm).

SCHEME 3. Synthesis of Aristoyagonine (2a) and Aristocularines (2c,d)



	R^2	R^6
20	OMe	Bn
21	H	Me
22	H	Bn

	R^1	R^2	R^6
17 (88%)	Me	OMe	Bn
18 (91%)	Me	H	Me
19 (81%)	PMB	H	Bn

	R^1	R^2	R^6
14 (67%)	Me	OMe	Bn
15 (75%)	Me	H	Me
16 (66%)	PMB	H	Bn

	R^1	R^2	R^3	R^4	R^5	R^6
26 (42%; *Z/E* 70:30)	Me	OMe	OMe	OMe	H	Bn
27 (52%; *Z/E* 100:0)	Me	H	H	H	H	Me
28 (48%; *Z/E* 100:0)	PMB	H	H	O-CH$_2$-O		Bn

PMB = *para*-Methoxybenzyl

	R^1	R^2	R^3	R^4	R^5	
8 (42%)	Me	OMe	OMe	OMe	H	**2a** (80%)
9 (52%)	Me	H	H	H	H	**2c** (76%)
10 (48%)	PMB	H	H	O-CH$_2$-O		**2d** (82%)

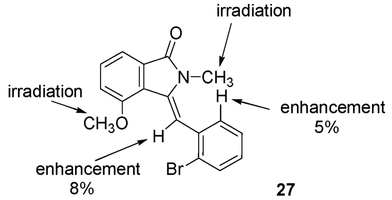
type reaction, could be intercepted by addition of the appropriate bromobenzaldehyde derivatives **11**−**13** through a simple one-pot reaction. Gratifyingly, conducting the reaction according to this procedure afforded straightforwardly the arylmethylene isoindolinones **26**−**28**. Compounds **27** and **28** were obtained exclusively in *Z* forms while model **26** was obtained in both *Z* and *E* forms with the *Z* form predominant by a large margin (*Z*/*E* 70:30).

The configuration of the double bond was unambiguously established from their ^{1}H NMR spectra with nOe experiments.[18] Retrieval of the phenolic functions by treatment of **26** and **28** by BCl$_3$ and **27** by BBr$_3$ proceeded uneventfully to deliver the deprotected models **8**−**10**, candidates for the annulation step. Noteworthily this operation did not spare the stereochemistry of the exocyclic double bond as witnessed by the exclusive formation of the *Z*-configured isomer **8** by treatment of (*Z*,*E*)-**26**. The *Z* configuration was unambiguously confirmed on the basis of nOe effects in the ^{1}H NMR spectra.[19] Stereochemical considerations about the central double bond were not crucial for the creation of the diaryl ether linkage ensuring the construction of the dibenzoxepine ring system. As a means of assembling this heterocyclic unit the diaryl ether coupling was accomplished utilizing a recently published catalytic copper-mediated method[20] [5 mol % of (CuOTf)$_2$·PhMe, Cs$_2$CO$_3$, pyridine, 110 °C, 24 h)]. Gratifyingly, this protocol delivered the annulated models **2c**,**d** and thus afforded straightforwardly the target natural product aristoyagonine (**2a**) with an overall yield of 26% for the four steps (starting from the precursor **20**).

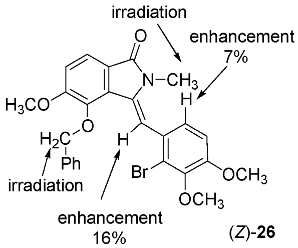
In summary, the new synthetic protocol consisting of sequential construction of phosphorylated 4-alkoxyisoin-

---

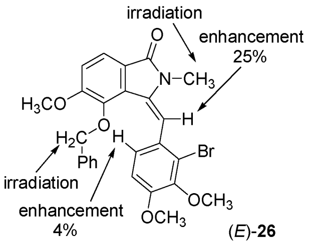
[18] Irradiation of the *N*-methyl H$_3$ (δ 2.90 ppm) in **27** led to increased intensity of the downfield aromatic proton at C-6′ (δ 7.30 ppm, 5%) whereas the effect of irradiation of the *O*-methyl H$_3$ (δ 3.99 ppm) was an increased intensity of the vinylic proton (δ 7.25 ppm, 8%). nOe experiments with (*Z*)-**26** displayed enhancements between the *N*-methyl H$_3$ (δ 2.89 ppm) and the aromatic proton at C-6′ (δ 6.94 ppm, 7%) and between the vinylic proton (δ 7.21 ppm, 16%) and the *O*-benzyl H$_2$ (δ 5.20 ppm). For the minor isomer (*E*)-**26** enhancements of 25% were observed between *N*-methyl H$_3$ (δ 3.39 ppm) and the vinylic proton (δ 6.47 ppm) and of 4% between the *O*-benzyl H$_2$ (δ 4.31 ppm) and the aromatic proton at C-6′ (δ 6.47 ppm).



27



(*Z*)-**26**



(*E*)-**26**

dolinones, Horner-type reaction, deprotection, and ultimate diaryl ether coupling has been applied to an efficient construction of the aristocularine skeleton. The advantage of this synthesis lies in the small number of synthetic steps and the ease of elaboration of the intermediates involved in the assembly of these alkaloids. The synthetic potential of this method also has been demonstrated by the third known total synthesis of the alkaloid aristoyagonine.

Experimental Section

Typical Procedure for the Synthesis of the Phosphorylated Isoindolinones 14−16. A solution of KHMDS (0.5 M in toluene, 8.8 mL, 4.4 mmol) was added dropwise to a carefully degassed solution of the phosphorylated 2-methoxybenzamide derivative **17**−**19** (4.0 mmol) and 18-crown-6 (1.16 g, 4.4 mmol) in THF (50 mL) at −78 °C under Ar. The solution was stirred for 15 min and then allowed to warm to room temperature over a period of 2 h. Aqueous NH_4Cl solution (10%, 10 mL) was added and after dilution with water the mixture was extracted with Et_2O (2 × 25 mL) and CH_2Cl_2 (2 × 25 mL). The organic extracts were washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. Flash column chromatography on silica gel with ethyl acetate/hexanes (9:1) as eluent followed by recrystallization from hexane−toluene afforded the phosphorylated isoindolinones **14**−**16**.

4-Benzyloxy-3-diphenylphosphinoyl-5-methoxy-2-methyl-2,3-dihydro-1*H*-isoindol-1-one (14). White solid, 1.29 g (67%); mp 161−162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 3 H), 3.85 (s, 3 H), 4.74 (s, 2 H), 4.87 (d, J_{HP} = 7.6 Hz, 1 H), 6.98 (d, J = 8.1 Hz, 1 H), 7.09−7.13 (m, 2 H), 7.25−7.47 (m, 12 H), 7.61−7.68 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.8, 56.3, 63.6 (d, J_{CP} = 70 Hz), 74.4, 113.7, 119.6, 126.9 (d, J_{CP} = 2 Hz), 127.9 (d, J_{CP} = 97 Hz), 128.2, 128.21 (d, J_{CP} = 12 Hz), 128.25 (d, J_{CP} = 12 Hz), 128.26, 128.7, 130.8 (d, J_{CP} = 96 Hz), 131.6 (d, J_{CP} = 9 Hz), 131.7 (d, J_{CP} = 8 Hz), 132.2 (d, J_{CP} = 3 Hz), 132.4 (d, J_{CP} = 3 Hz), 132.8 (d, J_{CP} = 3 Hz), 137.0, 142.5 (d, J_{CP} = 3 Hz), 155.2 (d, J_{CP} = 2 Hz), 168.3; ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.3. Anal. Calcd for $C_{29}H_{26}NO_4P$: C, 72.04; H, 5.42; N, 2.90. Found: C, 72.35; H, 5.20; N, 3.09.

Typical Procedure for the Synthesis of the 3-Arylmethyleneisoindolinones 26−28. The synthesis was initially carried out as described above. After addition of the metalating agent at −78 °C, the reaction mixture was stirred for an additional 15 min and then treated by dropwise addition of a solution of 2-bromobenzaldehyde derivative **11**−**13** (4.0 mmol) in THF (10 mL). The mixture was stirred at −78 °C for 30 min, warmed to 0 °C over a period of 1 h, and subsequently warmed to room temperature for a longer period (2 h). Aqueous NH_4Cl solution (10%, 10 mL) was added followed by water and the aqueous phase was extracted with Et_2O (2 × 30 mL). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under vacuum to leave a crude solid residue that was purified by recrystallization in EtOH.

(*Z*)-4-Benzyloxy-3-(2-bromo-3,4-dimethoxybenzylidene)-5-methoxy-2-methyl-2,3-dihydro-1*H*-isoindol-1-one (26). The arylmethyleneisoindolinone **26** was obtained as a mixture of unseparable *Z* and *E* isomers (0.96 g, 42%). The isomeric ratio (*Z*/*E* 70:30) was determined from the ^{1}H NMR spectrum and integration of the *N*-CH_3 protons [δ 2.89 ppm for (*Z*)-**26** and δ 3.39 ppm for (*E*)-**26**]. The crude mixture dissolved in hexane (100 mL) was refluxed overnight with cat. I_2 to give rise exclusively and quantitatively to the *Z* isomer, which was ultimately purified by recrystallization in EtOH to afford (*Z*)-**26** as pale yellow crystals; mp 132−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (s, 3 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 3.96 (s, 3 H), 5.20 (s, 2 H), 6.85 (d, J = 8.5 Hz, 1 H), 6.94 (d, J = 8.5 Hz, 1 H), 7.04 (d, J = 8.3 Hz, 1 H), 7.21 (s, 1 H), 7.30−7.36 (m, 3 H), 7.51 (d, J = 7.8 Hz, 2 H), 7.60 (d, J = 8.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.4, 56.1, 56.4, 60.6, 74.7, 110.6, 111.1, 113.1, 119.6, 120.1, 122.6, 126.6, 128.3, 128.5, 128.6, 129.4, 129.6, 135.5, 136.9, 143.0, 152.8, 156.4, 168.5. Anal. Calcd for $C_{26}H_{24}BrNO_5$: C, 61.19; H, 4.74; N, 2.74. Found: C, 60.98; H, 4.84; N, 2.50.

Typical Procedure for the Synthesis of the Deprotected 3-Arylmethyleneisoindolinones 8−10. A solution of BCl_3 (1 M in CH_2Cl_2, 1.06 mL, 1.06 mmol, 2 equiv, for **26** and **28**) or BBr_3 (1 M in CH_2Cl_2, 1.06 mL, 1.06 mmol, 2 equiv, for **27**) was added by syringe to a cooled solution (−78 °C) of the protected arylmethylene isoindolinone **26**−**28** (0.53 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at −78 °C for 2 h and MeOH (5 mL) was subsequently added three times. The organic solvents were removed in a vacuum, the crude solid residue was dissolved in Et_2O (25 mL), and the resulting ethereal solution was washed with brine and dried over Na_2SO_4. Flash column chromatography on silica gel with ethyl acetate/hexanes (1:1) as eluent afforded the phenolic derivatives **8**−**10**.

(*Z*)-3-(2-Bromo-3,4-dimethoxybenzylidene)-4-hydroxy-5-methoxy-2-methyl-2,3-dihydro-1*H*-isoindol-1-one (8). Pale yellow crystals from EtOH, 174 mg (78%); mp 207−208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (s, 3 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 3.95 (s, 3 H), 6.53 (s, 1 H), 6.86 (d, J = 8.5 Hz, 1 H), 6.95 (d, J = 8.2 Hz, 1 H), 7.02 (d, J = 8.5 Hz, 1 H), 7.09 (s, 1 H), 7.40 (d, J = 8.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.2, 56.1, 56.6, 60.5, 110.6, 110.7, 110.9, 115.4, 120.1, 122.3, 122.9, 126.7, 129.6, 135.6, 141.1, 146.4, 149.9, 152.7, 168.6. Anal. Calcd for $C_{19}H_{18}BrNO_5$: C, 54.30; H, 4.32; N, 3.33. Found: C, 54.44; H, 4.24; N, 3.52.

Typical Procedure for the Synthesis of the Aristocularines 2a,c,d. A solution of compound **8**−**10** (0.6 mmol), Cs_2CO_3 (277 mg, 0.85 mmol), and copper(I) trifluoromethanesulfonate toluene complex (15.5 mg, 0.03 mmol) in pyridine (10 mL) was refluxed for 24 h. The reaction mixture was poured into 1 M HCl (5 mL) and extracted with ethyl acetate (2 × 15 mL). The organic layer was stirred with 10% NaOH solution (20 mL) and then washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow solid. Aristoyagonine[2] (**2a**) was obtained by recrystallization from MeOH as bright yellow crystals, 163 mg (80%).

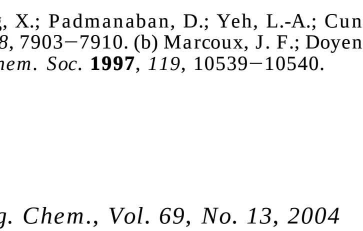
Acknowledgment. This research was supported by the Centre National de la Recherche Scientifique and MENESR (grant to A.M.). We also acknowledge helpful discussions and advice from Dr. T. G. C. Bird (AstraZeneca Pharma).

Supporting Information Available: General methods and materials and characterization for all other substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049869G

---

(19) For example, a sizable nOe effect (10%) of the aromatic proton C-6′ (δ 7.02 ppm) was observed upon irradiation of the *N*-methyl group (δ 2.92) for compound **8**.



8

(20) (a) Xing, X.; Padmanaban, D.; Yeh, L.-A.; Cuny, G. D. *Tetrahedron* **2002**, *58*, 7903−7910. (b) Marcoux, J. F.; Doyen, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539−10540.