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First total synthesis of cichorine and zinnimidine

Anne Moreau, Axel Couture,* Eric Deniau, Pierre Grandclaudon and Stéphane Lebrun
UMR 8009 "Chimie Organique et Macromoléculaire", Laboratoire de Chimie Organique Physique, Bâtiment C3(2), Université des Sciences et Technologies de Lille, 59655, Villeneuve d'Ascq Cédex, France. E-mail: axel.couture@univ-lille1.fr; Fax: +33(0)3 20 33 63 09; Tel: +33(0)3 20 43 44 32

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The first total synthesis of the phytotoxins cichorine and zinnimidine is described. The synthetic tactics involve the sequential connection of the dense and diverse functionalities on the aromatic nucleus followed by a Parham cyclization process, giving rise to the lactam unit embedded in the title compound framework.

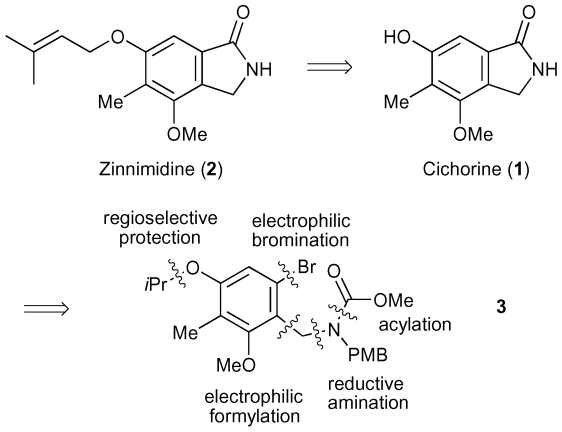
Introduction

Cichorine (**1**) and zinnimidine (**2**) are eminent representatives of phytotoxins, which have been isolated from the stationary liquid cultures of a variety of phytopathogenic fungi from the genus *Alternaria*.[1] Recent interest stimulated in the scientific community for this class of isoindol-1-ones stems mainly from their implication in diseases of commercially important plants, namely through necrosis of the tips and margins of infected specimens.[1] Cichorine (**1**), which has been also isolated as a minor component from the culture filtrate of *Aspergillus silvaticus*, was found to be highly active on knapweed, corn oats and soyabeans.[2,3] Zinnimidine (**2**) has been produced by the fungus *Alternaria porri* (Ellis) Ciferi, the casual fungus of the black spot disease in stone-leeks and onions.[4] Finally, the fungal metabolites **1** and **2** have been isolated from *Alternaria cichorii*, which causes foliar blight of Russian knapweed, an important pest weed.[2] As far as we are aware, no total synthesis of these two phytotoxins have appeared in the literature. This is undoubtedly due to the difficulties associated with the construction of the compact isoindolinone framework, densely and diversely functionalized on the basic aromatic nucleus. Due to the diverse biological activities of many of their derivatives,[5] the chemistry of isoindolinones has been the focus of new synthetic methodologies during the last few years and organic chemists have at their disposal a great number of synthetic methods for the preparation of these bicyclic lactams. The main general synthetic approaches involve: (i) the free radical bromination of 2-methylbenzoyl ester derivatives and subsequent treatment with an appropriate primary amine;[6] (ii) the condensation of a primary amine with the corresponding phthalides;[7] (iii) the dephosphorylation of the corresponding 3-phosphorylated parent models;[8] (iv) the reduction of phthalimides *via* their aminals or thioaminals;[9] and, finally, (v) the reaction of *o*-phthalaldehyde with a primary amine.[10] All these methods are simple and proceed in good yields. Unfortunately, their applicability is generally unsatisfactory mainly because of restrictions in the choice of substituents, namely in their nature, number and their position on the aromatic nucleus. Thus, the first method does not tolerate the presence in the parent models of substituents sensitive to the bromination step (*e.g.* an additional methyl group). Issues raised by elaboration of diversely substituted isoindolinones by applying the second and third methods may not be simply addressed from their corresponding oxo analogues or their phosphorylated derivatives. Finally, the last synthetic methods genuinely lack selectivity and hence have been confined to the synthesis of bare or symmetrically substituted models. Consequently, all these strategies will be inevitably plagued with difficulties associated with the exquisite arrangement of diverse and dense functionalities within the compact molecular framework of alkaloids such as cichorine (**1**) and zinnimidine (**2**).

Results and discussion

In the course of our ongoing project dealing with the synthesis and subsequent biological evaluation of a variety of isoindolinone-centered natural products[11] we herein wish to disclose an efficient synthetic approach to isoindolinones illustrated by the first total synthesis of the exemplary representatives of the *Alternaria* species, *i.e.* cichorine (**1**) and zinnimidine (**2**). Our strategy is based upon the exploitation of the Parham cyclization process for the creation of the five-membered lactam unit embedded in the isoindolinone framework. The protocol developed by Parham hinges upon aromatic lithiation, usually carried out by lithium–halogen exchange and subsequent reaction with an internal electrophile.[12] This technique occupies a place of choice in the arsenal of synthetic tactics for the assembling of carbo- and heterocyclic systems, but applications for the elaboration of five-membered lactams are quite scarce and have been confined thus far to the construction of dibenzoindolones,[13] chromeno-[14] and arylmethylene isoindolinones.[15]

We then anticipated that zinnimidine (**2**) would be obtained by prenylation of cichorine (**1**) (Scheme 1) and we conjectured that this fused alkaloid would be conceivably assembled by a Parham type cyclization of the pentasubstituted aromatic carbamate **3**, incorporating differentiated protecting groups on the sensitive hydroxy phenolic and *N*-acyl functionalities.



Scheme 1 Retrosynthetic analysis and disconnections for the synthesis of the parent compound **3**.

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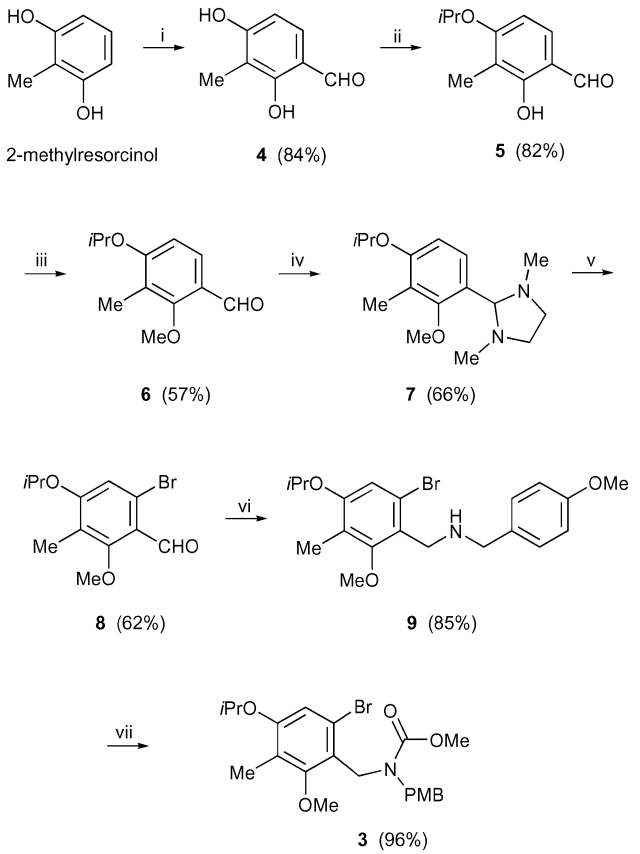
A contentious issue in the elaboration of this rather congested compound was the initial judgement of the proper strategy for the tailored incorporation of the diverse aromatic substituents and, above all, of the appropriate functionalities liable to secure the creation of the lactam unit. Retrosynthetic analysis led to the disconnections indicated on Scheme 1.

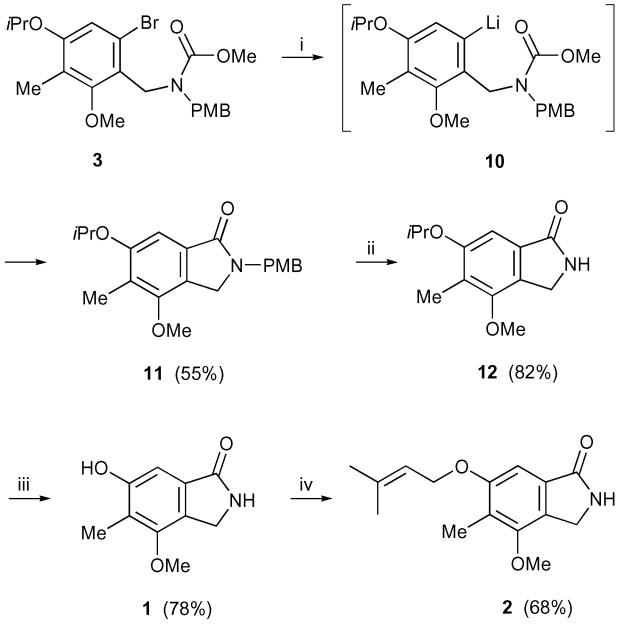
It was assumed that the installation of the carbamate function, acting as the internal electrophile, would be achieved by acylation of the corresponding protected amine, produced by a reductive amination process involving the appropriate amine and the suitably substituted carboxaldehyde. The bromine atom would be regioselectively connected to the benzene nucleus by an electrophilic process exploiting the presence of the vicinal carboxaldehyde function.

The first facet of the synthesis was then the elaboration of the requisite tetrasubstituted benzaldehyde derivative **6**. This compound was readily synthesized by the three step sequence depicted in Scheme 2. Formylation of 2-methylresorcinol with $POCl_3$–DMF proceeded regioselectively to afford the benzaldehyde derivative **4** in an excellent yield. Sequential *O*-alkylations of this biphenolic compound were performed in basic medium but under differentiated conditions. Thus, alkylation with isopropyl iodide[16] was achieved in the polar aprotic solvent acetone, which diminishes hydrogen bonding interactions between the vicinal carboxaldehyde and phenol functions in **4**, thus favouring alkylation of the remote hydroxy phenolic group. *O*-Methylation of the resulting monophenolic derivative **5** was readily achieved under standard conditions to deliver the required contiguously and diversely substituted benzaldehyde **6**, albeit in moderate yield (47% over two steps). We next planned to install the bromine atom at the mandatory vicinal position of the carboxaldehyde function. Due to the erratic nature of aromatic bromination processes, a metallation–electrophilic bromination process was more appealing. 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 brominating agents, we found that adding 2 eq. of *tert*-butyllithium in pentane to 1 eq. of imidazolidine **7**[17] in Et_2O at −30 °C and then quenching with 1,2-dibromotetrachloroethane led to bromination exclusively adjacent to the imidazolidine group. Regeneration of the formyl functionality provided a 62% yield of the desired 6-bromo-4-isopropoxy-2-methoxy-3-methylbenzaldehyde (**8**). The subsequent synthesis of the secondary amine **9**, incorporating the nitrogen protecting group PMB (*para*-methoxybenzyl), was achieved by a reductive amination process and the dibenzylamine **9** was delivered with a fairly good yield. Finally, treatment of **9** with methyl chloroformate provided almost quantitatively the carbamate **3** (82% over two steps), a candidate for the planned Parham cyclization process.

To ensure the formation of the lithiated intermediate **10**, a THF solution of the arylbromide **3** was exposed to *tert*-butyllithium at −100 °C (Scheme 3). The ring-closure was instantaneous as demonstrated by the isolation solely of the annulated compound **11** upon immediate aqueous work-up. Subsequent benzylic lactam deprotection was obtained by treatment of **11** with TFA in the presence of the carbocation scavenger anisole, to provide the monoprotected isoindolinone **12**. Finally, treatment of **12** with boron chloride (BCl_3) in dichloromethane under mild conditions triggered off the cleavage of the phenolic isopropyl protecting group[16] and this simple operation delivered the target natural product cichorine (**1**). This compound can be regarded as an immediate precursor of zinnimidine (**2**), which was easily obtained by prenylation of the 6-OH group (Scheme 3). By the reaction sequence depicted in Scheme 2 and Scheme 3 the phytotoxins **1** and **2** were obtained respectively in 4.8% (over 10 steps for **1**) and 3.3% yield (over 11 steps for **2**), starting from 2-methylresorcinol. The constitution of the target, final compounds **1** and **2** was secured by matching their ^1H and ^{13}C NMR, IR and mass spectra with those published for the products extracted from vegetal sources.[2–4]



Scheme 2 *Reagents and conditions*: (i) $POCl_3$, DMF, 20 °C 12 h; (ii) *i*PrI, K_2CO_3, acetone, reflux, 12 h; (iii) MeI, K_2CO_3, DMF, 40 °C, 12 h; (iv) *N*,*N*′-dimethylethylenediamine, toluene, reflux, 3 h; (v) *t*BuLi, Et_2O, Ar, −30 °C, then 20 °C, 6 h, then −30 °C, $(BrCl_2C)_2$, then 20 °C, 12 h, then HCl 10%, 20 °C, 30 min; (vi) *p*-$CH_3OC_6H_4CH_2NH_2$, toluene, reflux, 3 h, then $NaBH_4$, MeOH, 20 °C, 2 h; (vii) ClCOOMe, NEt_3, CH_2Cl_2, 0 °C, then 20 °C, 3 h.



Scheme 3 *Reagents and conditions*: (i) *t*BuLi, THF, −100 °C, Ar, 30 min; (ii) TFA, anisole, reflux, 48 h; (iii) BCl_3, CH_2Cl_2, −78 °C, 2 h; (iv) 1-bromo-3-methylbut-2-ene, K_2CO_3, acetone, reflux, 12 h.

Conclusions

A simple and efficient first total synthesis of the naturally occurring isoindolinones cichorine (**1**) and zinnimidine (**2**) from *Alternaria* species has been disclosed. The synthetic approach clearly emphasizes the prominent place of the Parham cyclization process in the arsenal of the synthetic tactics for the assembling of heterocyclic systems, namely alkaloids.

Experimental

General methods

Mps were determined on a Reichert–Thermopan apparatus and are uncorrected. Infrared spectra were recorded on a FT-IR Bruker Vector 22 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer. Coupling constants (J) are given in Hz and rounded to the nearest 0.1 Hz. Elemental analyses were determined by the CNRS microanalysis centre. The silica gel used for flash column chromatography was Merck Kieselgel of 0.040–0.063 mm particle size. Dry glassware was obtained by oven-drying and assembly under Ar. Ar was used as the inert atmosphere and was passed through a drying tube to remove moisture. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Tetrahydrofuran (THF) and diethylether (Et_2O) were distilled from sodium benzophenone ketyl immediately before use. Methanol (MeOH) was distilled from magnesium turnings and dichloromethane (CH_2Cl_2) from CaH_2, before storage on 4 Å molecular sieves.

Starting material

The aldehyde **4** was prepared according to a standard procedure.[18]

2-Hydroxy-4-isopropoxy-3-methylbenzaldehyde 5

A stirred solution of the benzaldehyde derivative **4** (4.50 g, 29.6 mmol) and isopropyl iodide (5.35 g, 31.5 mmol) in acetone (100 mL) was refluxed with K_2CO_3 (4.30 g, 31.2 mmol) for 12 h. After cooling and filtration on celite, the solvent was removed under a reduced pressure to leave an oily residue, which was purified by flash column chromatography on silica using Et_2O–hexanes (50 : 50) as eluent to give the benzaldehyde **5** (4.70 g, 82%) as a colourless oil (found: C, 67.8; H, 7.4%. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%); IR ν_{max} (film)/cm^{-1} 3390 (OH), 1640 (CHO); ^{1}H NMR δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.36 (6 H, d, $J_{1,3}$ 5.9, 2 × CHCH_3), 2.07 (3 H, s, ArCH_3), 4.66 (1 H, heptuplet, $J_{1,3}$ 5.9, CHMe$_2$), 6.52 (1 H, d, $J_{1,3}$ 8.8, H$_{ar}$), 7.31 (1 H, d, $J_{1,3}$ 8.8, H$_{ar}$), 9.68 (1 H, s, CHO); ^{13}C NMR δ_C (75 MHz; $CDCl_3$; Me_4Si) 7.5 (CH_3), 22.2 (2 × CH_3), 70.7 (ArOCH), 104.7 (CH_{ar}), 114.1 (C_{ar}), 114.9 (C_{ar}), 133.0 (CH_{ar}), 161.4 (C_{ar}), 163.1(C_{ar}), 194.5 (CHO).

4-Isopropoxy-2-methoxy-3-methylbenzaldehyde 6

A solution of the benzaldehyde **5** (2.40 g, 12.4 mmol) and methyl iodide (2.0 g, 14.0 mmol) in DMF (50 mL) was stirred with K_2CO_3 (8.55 g, 62 mmol) at 40 °C for 12 h. After cooling and filtration on celite, the solvent was removed under a reduced pressure to leave a solid residue, which was purified by flash column chromatography on silica using Et_2O–hexanes (50 : 50) as eluent to give the benzaldehyde **6** (1.47 g, 57%) as a white solid; mp 44–45 °C (found: C, 69.3; H, 7.6%. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.75%); IR ν_{max} (KBr)/cm^{-1} 1679 (CHO); ^{1}H NMR δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.35 (6 H, d, $J_{1,3}$ 5.9, 2 × CHCH_3), 2.13 (3 H, s, ArCH_3), 3.84 (3 H, s, OCH_3), 4.64 (1 H, m, CHMe$_2$), 6.71 (1 H, d, $J_{1,3}$ 8.8, H$_{ar}$), 7.70 (1 H, d, $J_{1,3}$ 8.8, H$_{ar}$), 10.20 (1 H, s, CHO); ^{13}C NMR δ_C (75 MHz; $CDCl_3$; Me_4Si) 8.7 (CH_3), 22.1 (CH_3), 22.15 (CH_3), 63.1 (OCH_3), 70.6 (ArOCH), 108.4 (CH_{ar}), 120.8 (C_{ar}), 122.3 (C_{ar}), 127.7 (CH_{ar}), 162.7 (C_{ar}), 162.9 (C_{ar}), 189.1 (CHO).

2-(4-Isopropoxy-2-methoxy-3-methylphenyl)-1,3-dimethylimidazolidine 7

A solution of the benzaldehyde **6** (2.39 g, 11.5 mmol) and N,N'-dimethylethylenediamine (1.06 g, 12.0 mmol) in toluene (75 mL) was refluxed in a Dean–Stark apparatus for 3 h. The solvent was removed under a reduced pressure to leave an oily residue, which was purified by distillation under a reduced pressure (102–103 °C; 10^{-2} mm Hg) to give the imidazolidine **7** (2.11 g, 66%) as a yellow oil (found: C, 68.8; H, 9.6; N, 10.0%. $C_{16}H_{26}N_2O_2$ requires C, 69.0; H, 9.4; N, 10.1%); IR ν_{max} (film)/cm^{-1} 2760 (NCH_3); ^{1}H NMR δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.31 (6 H, d, $J_{1,3}$ 6.1, 2 × CHCH_3), 2.13 (3 H, s, ArCH_3), 2.18 (6 H, s, 2 × NCH_3), 2.52–2.58 (2 H, m, NCH_2), 3.33–3.38 (2 H, m, NCH_2), 3.69 (3 H, s, OCH_3), 4.51 (1 H, heptuplet, $J_{1,3}$ 6.1, CHMe$_2$), 6.69 (1 H, d, $J_{1,3}$ 8.5, H$_{ar}$), 7.40 (1 H, d, $J_{1,3}$ 8.5, H$_{ar}$); ^{13}C NMR δ_C (75 MHz; $CDCl_3$; Me_4Si) 9.4 (CH_3), 22.3 (2 × CH_3), 39.7 (2 × NCH_3), 53.3 (2 × NCH_2), 61.3 (OCH_3), 70.2 (ArOCH), 84.4 (NCHN), 109.7 (CH_{ar}), 119.5 (C_{ar}), 123.8 (C_{ar}), 126.8 (CH_{ar}), 156.8 (C_{ar}), 159.3 (C_{ar}).

6-Bromo-4-isopropoxy-2-methoxy-3-methylbenzaldehyde 8

*t*BuLi (1.7 M in pentane, 10.0 mL, 17.0 mmol) was added dropwise at −30 °C under Ar to a solution of the imidazolidine **7** (2.35 g, 8.4 mmol) in dry Et_2O (30 mL). The solution was allowed to warm to rt, stirred at this temperature for 6 h, then re-cooled to −30 °C. A solution of 1,2-dibromotetrachloroethane (5.50 g, 16.9 mmol) in Et_2O (10 mL) was added dropwise at −30 °C, the mixture was then allowed to warm to rt and stirring at rt was maintained for 12 h. The solution was poured onto a 10% HCl aqueous solution (50 mL), the mixture was stirred for 30 min and extracted with Et_2O (4 × 25 mL). The combined extracts were washed with water and brine, dried (Na_2SO_4) and evaporated under a reduced pressure to leave an oily residue, which was purified by column chromatography on silica using Et_2O–hexanes (50 : 50) as eluent to give the aldehyde **8** (1.49 g, 62%) as a yellow oil (found: C, 50.4; H, 5.4%. $C_{12}H_{15}BrO_3$ requires C, 50.2; H, 5.3%); IR ν_{max} (film)/cm^{-1} 1685 (CHO); ^{1}H NMR δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.35 (6 H, d, $J_{1,3}$ 6.1, 2 × CHCH_3), 2.05 (3 H, s, ArCH_3), 3.79 (3 H, s, OCH_3), 4.59 (1 H, heptuplet, $J_{1,3}$ 6.1, CHMe$_2$), 6.80 (1 H, s, H$_{ar}$), 10.23 (1 H, s, CHO); ^{13}C NMR δ_C (75 MHz; $CDCl_3$; Me_4Si) 8.6 (CH_3), 22.0 (2 × CH_3), 62.4 (OCH_3), 71.1 (ArOCH), 114.0 (CH_{ar}), 120.3 (C_{ar}), 121.5 (C_{ar}), 124.0 (C_{ar}), 161.4 (C_{ar}), 162.2 (C_{ar}), 189.7 (CHO).

N-(6-Bromo-4-isopropoxy-2-methoxy-3-methyl)-*N*-(4-methoxybenzyl)amine 9

A solution of the aldehyde **8** (1.15 g, 4.0 mmol) and *para*-methoxybenzylamine (0.55 g, 4.0 mmol) in toluene (50 mL) was refluxed in a Dean–Stark apparatus for 3 h. The solvent was evaporated under a reduced pressure and the crude imine was used without further purification. The imine was dissolved in MeOH (50 mL) and treated with sodium borohydride (0.30 g, 8.0 mmol). After stirring for 2 h, NH_4Cl (1 g) was added and stirring was maintained for 30 min. The solvent was evaporated under a reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL). The solution was washed with water and brine, then concentrated under a vacuum. Purification by column chromatography on silica using ethyl acetate–hexanes (90 : 10) as eluent afforded the amine **9** (1.39 g, 85%) as a yellow oil (found: C, 59.1; H, 6.35; N, 3.7%. $C_{20}H_{26}BrNO_3$ requires C, 58.8; H, 6.4; N, 3.4%); IR ν_{max} (film)/cm^{-1} 3335 (NH); ^{1}H NMR δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.32 (6 H, d, $J_{1,3}$ 6.1, 2 × CHCH_3), 2.08 (3 H, s, ArCH_3), 3.71 (3 H, s, OCH_3), 3.74 (2 H, s, NCH_2), 3.79 (3 H, s, OCH_3), 3.85 (2 H, s, NCH_2), 4.46 (1 H, heptuplet, $J_{1,3}$ 6.1, CHMe$_2$), 6.84 (1 H, s, H$_{ar}$), 6.85 (2 H, d, $J_{1,3}$ 8.5, H$_{ar}$), 7.27 (2 H, d, $J_{1,3}$ 8.5, H$_{ar}$); ^{13}C NMR δ_C (75 MHz; $CDCl_3$; Me_4Si) 9.5 (CH_3), 22.1 (2 × CH_3), 47.5 (NCH_2), 55.3 (OCH_3), 58.2 (NCH_2), 61.4

(OCH_3), 70.8 (ArOCH), 113.5 (CH_{ar}), 113.6 (2 × CH_{ar}), 120.8 (C_{ar}), 121.8 (C_{ar}), 125.4 (C_{ar}), 129.4 (2 × CH_{ar}), 132.7 (C_{ar}), 156.6 (C_{ar}), 158.5 (C_{ar}), 158.6 (C_{ar}).

N-(6-Bromo-4-isopropoxy-2-methoxy-3-methyl)-*N*-(4-methoxybenzyl)carbamic acid methyl ester 3

Methyl chloroformate (0.56 g, 5.88 mmol) was added dropwise to a stirred solution of the amine **9** (1.60 g, 3.92 mmol) and triethylamine (0.79 g, 7.85 mmol) in CH_2Cl_2 (50 mL). After stirring for 3 h, the mixture was washed with water then brine and dried (Na_2SO_4). The solvent was evaporated under a reduced pressure to leave a residue, which was purified by column chromatography on silica using ethyl acetate–hexanes (30 : 70) as eluent to give the carbamate **3** (1.75 g, 96%) as a yellow oil (found: C, 56.4; H, 6.33; N, 2.9%. $C_{22}H_{28}BrNO_5$ requires C, 56.7; H, 6.05; N, 3.0%); IR ν_{max} (film)/cm^{-1} 1725 (C=O); ^{1}H NMR δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.31 (6 H, d, $J_{1,3}$ 5.9, 2 × CHCH_3), 2.04 (3 H, s, ArCH_3), 3.61 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 4.22 (2 H, br. s, NCH_2), 4.44 (1 H, heptuplet, $J_{1,3}$ 5.9, CHMe$_2$), 4.71 (2 H, br. s, NCH_2), 6.74 (2 H, d, $J_{1,3}$ 8.5, H_{ar}), 6.77 (1 H, s, H_{ar}), 7.06 (2 H, br. s, H_{ar}); ^{13}C NMR δ_C (75 MHz; $CDCl_3$; Me_4Si) 9.5 (CH_3), 22.1 (2 × CH_3), 45.1 (NCH_2), 52.7 (OCH_3), 55.2 (OCH_3), 60.2 (NCH_2), 60.9 (OCH_3), 70.7 (ArOCH), 113.5 (CH_{ar}), 113.4 (2 × CH_{ar}), 120.7 (C_{ar}), 121.4 (C_{ar}), 122.4 (C_{ar}), 128.3 (2 × CH_{ar}), 130.4 (C_{ar}), 157.1 (C_{ar}), 158.4 (C_{ar}), 159.5 (2 × C_{ar}).

6-Isopropoxy-4-methoxy-2-(4-methoxybenzyl)-5-methyl-2,3-dihydro-1*H*-isoindol-1-one 11

*t*BuLi (1.7 M in pentane, 2.2 mL, 3.68 mmol) was added dropwise at −100 °C under Ar to a solution of the carbamate **3** (1.56 g, 3.35 mmol) in THF (40 mL). The solution was stirred at −100 °C for 30 min, then aqueous saturated NH_4Cl solution was added (5 mL). The cooled mixture was extracted with Et_2O (2 × 25 mL). The combined extracts were dried (Na_2SO_4) and evaporated under a reduced pressure to leave a solid, which was purified by column chromatography on silica using ethyl acetate–hexanes (50 : 50) as eluent to give the isoindolinone **11** (0.68 g, 55%) as white crystals, mp 74–75 °C (found: C, 70.7; H, 7.0; N, 3.85%. $C_{21}H_{25}NO_4$ requires C, 71.0; H, 7.1; N, 3.9%); IR ν_{max} (KBr)/cm^{-1} 1675 (C=O); ^{1}H NMR δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.35 (6 H, d, $J_{1,3}$ 6.1, 2 × CHCH_3), 2.14 (3 H, s, ArCH_3), 3.78 (6 H, s, 2 × OCH_3), 4.25 (2 H, s, NCH_2), 4.61 (1 H, heptuplet, $J_{1,3}$ 6.1, CHMe$_2$), 4.71 (2 H, s, NCH_2), 6.85 (2 H, d, $J_{1,3}$ 8.5, H_{ar}), 7.11 (1 H, s, H_{ar}), 7.22 (2 H, d, $J_{1,3}$ 8.5, H_{ar}); ^{13}C NMR δ_C (75 MHz; $CDCl_3$; Me_4Si) 9.7 (CH_3), 22.1 (2 × CH_3), 45.8 (NCH_2), 47.5 (NCH_2), 55.3 (OCH_3), 59.7 (OCH_3), 70.7 (ArOCH), 102.7 (CH_{ar}), 114.1 (2 × CH_{ar}), 123.2 (C_{ar}), 123.8 (C_{ar}), 129.2 (C_{ar}), 129.4 (2 × CH_{ar}), 131.4 (C_{ar}), 156.3 (C_{ar}), 157.6 (C_{ar}), 159.1 (C_{ar}), 168.5 (CO).

6-Isopropoxy-4-methoxy-5-methyl-2,3-dihydro-1*H*-isoindol-1-one 12

A solution of the isoindolinone **11** (0.53 g, 1.5 mmol) and trifluoroacetic acid (TFA, 1.71 g, 15.0 mmol) in anisole (2.5 mL) was refluxed for 48 h. The mixture was concentrated under a vacuum and the residue was dissolved in CH_2Cl_2 (10 mL). Triethylamine (1.5 mL) was added and the mixture was stirred for 30 min, then washed with water (2 × 20 mL) and dried ($MgSO_4$). The solvent was evaporated under a reduced pressure to leave a white solid, which was recrystallized from EtOH to afford the isoindolinone **12** (0.29 g, 82%) as white crystals, mp 122–123 °C (found: C, 66.6; H, 7.1; N, 6.1%. $C_{13}H_{17}NO_3$ requires C, 66.35; H, 7.3; N, 5.95%); IR ν_{max} (KBr)/cm^{-1} 3220 (NH), 1678 (C=O); ^{1}H NMR δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.30 (6 H, d, $J_{1,3}$ 6.1, 2 × CHCH_3), 2.09 (3 H, s, ArCH_3), 3.89 (3 H, s, OCH_3), 4.49 (2 H, s, NCH_2), 4.66 (1 H, heptuplet, $J_{1,3}$ 6.1, CHMe$_2$), 6.94 (1 H, s, H_{ar}), 8.56 (1 H, br s, NH); ^{13}C NMR δ_C (75 MHz; $CDCl_3$; Me_4Si) 9.6 (CH_3), 21.9 (2 × CH_3), 43.3 (NCH_2), 58.9 (OCH_3), 70.2 (ArOCH), 101.5 (CH_{ar}), 121.6 (C_{ar}), 124.7 (C_{ar}), 132.2 (C_{ar}), 153.5 (C_{ar}), 156.5 (C_{ar}), 169.8 (CO).

6-Hydroxy-4-methoxy-5-methyl-2,3-dihydro-1*H*-isoindol-1-one (cichorine) 1

A solution of BCl_3 (1 M in CH_2Cl_2, 1.06 mL, 1.06 mmol) was added dropwise with stirring to a solution of the isoindolinone **12** (0.20 g, 0.85 mmol) in CH_2Cl_2 (15 mL) maintained at −78 °C under Ar. The mixture was stirred at −78 °C for 2 h, then MeOH (3 × 5 mL) was added. The solvent was evaporated under a reduced pressure and the solid residue was dissolved in Et_2O (25 mL). The solution was washed with brine (20 mL), dried ($MgSO_4$) and evaporated under a reduced pressure to leave a solid residue, which was purified by column chromatography on silica using ethyl acetate–hexanes (50 : 50) as eluent to give the cichorine **1** (0.13 g, 78%) as white crystals, mp 215–216 °C (from EtOH) (lit.,[19] 217 °C); ^{13}C NMR δ_C (75 MHz; DMSO-d_6; Me_4Si) 9.4 (CH_3), 43.2 (NCH_2), 58.9 (OCH_3), 103.0 (CH_{ar}), 119.1 (C_{ar}), 123.1 (C_{ar}), 132.0 (C_{ar}), 153.6 (C_{ar}), 156.5 (C_{ar}), 169.9 (CO).

4-Methoxy-5-methyl-6-(3-methylbut-2-enyloxy)-2,3-dihydro-1*H*-isoindol-1-one (zinnimidine) 2

A stirred solution of cichorine **1** (100 mg, 0.52 mmol) and 1-bromo-2-methylbut-2-ene (93 mg, 0.62 mmol) in acetone (15 mL) was refluxed with K_2CO_3 (0.11 g, 0.80 mmol) for 12 h. The mixture was filtered on celite, concentrated under a vacuum, then the solid residue was dissolved in Et_2O (15 mL). The cooled solution was washed with water, 10% NaOH solution (2 × 15 mL), brine and dried (Na_2SO_4). The organic layer was evaporated under a reduced pressure to afford the zinnimidine **2** (93 mg, 68%), which was purified by recrystallization from EtOH. White crystals, mp 136–138 °C (lit.,[4] 136–138 °C).

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