Total syntheses of (±)-cherylline and (±)-latifine

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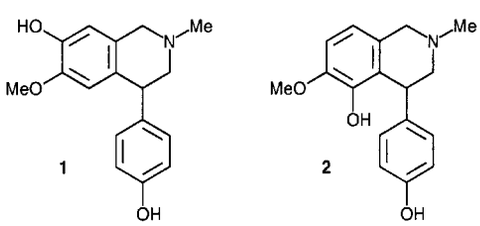
A new total synthesis of the two phenolic alkaloids (±)-cherylline **1** and (±)-latifine **2** isolated from *Crinum* species is described. The two key steps in the elaboration of these natural products are an anionic variant of the Fries rearrangement which gives access to the congested *o*-aroylbenzoic acid derivatives **26** and **27**, and an intramolecular Horner reaction involving the corresponding *N*-phosphorylmethylbenzamide derivatives **8** and **9**.

Introduction

Cherylline **1**[1] and latifine **2**[2] are new representatives of the rare



3 X = H Y = OR, halogen,
4 X = Br Y = OH
5 X = H Y = OH

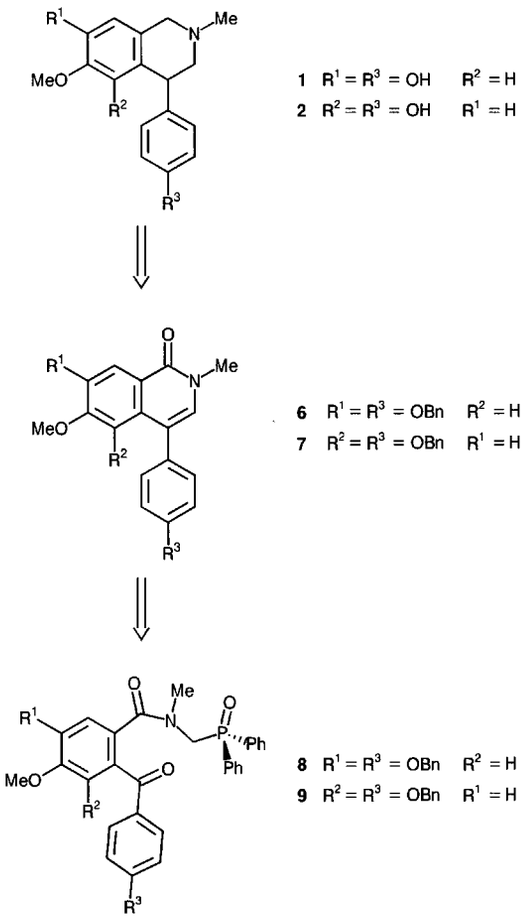
phenolic *Amaryllidaceae* alkaloids which have been recently isolated from several *Crinum* species,[3,4] namely *Crinum latifolium*, a plant used as rubefacient and tonic,[5] and *Crinum powelli*. The structure determination of these unique alkaloids has revealed latifine to be the first isoquinoline alkaloid possessing a 4-phenyl-5,6-dioxygenated substitution pattern and that it is isomeric with cherylline, which is the only 4-phenyl-6,7-dioxygenated isoquinoline alkaloid so far known.[4,6]

Despite the fact that synthetic studies on aryl 1,2,3,4-tetrahydroisoquinolines have attracted much attention owing to their potential biological activities[7,8] and notwithstanding the increasing medicinal interest in the 4-aryl members of this family,[9–12] synthetic methods for the elaboration of these alkaloids, scarce as they are, genuinely lack flexibility and universality. Thus cherylline has been synthesized in different ways, the most common ones involving the acid-catalyzed cyclization of suitably substituted norbelladine derivatives **3**.[13] The methods employed differ mainly in the nature of the leaving group Y prone to generate the carbocationic species involved in the annulation step. The same methodology has been applied to the synthesis of regioisomeric latifine but it requires the preliminary incorporation of a bromine atom in the opened model **4** in order to circumvent the problem of regioselectivity and to favour coupling of the carbocation *ortho* to the hydroxy group.[14] Cherylline has also been prepared from the trihydroxy derivative **5** by adapting a sophisticated route which mimics the biogenetic pathway operative in the formation of *Amaryllidaceae*.[13a,c] It is also accessible by a synthetic route based upon the Bischler–Napieralski reaction of *N*-formyl[13b] and isocyanide[15] derivatives of polyalkoxyphenethylamines accompanied by several protection and deprotection steps. This synthetic approach has also been successfully used for the enantioselective synthesis of (−)-cherylline which could equally be obtained by Polonovski reaction of correctly substituted dibenzazocine *N*-oxides.[16] Paradoxically, latifine has not elicited the same interest from the scientific community and total syntheses of this structurally challenging alkaloid are extremely rare. An original and elegant method relying upon the Claisen rearrangement of benzyloxycinnamyl methoxyphenyl ether has been reported.[17] Extension to the enantioselective synthesis of the unnatural enantiomer was envisaged in the sequel but the observed specific rotation of the synthetic material is open to discussion.[17]

Results and discussion

We describe here a conceptually new synthetic route which gives equally easily access to the two alkaloids cherylline **1** and latifine **2**. Our approach to the synthesis of compounds **1** and **2**, which is depicted in the retrosynthetic Scheme 1, involved two phases. Of central importance was the construction of the 4-arylisoquinolone template contiguously and differentially substituted by phenolic methyl- and benzyl-protected hydroxy groups on the environmentally different aromatic moieties. Once prepared, sequential reduction of the carbonyl function and of the surviving N–C=C unit of the annulated compounds **6** and **7** generated the tetrahydroisoquinoline ring system, and *O*-deprotection of the aromatic amines thus obtained completed the synthesis of the target natural products. For the assembly of the isoquinolones **6** and **7** equipped with a pendant aromatic unit at the 4-position of the heterocyclic nucleus we have taken advantage of the remarkable nucleophilicity of the stabilized α-amino carbanions deriving from the phosphorylated *o*-aroylbenzamide derivatives **8** and **9** and their ability to generate the N–C=C moiety inter-[18] and intra-molecularly.[19]

The synthesis of the phosphorylated benzamide derivatives started with the elaboration of the diprotected *o*-aroylbenzoic acid derivatives **26** and **27**, which is presented in Scheme 2. The key step in the elaboration of these rather congested benzophenone derivatives is an anionic homologous variant of the Fries rearrangement.[20] Initially the benzyl protected bromomethoxybenzaldehyde derivatives **11** and **12** were obtained by



Scheme 1

sequential benzyl protection followed by bromination of the syringaldehyde **10** for **11** and by reversing the sequence for **12**. Reduction of the aldehydes **11** and **12** delivered the benzylic alcohols **13** and **14** which were subsequently treated with 4-benzyloxybenzoic acid **15** according to the Mitsonobu protocol to provide the ester precursors **16** and **17**. At this stage it was anticipated that the aryllithium species **18** and **19** could be readily obtainable from the corresponding aryl bromide by low temperature halogen–metal exchange with *n*-butyllithium, since this reaction is known to proceed at a significantly greater rate than the alternative pathway of ester attack.[21] We further assumed that these aryllithium species **18** and **19** would undergo intramolecular attack of the ester moiety and thus generate the desired ketone linkage between the two aromatic components.[20] Indeed, such a rearrangement might be expected to prove very favourable in the light of the greater thermodynamic stability of the resultant alkoxide ions **20** and **21**. Compounds **16** and **17** were thus subjected to halogen–lithium exchange at low temperature (−95 °C) with *n*-butyllithium followed by warming the reaction mixture to −50 °C. To our delight this treatment gave the desired rearrangement and protic work up resulted in the formation of the benzophenone derivatives **22** and **23**. Although these could be isolated, they proved somewhat unstable and direct oxidation to aldehydes **24** and **25** with tetrapropylammonium perruthenate(VII) (TPAP) and 4-methylmorpholine *N*-oxide (NMO)[22] was generally more convenient. With these materials in hand, we then employed sodium chlorite oxidation[23] to obtain the carboxylic acids **26** and **27**. Connection of the aminomethyldiphenylphosphine oxide appendage at the eastern part of the molecule was effected by reaction of the carboxylic acids **26** and **27** with *N*-diphenylphosphinoylmethyl-*N*-methylamine **28** under standard conditions (DCC, DMAP) (Scheme 3). The phosphorylated amine **28** was readily obtained beforehand by treatment of the appropriate hexahydrotriazine with diphenylphosphine oxide.[24] This coupling protocol provided the fully benzyl-protected 4-arylisoquinolone progenitors **8** and **9** in excellent yields.

Exposure of the phosphorylated benzamide derivatives **8** and **9** to potassium bis(trimethylsilyl)amide (KHMDS, 1 equiv.) at −78 °C in THF induced the formation of the phosphoryl stabilized α-amino carbanion. Addition of this suitably placed carbon nucleophile to the vicinal aroyl moiety causes the annulation reaction. Warming the reaction mixture to room temperature ensured completion of the reaction and protic work up afforded straightforwardly the 4-arylisoquinolones **6** and **7** in excellent yields, probably due to the high degree of conjugation of the fused compounds. For the final access to the targeted natural products **1** and **2**, sequential reduction of the carbonyl and enamine functions was subsequently envisaged. It was found more judicious to adopt an expeditious protocol that precludes isolation of the intermediates. To this end, the 4-arylisoquinolones **6** and **7** were first treated with $LiAlH_4$ in THF which led intermediately to the 4-aryl-1,2-dihydroisoquinolines **29** and **30.**

The adoption of the benzyl-derived protecting groups for the latent functionalities in this double reduction process was rewarded here: mild palladium-catalyzed hydrogenolysis of the transient dihydroisoquinolines **29** and **30** at ambient temperature in the presence of ammonium formate caused reduction of the N–C=C unit and the concomitant deprotection of the hydroxy phenolic groups. This protocol resulted in the generation of (±)-cherylline **1** and (±)-latifine **2** with very satisfactory yields (47 and 44% respectively over the last four steps). The final compounds exhibited characterisation data consistent with the proposed structures and ^1H, ^{13}C NMR spectra that correlated precisely with that of authentic samples.[1,2]

Experimental

General methods

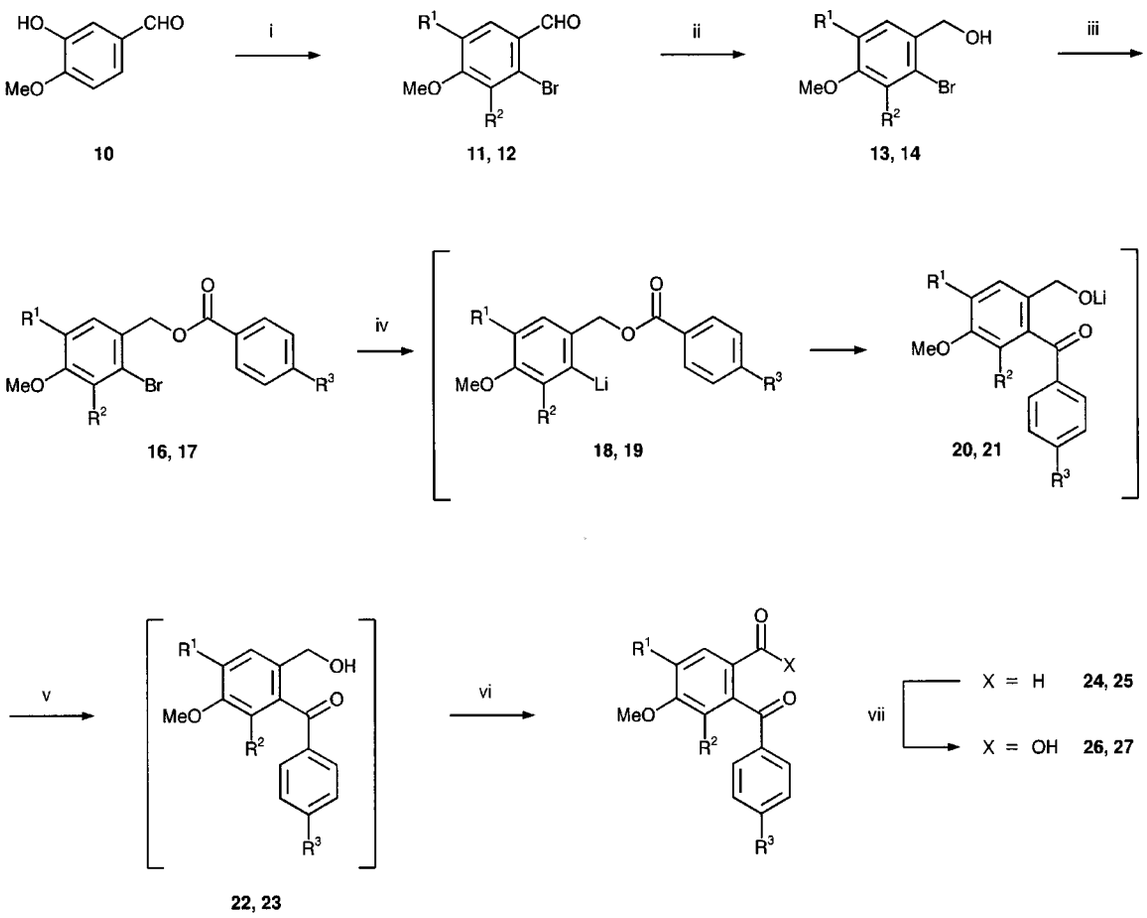
Mps were determined on a Reichert-Thermopan apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 881 spectrometer. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AM 300 spectrometer and were referenced against internal tetramethylsilane; ^{31}P NMR (121 MHz) spectra were referenced against H_3PO_4 as external standard. Coupling constants (*J*) are given in Hz and rounded to the nearest 0.1 Hz. Mass spectra analyses (MALDI/TOF) were performed on a Finnigan MAT Vision 2000 spectrometer. Elemental analyses were determined by the CNRS microanalysis centre. TLC was performed with plates coated with Kieselgel G (Merck). The plates were developed with hexane–ethyl acetate. 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) was distilled from sodium benzophenone ketyl immediately before use and dichloromethane (CH_2Cl_2) was distilled from CaH_2. Methanol and ethanol were distilled from magnesium turnings and acetonitrile from CaH_2 before storage on 4 Å molecular sieves.

Starting materials

Aldehydes **11**,[25] **12**,[26] benzylic alcohols **13**,[27] **14**[28] and benzyl protected benzoic acid **15**[29] were prepared according to standard procedures. The phosphorylated amine **28**[24] was synthesized according to an already reported procedure.

General procedure for the synthesis of esters 16 and 17

A solution of carboxylic acid **15** (2.5 g, 11 mmol), benzylic



Compound	R^1	R^2	R^3
11,13,16,18,20,22,24,26	OBn	H	OBn
12,14,17,19,21,23,25,27	H	OBn	OBn

Scheme 2 *Reagents and conditions*: i, BnBr, K_2CO_3, DMF, reflux, then Br_2, AcONa, AcOH (for **11**) or Br_2, AcOH, reflux, then BnBr, K_2CO_3, DMF, reflux (for **12**); ii, $NaBH_4$, EtOH, room temp.; iii, 4-$BnOC_6H_4CO_2H$ **15**, DEAD, Ph_3P, THF, 0 °C to room temp., 40 min; iv, BuLi, THF, −98 to −50 °C, 30 min; v, $NaHCO_3$, H_2O; vi, NMO, TPAP, MeCN, 25 °C, 30 min; vii, $NaClO_2$, $NaHPO_4$, 2-methylbut-2-ene, THF, Bu^{t}OH, H_2O, 25 °C, 8 h.

alcohol **13** or **14** (3.55 g, 11 mmol) and triphenylphosphine (3.17 g, 12.1 mmol) in THF (40 mL) was cooled to 0 °C and treated with diethyl azodicarboxylate (DEAD, 1.9 mL, 12.1 mmol). The resultant mixture was then warmed to 25 °C and stirred for 40 min. The reaction mixture was concentrated and the residue passed through a short column (silica gel, AcOEt–hexanes 1 : 5). The eluent was then concentrated and the residue purified by flash column chromatography using AcOEt–hexanes (40 : 60) as eluent to afford the esters **16** and **17** which were finally purified by recrystallization from MeOH.

(5-Benzyloxy-2-bromo-4-methoxyphenyl)methyl 4-benzyloxybenzoate 16. White crystals (4.98 g, 85%), mp 96–97 °C (Found: C, 65.2; H, 4.8. $C_{29}H_{25}BrO_5$ requires C, 65.3; H, 4.7%); ν_{max}(KBr)/cm^{-1} 1707 (CO); δ_H($CDCl_3$) 3.88 (3 H, s, OCH_3), 5.13 (4 H, two s, OCH_2Ph), 5.28 (2 H, s, $COOCH_2Ph$), 6.98 (2 H, d, *J* 9.0, H_{arom}), 7.02 (1 H, s, H_{arom}), 7.08 (1 H, s, H_{arom}), 7.25–7.44 (10 H, m, H_{arom}), 7.96 (2 H, d, *J* 9.0, H_{arom}); δ_C($CDCl_3$) C, 114.6 (C–Br), 122.6, 128.6, 136.2, 136.5, 147.4 (C–O), 150.2 (C–O), 162.6 (C–O), 165.9 (C=O); CH, 114.5, 115.8, 116.0, 127.3, 127.5, 128.0, 128.2, 128.7, 131.8; CH_2, 65.9, 70.1, 71.2; CH_3, 56.3; *m*/*z* (MH^+) 533, 535.

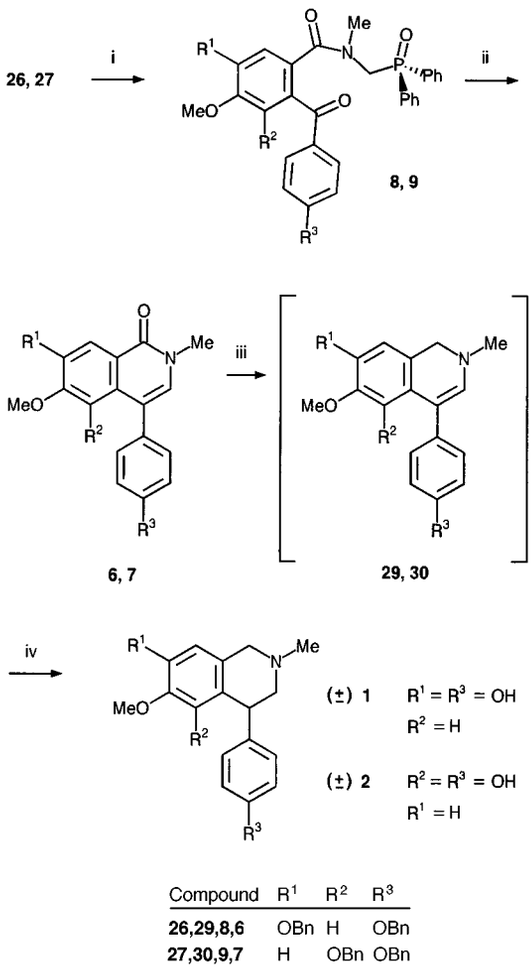
(3-Benzyloxy-2-bromo-4-methoxyphenyl)methyl 4-benzyloxybenzoate 17. White crystals (4.69 g, 80%), mp 105–106 °C (Found: C, 65.3; H, 4.65. $C_{29}H_{25}BrO_5$ requires C, 65.3; H, 4.7%); ν_{max}(KBr)/cm^{-1} 1714 (CO); δ_H($CDCl_3$) 3.88 (3 H, s, OCH_3), 5.06 (2 H, s, OCH_2Ph), 5.11 (2 H, s, OCH_2Ph), 5.40 (2 H, s, $COOCH_2Ph$), 6.89 (1 H, d, *J* 8.5, H_{arom}), 7.00 (2 H, d, *J* 9.0, H_{arom}), 7.24 (1 H, d, *J* 8.5, H_{arom}), 7.31–7.60 (10 H, m, H_{arom}), 8.05 (2 H, d, *J* 9.0, H_{arom}); δ_C($CDCl_3$) C, 120.2 (C–Br), 122.8, 128.6, 136.2, 137.0, 153.8 (C–O), 162.6 (C–O), 166.0 (C=O); CH, 111.0, 114.5, 125.8, 127.5, 128.1, 128.2, 128.4, 128.5, 128.7, 131.8; CH_2, 66.2, 70.1, 74.6; CH_3, 56.2; *m*/*z* (MH^+) 533, 535.

General procedure for the synthesis of *o*-aroybenzylic alcohols 22 and 23

A solution of ester **16** or **17** (1.07 g, 2 mmol) in THF (30 mL) was cooled to −98 °C and treated with Bu^{n}Li (2.2 mmol, 1.38 mL, 1.6 M in hexanes). The resultant mixture was then warmed to −50 °C and stirred for 30 min. After quenching the reaction with saturated aqueous $NaHCO_3$ (50 mL), the THF was evaporated *in vacuo* and the residue extracted with AcOEt (2 × 100 mL). The combined organic layers were washed with brine (100 mL) and then dried (Na_2SO_4), filtered and concentrated. The residue containing the benzylic alcohols **22** and **23** was used directly in the next step without further purification.

General procedure for oxidation of benzylic alcohols 22 and 23 to benzaldehydes 24 and 25

A suspension of the crude benzylic alcohol derivative **22** or **23**, NMO (352 mg, 3 mmol) and activated 3 Å molecular sieves in acetonitrile (10 mL) was treated with TPAP (35.2 mg, 0.1 mmol) and stirred at 25 °C for 30 min. The reaction mixture



Compound	R^1	R^2	R^3
26,29,8,6	OBn	H	OBn
27,30,9,7	H	OBn	OBn

Scheme 3 *Reagents and conditions*: i, DCC, DMAP, CH_3NHCH_2-$P(O)Ph_2$ **28**, CH_2Cl_2, room temp., 12 h; ii, KHMDS, THF, −78 °C to room temp., 30 min; iii, $LiAlH_4$, THF, reflux, 2 h; iv, HCO_2NH_4, Pd/C, MeOH, reflux, 30 min.

was then diluted with AcOEt and filtered through a pad of silica gel. The filtrate was concentrated and the residue purified by flash column chromatography using AcOEt–hexanes (50 : 50) as eluent to afford the aldehydes **24** and **25**.

5-Benzyloxy-2-(4-benzyloxybenzoyl)-4-methoxybenzaldehyde 24. White crystals (0.72 g, 80% over two steps), mp 134–135 °C (Found: C, 76.9; H, 5.4. $C_{29}H_{24}O_5$ requires C, 77.0; H, 5.35%); ν_{max}(KBr)/cm^{-1} 1680 (CO), 1650 (CO); δ_H($CDCl_3$) 3.93 (3 H, s, OCH_3), 5.15 (2 H, s, OCH_2Ph), 5.26 (2 H, s, OCH_2Ph), 7.00 (1 H, s, H_{arom}), 7.04 (2 H, d, *J* 8.6, H_{arom}), 7.31–7.35 (10 H, m, H_{arom}), 7.62 (1 H, s, H_{arom}), 7.82 (2 H, d, *J* 8.6, H_{arom}), 9.87 (1 H, s, CHO); δ_C($CDCl_3$) C, 128.0, 128.9, 130.9, 135.9, 137.2, 149.6 (C–O), 153.4 (C–O), 163.3 (C–O), 194.2 (C=O); CH, 111.4, 114.8, 127.5, 127.6, 128.3, 128.4, 128.6, 128.8, 132.6, 189.1 (CH=O); CH_2, 70.3, 71.0; CH_3, 56.4; *m*/*z* (MH^+) 453.

3-Benzyloxy-2-(4-benzyloxybenzoyl)-4-methoxybenzaldehyde 25. White crystals (0.68 g, 86% over two steps), mp 86–87 °C (Found: C, 77.0; H, 5.4. $C_{29}H_{24}O_5$ requires C, 77.0; H, 5.35%); ν_{max}(KBr)/cm^{-1} 1680 (CO), 1660 (CO); δ_H($CDCl_3$) 3.99 (3 H, s, OCH_3), 4.92 (2 H, s, OCH_2Ph), 5.09 (2 H, s, OCH_2Ph), 6.97 (2 H, d, *J* 8.9, H_{arom}), 7.13 (1 H, d, *J* 8.6, H_{arom}), 7.19–7.31 (5 H, m, H_{arom}), 7.33–7.46 (5 H, m, H_{arom}), 7.76 (1 H, d, *J* 8.6, H_{arom}), 7.78 (1 H, d, *J* 8.9, H_{arom}), 9.75 (1 H, s, CHO); δ_C($CDCl_3$) C, 128.1, 128.8, 130.7, 135.3, 136.8, 148.5 (C–O), 157.9 (C–O), 163.1 (C–O), 193.7 (C=O); CH, 112.1, 114.7, 127.5, 127.9, 128.2, 128.7, 131.6, 188.9 (CH=O); CH_2, 70.2, 75.9; CH_3, 56.2; *m*/*z* (MH^+) 453.

General procedure for oxidation of benzaldehydes 24 and 25 to benzoic acids 26 and 27

A solution of aldehyde **24** or **25** (4.5 g, 10 mmol) in THF (45 mL), Bu′OH (45 mL) and water (15 mL) was treated with 2-methylbut-2-ene (80 mmol, 40 mL, 2.0 M in THF), NaH_2PO_4 (30 mmol, 30 ml, 1.0 M in THF) and 80% $NaClO_2$ (3.39 mg, 30 mmol). The reaction mixture was stirred at 25 °C until the oxidation was complete (8 h) and the organic solvents were then evaporated *in vacuo*. The residue was then treated with $KHSO_4$ (100 mL, 0.5 M in water) and the resultant aqueous mixture was extracted with AcOEt (2 × 100 mL). The combined layers were washed with water (100 ml), saturated Na_2SO_3 (50 mL) and brine (100 mL) and then dried (Na_2SO_4), filtered and concentrated. Purification of the residue by recrystallization of the products from hexane–toluene then afforded the corresponding *o*-aroylbenzoic acid derivatives **26** and **27**.

2-(4-Benzyloxybenzoyl)-4-methoxy-5-benzyloxybenzoic acid 26. White crystals (3.88 g, 83% before recrystallization), mp 167–168 °C (Found: C, 74.45; H, 5.2. $C_{29}H_{24}O_6$ requires C, 74.35; H, 5.15%); ν_{max}(KBr)/cm^{-1} 1675 (CO), 1665 (CO); δ_H($CDCl_3$) 3.81 (3 H, s, OCH_3), 5.17 (2 H, s, OCH_2Ph), 5.23 (2 H, s, OCH_2Ph), 6.98 (1 H, s, H_{arom}), 7.09–7.17 (2 H, m, H_{arom}), 7.28–7.65 (13 H, m, H_{arom}), 11.25 (1 H, s, COOH); δ_C($CDCl_3$) C, 129.5, 133.2, 135.8, 136.5, 136.6, 147.6 (C–O), 151.2 (C–O), 162.0 (C–O), 166.4 (COOH), 194.5 (C=O); CH, 110.5, 113.2, 114.6, 127.8, 127.9, 128.5, 128.6, 129.3, 131.1; CH_2, 69.5, 70.0; CH_3, 56.0; *m*/*z* (MH^+) 469.

2-(4-Benzyloxybenzoyl)-4-methoxy-3-benzyloxybenzoic acid 27. White crystals (4.16 g, 89% before recrystallization), mp 174–175 °C (Found: C, 74.5; H, 5.1. $C_{29}H_{24}O_6$ requires C, 74.35; H, 5.15%); ν_{max}(KBr)/cm^{-1} 1680 (CO), 1655 (CO); δ_H($CDCl_3$) 3.96 (3 H, s, OCH_3), 4.77 (2 H, s, OCH_2Ph), 5.15 (2 H, s, OCH_2Ph), 7.04–7.15 (4 H, m, H_{arom}), 7.18–7.49 (9 H, m, H_{arom}), 7.62 (2 H, d, *J* 8.8, H_{arom}), 7.85 (1 H, d, *J* 8.6, H_{arom}), 11.25 (1 H, s, COOH); δ_C($CDCl_3$) C, 121.2, 130.8, 136.5, 136.7, 136.8, 143.8 (C–O), 156.2 (C–O), 162.0 (C–O), 165.9 (COOH), 192.8 (C=O), CH, 112.6, 114.6, 127.5, 127.8, 127.9, 128.0, 128.1, 128.5, 130.6; CH_2, 69.5, 74.6; CH_3, 56.2; *m*/*z* (MH^+) 469.

General procedure for the synthesis of the phosphorylated *o*-aroylbenzamide derivatives 8 and 9

A solution of the benzoic acid derivative **26** or **27** (1 g, 2.14 mmol) in anhydrous CH_2Cl_2 (50 mL) was added with vigorous stirring under Ar to a cooled solution (0 °C) of the phosphorylated amine **28** (0.52 g, 2.14 mmol), DCC (0.45 g, 2.14 mmol) and DMAP (30 mg, 0.214 mmol) in anhydrous CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 2 h, then filtered on Celite and the solvent was evaporated on a rotary vacuum evaporator. The crude phosphorylated benzamide **8** or **9** was purified by flash column chromatography using acetone–hexane (65 : 35) as eluent and finally recrystallized from hexane–toluene.

***N*-Diphenylphosphinoylmethyl-*N*-methyl-2-(4-benzyloxybenzoyl)-4-methoxy-5-benzyloxybenzamide 8.** White crystals (1.16 g, 78%), mp 75–76 °C (Found: C, 74.3; H, 5.4; N, 2.2. $C_{43}H_{38}NO_6P$ requires C, 74.2; H, 5.5; N, 2.0%); ν_{max}(KBr)/cm^{-1} 1641 (CO), 1637 (CO), 1166 (PO); δ_H($CDCl_3$) 2.98 (3 H, s, NCH_3), 3.80 (3 H, s, OCH_3), 4.44 (2 H, d, *J* 5.1, NCH_2P), 4.90 (2 H, s, OCH_2Ph), 5.11 (2 H, s, OCH_2Ph), 5.98 (1 H, s, H_{arom}), 6.97 (1 H, s, H_{arom}), 6.98 (2 H, d, *J* 8.8, H_{arom}), 7.26–7.58 (17 H, m, H_{arom}), 7.73 (2 H, d, *J* 8.8, H_{arom}), 7.87–7.94 (3 H, m, H_{arom}); δ_C($CDCl_3$) C, 130.0, 130.3, 130.4, 131.1 (C_{arom}–P, d, J_{CP} 94), 135.6, 136.0, 149.1 (C–O), 150.2 (C–O), 162.8 (C–O), 170.5 (NC=O), 194.0 (C=O); CH, 111.9, 113.9, 114.4, 127.5, 128.3 (d, J_{CP} 6), 128.6, 128.7, 128.8, 131.2, (d, J_{CP} 10), 132.3 (d, J_{CP} 14);

CH_2, 47.3 (CH_2–P, d, J_{CP} 76), 70.1, 70.9; CH_3, 39.3 (NCH_3), 56.3 (OCH_3); δ_P($CDCl_3$) 31.5; *m*/*z* (MH^+) 696.

***N*-Diphenyphosphinoylmethyl-*N*-methyl-2-(4-benzyloxybenzoyl)-4-methoxy-3-benzyloxybenzamide 9.** White crystals (1.22 g, 82%), mp 83–84 °C (Found: C, 74.05; H, 5.45; N, 1.95. $C_{43}H_{38}NO_6P$ requires C, 74.2; H, 5.5; N, 2.0%); ν_{max}(KBr)/cm^{-1} 1639 (CO), 1633 (CO), 1170 (PO); δ_H($CDCl_3$) 3.15 (3 H, s, NCH_3), 3.87 (3 H, s, OCH_3), 4.47 (2 H, br s, NCH_2P), 4.84 (2 H, s, OCH_2Ph), 5.08 (2 H, s, OCH_2Ph), 6.82 (1 H, d, *J* 8.5, H_{arom}), 6.92 (2 H, d, *J* 8.7, H_{arom}), 6.95–7.53 (18 H, m, H_{arom}), 7.71 (2 H, d, *J* 8.7, H_{arom}), 7.85–7.89 (3 H, m, H_{arom}); δ_C($CDCl_3$) C, 125.3, 130.9 (C_{arom}–P, d, J_{CP} 98), 134.0, 136.3, 136.7, 153.4 (C–O), 162.9 (C–O), 169.8 (NC=O), 193.9 (C=O); CH, 112.5, 114.4, 122.7, 127.4, 127.8, 128.1 (d, J_{CP} 13.5), 128.2, 128.3, 128.7 (d, J_{CP} 9), 129.0, 131.1 (d, J_{CP} 10), 132.1 (d, J_{CP} 13.5); CH_2, 47.1 (CH_2–P, d, J_{CP} 75), 70.1, 75.4; CH_3 39.4 (NCH_3), 56.0 (OCH_3); δ_P($CDCl_3$) 31.5; *m*/*z* (MH^+) 696.

General procedure for the synthesis of 4-aryl-1(2*H*)-isoquinolones 6 and 7

A solution of KHMDS (1.5 mL, 0.75 mmol, 0.5 M in toluene) was added dropwise to a stirred solution of parent amide **8** or **9** (0.5 g, 0.72 mmol) in THF (30 mL) at −78 °C under Ar. The solution was stirred for 30 min at −78 °C after which it was warmed to room temperature and stirred for an additional 30 min. After this, several drops of dilute HCl (10%), water (10 mL), Et_2O (20 mL) and CH_2Cl_2 (20 mL) were added to the reaction mixture. The organic layer was separated, rinsed with brine, dried ($MgSO_4$) and concentrated to dryness. The crude products were purified by flash column chromatography using AcOEt–hexanes (60:40) as eluent and finally recrystallized from hexane–toluene.

4-(4-Benzyloxyphenyl)-6-methoxy-7-benzyloxy-1(2*H*)-isoquinolone 6. White crystals (0.29 g, 85%), mp 168–169 °C (Found: C, 77.8; H, 5.65; N, 3.0. $C_{31}H_{27}NO_4$ requires C, 78.0; H, 5.7; N, 2.9%); ν_{max}(KBr)/cm^{-1} 1645 (CO); δ_H($CDCl_3$) 3.60 (3 H, s, NCH_3), 3.80 (3 H, s, OCH_3), 5.12 (2 H, s, OCH_2Ph), 5.27 (2 H, s, OCH_2Ph), 6.90 (2 H, s, H_{arom}), 7.07 (2 H, d, *J* 8.5, H_{arom}), 7.27–7.51 (12 H, m, H_{arom}), 7.96 (1 H, s, H_{arom}); δ_C($CDCl_3$) C, 118.6, 119.8, 129.2, 132.2, 136.5, 136.8, 148.2 (C–O), 153.5 (C–O), 158.4 (C–O), 161.4 (NC=O); CH, 105.3, 109.8, 115.0, 127.5, 127.6, 128.0, 128.1, 128.5, 128.6, 130.1 (CH=), 130.9; CH_2, 70.1, 70.8; CH_3, 37.0 (NCH_3), 55.9 (OCH_3); *m*/*z* (MH^+) 478.

4-(4-Benzyloxyphenyl)-6-methoxy-5-benzyloxy-1(2*H*)-isoquinolone 7. White crystals (0.28 g, 82%), mp 204–205 °C (Found: C, 78.05; H, 5.6; N, 3.2. $C_{31}H_{27}NO_4$ requires C, 78.0; H, 5.7; N, 2.9%); ν_{max}(KBr)/cm^{-1} 1644 (CO); δ_H($CDCl_3$) 3.58 (3 H, s, NCH_3), 3.92 (3 H, s, OCH_3), 4.30 (2 H, s, OCH_2Ph), 4.98 (2 H, s, OCH_2Ph), 7.18–7.47 (11 H, m, H_{arom}), 8.38 (1 H, d, *J* 8.9, H_{arom}); δ_C($CDCl_3$) C, 116.5, 120.7, 131.4, 132.0, 136.9, 137.2, 142.3 (C–O), 156.0 (C–O), 158.0 (C–O), 161.8 (NC=O); CH, 112.1, 113.7, 125.6, 127.5, 127.6, 127.8, 128.0, 128.3, 128.6, 130.9, 133.8 (CH=); CH_2, 70.1, 75.4; CH_3, 36.6 (NCH_3), 56.0 (OCH_3); *m*/*z* (MH^+) 478.

General procedure for the synthesis of the targeted (±)-cherylline 1 and (±)-latifine 2

A solution of isoquinolone **6** or **7** (500 mg, 1.05 mmol) in anhydrous THF (20 mL) was treated with $LiAlH_4$ (250 mg, 5.25 mmol) added portionwise at 0 °C under Ar over a period of 30 min. The resultant mixture was stirred at 0 °C for an additional 30 min then warmed to room temperature and gently refluxed for 2 h. The excess of hydride was destroyed by careful addition of EtOH, the reaction mixture was filtered on Celite and the solvents were subsequently removed under vacuum. The residue was then dissolved in anhydrous MeOH (20 mL) and the solution was treated with ammonium formate (0.66 g, 10.5 mmol) and Pd/C (10%, 20 mg). The resultant reaction mixture was refluxed for 30 min. MeOH was removed under vacuum and the crude product was dissolved in CH_2Cl_2 (30 mL), washed with water (10 mL) and dried (Na_2SO_4). Concentration under vacuum left an oily residue and final recrystallization from EtOH afforded the desired natural product **1** (0.185 g, 70% after recrystallization) or **2** (0.173 g, 65% after recrystallization). The analytical and spectral data of synthetic **1** and **2** matched those reported for the natural products.

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